Asciminib/ABL001

Oncology Clinical Trial Protocol CABL001A2301

A phase 3, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors

Supplement

This supplement contains

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1. Protocol

NOVARTIS

Clinical Development

ABL001

Oncology Clinical Trial Protocol CABL001A2301

A phase 3, multi-center, open-label, randomized study of oral ABL001 versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors

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List of abbreviations

ABL	Abelson proto-oncogene
AE	Adverse Event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute neutrophil count
AP	Accelerated phase
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATP	Adenosine triphosphate
AUC	Area under the curve
AV block	Atrioventricular block
BC	Blast crisis
BCRP	Breast Cancer Resistant Protein
BID	*bis in diem*/twice a day
BUN	Blood urea nitrogen
CBC	Complete Blood Count
CCA	Clonal chromosome abnormalities
CCyR	Complete Cytogenetic Response
CHR	Complete Hematological Response
CI	Confidence Interval
CMH	Cochran–Mantel–Haenszel
CML	Chronic myelogenous leukemia
CP	Chronic phase
CRO	Contract Research Organization
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP3A4	Cytochrome P450 3A4
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DLCO	Carbon monoxide diffusing capacity
DMC	Data Monitoring Committee
DNA	Desoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ELN	European Leukemia Network
EOT	End of Treatment
eRT	eResearchTechnology, Inc
hADME	Human ADME study (Absorption, Distribution, Metabolism and Excretion)
HDL	High density lipoprotein
ICF	Informed Consent Form

[redacted]

ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
K-M	Kaplan-Meyer
LDL	Low density lipoprotein
LFT	Liver function test
LLN	Lower limit of normal
LSC	Leukemia stem cell
MCyR	Major Cytogenetic Response
mCyR	Minor Cytogenetic Response
MMR	Major Molecular Response
MRI	Magnetic resonance imaging
OS	Overall survival
PAS	Pharmacokynetic analysis set
PCR	Polymerase Chain Reaction
PCyR	Partial Cytogenetic Response
PD	Pharmacodynamic
P-gp	Permeability glycoprotein
Ph+	Philadelphia chromosome positive
PHI	Protected Health Information
PK	Pharmacokinetics
PLT	Platelets
PPS	Per-protocol set
QD	Quaque die/once a day
QT	Q to T interval (ECG)
QTcF	QTc Fredericia
REB	Research Ethics Board
RNA	Ribonucleic acid
RQ-PCR	Real time quantitative polymerase chain reaction
RU	Resource Utilization
SAE	Serious Adverse Event
SAP	The Statistical Analysis Plan (SAP) is a regulatory document which provides evidence of preplanned analyses
SC	Steering committee
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard Operating Procedure
TBIL	Total bilirubin
TKI	Tyrosine Kinase Inhibitor
TTF	Time to treatment failure
UGT	Uridin diPhospho-glucuronosyltransferase
ULN	Upper limit of normal

[redacted]

USPI	US prescribing information
WBC	White blood cell count

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

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Protocol summary:

Title	A phase 3, multi-center, open-label, randomized study of oral ABL001 versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors
Brief title	Study of efficacy of CML-CP patients treated with ABL001 versus bosutinib, previously treated with 2 or more TKIs
Sponsor and Clinical Phase	Novartis; Phase 3
Investigation type	Drug
Study type	Interventional
Purpose and rationale	**Purpose:** The purpose of this pivotal study is to compare the efficacy of ABL001 with that of bosutinib in the treatment of patients with CML-CP having previously been treated with a minimum of two prior ATP-binding site TKIs with BCR-ABL ratios ≥ 1% IS at screening. **Rationale:** There remains an unmet need for new compounds in patients with CML who have failed at least two prior TKIs. Current practice suggests that a second generation TKI will have been used for first line therapy for about one half of patients with CML, meaning that most patients who have failed at least two prior TKIs will have failed at least one if not two second generation TKIs: dasatinib and/or nilotinib. Potentially, such patients may also have failed bosutinib and/or ponatinib (Soverini 2014). Patients having failed at least two TKIs may have limited sensitivity to the remaining available agents and, thus, there exists a need for new safe and effective therapy. In addition, mutations will have developed in 21 to 33% of patients that prevent the use of specific TKIs, increasing the need for a better and alternative compound (Soverini 2014). Omacetaxine, a chemotherapeutic agent, is available for patients who have failed at least two prior TKIs under these conditions but only in the US and Canada. This agent is not available for most patients globally, where a bigger unmet medical need is present. Thus, there remains an unmet need for patients with CML who have failed at least two prior TKIs despite the existence of multiple agents.
Primary Objective and Key Secondary Objective	**Primary Objective:** To compare the Major Molecular Response (MMR) rate at 24 weeks of ABL001 versus bosutinib **Key Secondary Objective:** To compare MMR rate at 96 weeks of ABL001 versus bosutinib

[redacted]

Secondary Objectives	● To compare additional efficacy parameters of ABL001 versus bosutinib: ● cytogenetic response rate (Complete, Partial, Major, Minor, Minimal, no response) at and by all scheduled data collection time points, including 24, 48 and 96 weeks ● MMR rate at all scheduled data collection time points (except 24 and 96 weeks which are already covered by primary and key secondary endpoints) ● MMR rate by all scheduled data collection time points, including 24, 48 and 96 weeks ● Time to MMR ● Duration of MMR ● Time to CCyR ● Duration of CCyR ● Time to treatment failure ● Progression free survival ● Overall survival ● To compare the safety and tolerability profile of ABL001 versus bosutinib by type, frequency and severity of adverse events, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG and other safety data (vital signs, physical examination) ● To characterize the PK of ABL001 in the CML-CP population (Trough plasma concentrations, PK parameters in full PK group: Cmax, Tmax, AUC0-12h, CL/F)
Study design	This study is a randomized, phase 3, open-label, active-controlled multi-center study. Patients will be randomized to the novel BCR-ABL TKI ABL001 and bosutinib in a 2:1 ratio. The randomization is to be stratified to ensure the study population is balanced between the arms with respect to the patient's cytogenetic response status at baseline (Major Cytogenetic response (complete or partial) vs No major cytogenetic response (minor, minimal or none)). The study design incorporates a 2:1 randomization, allocating more patients to the ABL001 arm in order to learn more about the safety profile of the experimental therapy, whereas the safety of bosutinib therapy is well documented. Treatment duration for each patient in the present study is for up to 96 weeks after the last patient received the first dose, which should be adequate to address both the primary objective of the study, i.e. determination of the MMR rate at 24 weeks, as well as secondary efficacy and safety objectives.
Population	Two-hundred and twenty-two (222) patients with CML-CP who had prior treatment with two or more ATP binding site TKIs will be randomized on a 2:1 basis to receive either ABL001 or bosutinib. Patients with known history of T315I and/or V299L mutations at study entry will be excluded from the trial since bosutinib, the comparator, is not approved for these patients.
Inclusion criteria	Patients eligible for inclusion in this study have to meet **all** of the following criteria: 1. Male or female patients with a diagnosis of CML-CP ≥ 18 years of age 2. Patients must meet all of the following laboratory values at the screening visit: ● < 15% blasts in peripheral blood and bone marrow ● < 30% blasts plus promyelocytes in peripheral blood and bone marrow ● < 20% basophils in the peripheral blood ● ≥ 50 x 10^9/L (≥ 50,000/mm3) platelets ● Transient prior therapy related thrombocytopenia (< 50,000/mm3 for ≤30 days prior to screening) is acceptable ● No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly 3. BCR-ABL ratio ≥ 1% IS according to central laboratory at the screening examination

[redacted]

	4. Prior treatment with a minimum of 2 prior ATP-binding site TKIs (i.e. imatinib, nilotinib, dasatinib, radotinib or ponatinib) 5. Failure or intolerance to the last previous TKI therapy at the time of screening (adapted from the 2013 ELN Guidelines Bacarrani 2013) ● Failure is defined for CML-CP patients (CP at the time of initiation of last therapy) as follows. Patients must meet at least 1 of the following criteria. ● Three months after the initiation of therapy: No CHR or > 95% Ph+ metaphases ● Six months after the initiation of therapy: BCR-ABL ratio > 10% IS and/or > 65% Ph+ metaphases ● Twelve months after initiation of therapy: BCR-ABL ratio > 10% IS and/or > 35% Ph+ metaphases ● At any time after the initiation of therapy, loss of CHR, CCyR or PCyR ● At any time after the initiation of therapy, the development of new BCR-ABL mutations ● At any time after the initiation of therapy, confirmed loss of MMR in 2 consecutive tests, of which one must have a BCR-ABL ratio ≥ 1% IS ● At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cells: CCA/Ph+ ● Intolerance is defined as: ● Non-hematologic intolerance: Patients with grade 3 or 4 toxicity while on therapy, or with persistent grade 2 toxicity, unresponsive to optimal management, including dose adjustments (unless dose reduction is not considered in the best interest of the patient if response is already suboptimal) ● Hematologic intolerance: Patients with grade 3 or 4 toxicity (absolute neutrophil count [ANC] or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by manufacturer 6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2 7. Adequate end organ function as defined by (as per central laboratory tests): ● Total bilirubin ≤ 1.5 x ULN except for patients with Gilbert's syndrome who may only be included if total bilirubin ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN ● Aspartate transaminase (AST) ≤ 3.0 x ULN ● Alanine transaminase (ALT) ≤ 3.0 x ULN ● Serum amylase ≤ ULN ● Serum lipase ≤ ULN ● Alkaline phosphatase ≤ 2.5 x ULN ● Creatinine clearance ≥ 50ml/min as calculated using Cockcroft-Gault formula 8. Patients must avoid consumption of grapefruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed. 9. Written informed consent obtained prior to any screening procedures. 10. Patients must have the following electrolyte values (as per central laboratory tests) within normal limits or corrected to be within normal limits with supplements prior to first dose of study medication: ● Potassium ● Magnesium ● Total calcium (corrected for serum albumin)

[redacted]

Exclusion criteria	Patients eligible for this study must not meet **any** of the following criteria: 1. Known presence of the T315I or V299L mutation at any time prior to study entry 2. Known second chronic phase of CML after previous progression to AP/BC 3. Previous treatment with a hematopoietic stem-cell transplantation 4. Patient planning to undergo allogeneic hematopoietic stem cell transplantation 5. Cardiac or cardiac repolarization abnormality, including any of the following: ● History within 6 months prior to starting study treatment of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG) ● Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block) ● QTcF at screening ≥450 ms (male patients), ≥460 ms (female patients) ● Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following: ● Risk factors for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia ● Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointes that cannot be discontinued or replaced 7 days prior to starting study drug by safe alternative medication. ● Inability to determine the QTcF interval 6. Severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol (e.g. uncontrolled diabetes, active or uncontrolled infection, pulmonary hypertension) 7. History of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis 8. History of elevation in amylase or lipase (> ULN) within 1 year other than that which may have occurred with gallstones, trauma, or medical procedures 9. History of acute or chronic liver disease 10. Known presence of significant congenital or acquired bleeding disorder unrelated to cancer 11. History of other active malignancy within 3 years prior to study entry with the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively 12. Known history of Human Immunodeficiency Virus (HIV), chronic Hepatitis B (HBV), or chronic Hepatitis C (HCV) infection. Testing for Hepatitis B surface antigen (HBs Ag) and Hepatitis B core antibody (HBcAb / anti HBc) will be performed at screening 13. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or gastric bypass surgery) 14. Treatment with medications that meet one of the following criteria and that cannot be discontinued at least one week prior to the start of treatment with study treatment ● Moderate or strong inducers of CYP3A ● Moderate or strong inhibitors of CYP3A and/or P-gp ● Substrates of CYP3A4/5, CYP2C8, or CYP2C9 with narrow therapeutic index 15. Previous treatment with or known/ suspected hypersensitivity to ABL001 or any of its excipients. 16. Previous treatment with or known/ suspected hypersensitivity to bosutinib or any of its excipients.

[redacted]

	17. Participation in a prior investigational study within 30 days prior to randomization or within 5 half-lives of the investigational product, whichever is longer 18. Pregnant or nursing (lactating) women 19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 days after last dose of ABL001. Highly effective contraception methods include: ● Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception ● Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy) total hysterectomy or tubal ligation at least six weeks before taking study treatment). In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment ● Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject. ● Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. ● In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. 20. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. 21. Sexually active males unless they use a condom during intercourse while taking the drug during treatment and for 3 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via semen.
Investigational and reference therapy	ABL001 40 mg BID Bosutinib 500 mg QD
Efficacy assessments	Molecular response (RQ-PCR, mutational analysis) Cytogenetic response (Bone Marrow Aspirate)
Safety assessments	● Physical examination ● Vital Sign ● Height and weight ● ECOG performance status ● Laboratory chemistry and hematology ● Serology ● Electrocardiogram (ECG) ● Echocardiogram ● Pulmonary function tests with DLCO

[redacted]

Other assessments	● PK sampling (full/sparse) ● Bone Marrow Biopsy ● Patient Report Outcomes (MDASI-CML, PGIC, WPAI, EQ--5D-5L, resource utilization)
Data analysis	The primary efficacy variable of the study is the Major Molecular Response (MMR) rate at 24 weeks. A patient will be counted as having achieved MMR at 24 weeks if he meets the MMR criteria (BCR-ABL ratio ≤0.1%) at 24 weeks. The MMR rate at 24 weeks will be calculated based on the FAS and according to the Intent To Treat (ITT) principle. MMR rate and its 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. Confidence interval for the difference in MMR rate between treatment groups will be provided using the Wald method. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided. The key secondary endpoint is MMR rate at 96 weeks. Formal statistical testing of the key secondary endpoint will be performed only if the primary endpoint is significant by means of a gatekeeping procedure to control the overall alpha level.
Key words	Phase III, open-label, randomized trial, ABL001 bosutinib, CML-CP, prior treatment with 2 or more TKIs

[redacted]

Amendment 1 (10-Apr-2017)

Amendment rationale

This study is currently in the protocol submission phase. The protocol was submitted to the FDA only. The submissions to the other HA and IRB/EC will be performed once the amended protocol is available. As of 30 Mar 2017, no sites were initiated nor any patients screened for this study.

The primary purpose of this amendment is:

Patients with a mutation V299L are excluded from the study, due to the known inactivity of the comparator drug bosutinib. The designation of the mutation was inadvertently identified incorrectly throughout the protocol as V229L instead of V299L. The purpose of this amendment is to correctly identify the exclusionary mutation as "V299L" throughout the document.

In addition some inconsistencies that were discovered after the finalization of the initial protocol are corrected.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Protocol summary: The wrongly designated mutation V229L was corrected to V299L
- Protocol summary: The missing exclusion criteria number 18 "Pregnant or nursing (lactating) women" was added, to be consistent with Section 5.3.
- Section 1.2.2- Overview of bosutinib: The wrongly designated mutation V229L was corrected to V299L
- Section 2.5- Rationale for choice of comparators drug bosutinib: The wrongly designated mutation V229L was corrected to V299L
- [redacted]
- Section 5.1- Patient population: The wrongly designated mutation V229L was corrected to V299L
- Section 5.3- Exclusion criteria: The wrongly designated mutation V229L was corrected to V299L
- Section 6.4.4- Other concomitant medications: The duration of contraception was corrected to "3 days" after treatment discontinuation. Highly effective contraception needs to be continued until 3 days post treatment discontinuation.
- Table 7-1-Visit evaluation schedule: X for weight removed from Visit Week1 Day 1, to be consistent with Section 7.2.2.3.
- Table 7-1-Visit evaluation schedule: X for antineoplastic therapies since discontinuation of study treatment added to survival follow-up phase to be consistent with Section 7.1.6.

[redacted]

- Section 7.1.6- Discontinuation of study treatment: The criteria for study treatment discontinuation "documented lack of efficacy, disease progression" was removed. All patients (excluding patients that died, withdrew consent or are lost to follow-up), are followed up for survival after the treatment phase.
- Section 7.1.6- Discontinuation of study treatment: clarification added to distinguish between discontinuation of study treatment versus discontinuation of study.
- Section 7.2.2.1- Physical examination: clarification of methodology to assess extramedullary involvement.
- [redacted]
- Section 7.2.6- Patient reported outcomes: The statement "The original questionnaire will be kept with the patient's file as the source document." was removed. Questionnaires will be completed electronically; no paper copies will be kept in the source documents.
- Section 10.1.5-Pharmacokinetic analysis set: The number of consecutive days required for PK concentration evaluability was corrected to "3" days. ABL001 should be taken at least 3 consecutive days without interruption or dose modification prior to full PK day.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Chronic myeloid leukemia (CML) is a hematological stem cell disorder characterized by a specific chromosomal translocation leading to the Philadelphia (Ph) chromosome which is detected in 95% of patients (Nowell and Hungerford 1960; Rowley 1973). The molecular consequence of the translocation is the fusion of the *ABL1* proto-oncogene to the *BCR* gene resulting in the production of an activated form of the ABL1 protein tyrosine kinase (TK) (Bartram et al 1983; Heisterkamp et al 1983). BCR-ABL1 drives the growth factor independence, increased proliferation, genomic instability, suppression of apoptosis and alteration of the adhesive properties of CML cells (Hochhaus 2009) and the expression of BCR-ABL1 in mice results in the development of a CML-like disease (Daley et al 1990; Kelliher et al 1990). This evidence that *BCR-ABL1* is a genetic driver of CML was subsequently confirmed by the clinical efficacy of imatinib in patients [IRIS Study STI571A0106].

Clinically, CML is characterized by overproduction of immature myeloid cells and mature granulocytes in the spleen, bone marrow and peripheral blood. Most patients, however, present in the CP, characterized by splenomegaly and leukocytosis with generally few symptoms. CML progresses through three distinct phases of increasing refractoriness to therapy: chronic phase (CP), accelerated phase (AP), and blast crisis (BC). With conventional chemotherapy, such as busulfan or hydroxyurea, the median survival time commonly reported for CML was about 4 years, but progression to AP and BP was only slightly delayed. Interferon-alfa delayed progression significantly, with a median survival of approximately 6 years. However, during the last decade, TK inhibitor (TKI) therapy became the standard treatment for most patients with CML, with complete cytogenetic response rates of 70% to 90% and 5-year progression-free survival and overall survival of 80% to 95% commonly reported (Vardiman 2009).

The National Comprehensive Cancer Network (NCCN) guideline on CML (NCCN guideline v 1.2014) and the European Leukemia Net (ELN) (Baccarani et al 2013) recommend continuing TKI treatment indefinitely in all responding patients. The first TKI, imatinib mesylate (imatinib, STI571, Gleevec™/Glivec™), an adenosine triphosphate (ATP)-competitive TKI with selectivity towards BCR-ABL1, revolutionized treatment of CML and significantly improved the prognosis of patients since its approval in 2001. It is effective in most patients with CML at well-tolerated doses, and is indicated as frontline therapy for Ph+ CML-CP and in patients with Ph+ CML in blast crisis (BC), accelerated phase (AP), or in CP after failure of interferon-alpha therapy. However, despite the remarkable efficacy of imatinib, some patients are either intolerant to the drug or can develop resistance (O'Hare 2006). Imatinib resistance is primarily due to nucleotide substitutions in BCR-ABL, which encode mutant forms of protein's tyrosine kinase domain that impair imatinib binding. Over-expression of the BCR-ABL1 protein may also cause resistance. Rates of resistance increase with each stage of progression of CML (CP < AP < BC) (Branford 2003).

[redacted]

Multiple agents, including nilotinib, dasatinib, ponatinib, bosutinib, radotinib (Korea) and omacetaxine (USA, Canada) are able to combat various forms of imatinib-resistant CML and are currently approved for patients with CML-CP previously treated with prior therapy. With the exception of omacetaxine, which is a cytotoxic chemotherapeutic agent, all of these drugs are ATP-competitive TKIs. Like imatinib, nilotinib and dasatinib are also indicated for the treatment of patients with newly diagnosed CML. The activity of nilotinib or dasatinib in patients previously treated with a second generation TKI is not known. In contrast to the ATP-competitive TKIs, ABL001 inhibits the enzymatic activity of BCR-ABL1 through an allosteric mechanism.

There remains an unmet need for new compounds in patients with CML who have failed at least two prior TKIs. Current practice suggests that a second generation TKI will have been used for first line therapy for about one half of patients with CML, meaning that most patients who have failed at least two prior TKIs will have failed at least one if not two second generation TKIs: dasatinib and/or nilotinib. Potentially, such patients may also have failed bosutinib and/or ponatinib (Soverini 2014). Patients having failed at least two TKIs may have limited sensitivity to the remaining available agents and, thus, there exists a need for new safe and effective therapy. In addition, mutations will have developed in 21 to 33% of patients that prevent the use of specific TKIs, increasing the need for a better and alternative compound (Soverini 2014). Omacetaxine, a chemotherapeutic agent, is available for patients who have failed at least two prior TKIs under these conditions but only in the US and Canada. This agent is not available for most patients globally, where a bigger unmet medical need is present. Thus, there remains an unmet need for active and safe drugs in patients with CML who have failed at least two prior tyrosine kinase inhibitors (TKI), even in the presence of approved drugs, as described below.

1.2 Introduction to investigational treatment

1.2.1 Overview of ABL001

ABL001 is an orally bioavailable specific BCR-ABL inhibitor with a novel mechanism of action. In contrast to inhibitors such as imatinib, nilotinib and dasatinib that bind within the ATP-binding site of the ABL kinase domain, ABL001 inhibits ABL tyrosine kinase activity by binding to a particular allosteric site on the kinase domain, which has only been identified on ABL1, ABL2 and BCR-ABL1. Consequently, ABL001 is specific for the latter three enzymes.

ABL001 potently and selectively inhibits the proliferation of cell lines that express BCR-ABL1. By virtue of ABL001 not interacting with the ATP-binding site, the drug maintains activity against cells expressing clinically observed ATP-binding TKI resistance mutations.

1.2.1.1 Non-clinical experience

In vitro and in vivo pharmacology data

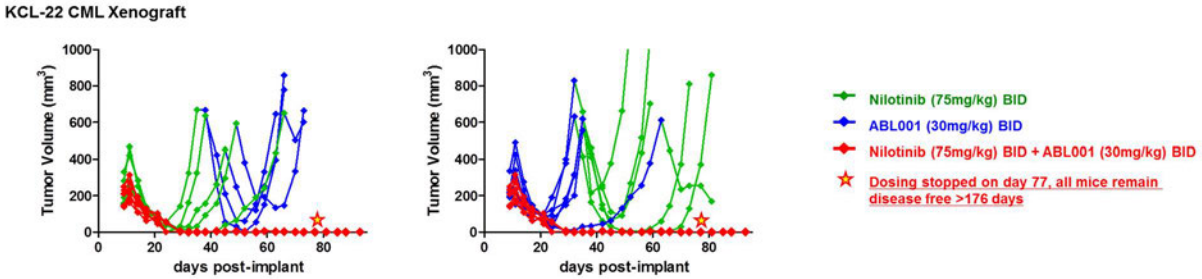
ABL001 displays potent anti-tumor activity in vivo with a clear pharmacokinetic (PK)/pharmacodynamic (PD)/Efficacy relationship [RD-2013-50145]. In a KCL-22 CML blast crisis (CML-BC) cell line mouse subcutaneous xenograft model, tumor regression was

[redacted]

observed at doses of 7.5mg/kg BID and above when ABL001 was administered alone. Efficacy in the KCL-22 xenograft model correlated with stable inhibition of the downstream PD marker phospho-STAT5, consistent with finding that ABL1 inhibits STAT5 phosphorylation in KCL22 cells with an IC_{90} value of approximately 20 nM.

The KCL-22 xenograft model was also used to assess the activity of ABL001 and nilotinib as single agents and in combination (Figure 1-1). In these experiments, when each agent was administered as monotherapy in sequence, initial sensitivity of the tumor was observed to each agent, but relapse occurred in each case. The mutations observed were as expected based on clinical experience (T315I for nilotinib) or modeling (A337V) for ABL001. In contrast, animals treated upfront with the combination of ABL001 and nilotinib achieved sustained tumor regression with no evidence of disease relapse during the 70 days of treatment or for 80 days following discontinuation of treatment. Note that in this KCL-22 model, the cells (derived from a blast crisis CML patient) were grown as a solid tumor rather than as disseminated disease. Also, this model is much more aggressive than chronic phase CML in patients.

Figure 1-1 KCL-22 CML Xenograft



These data are consistent with ABL001 being active against nilotinib-resistant mutations and nilotinib being active against ABL001-resistant mutations. Consequently, the findings support development of ABL001 both as single agent as well as in combination with TKIs as initial therapy of CML as well as therapy after progression on nilotinib.

In addition, due to ABL001 specifically targeting the ABL kinase family (ABL1, ABL2, BCR-ABL), ABL001 offers the potential for improved safety and tolerability when administered as monotherapy when compared to TKIs binding to the ATP site of BCR-ABL, which are less specific towards ABL. Thus, there is the potential for an improved safety profile of ABL001 in comparison to other TKIs.

Safety pharmacology and toxicology

An extensive toxicology safety evaluation program (subchronic, chronic, reproductive toxicology, phototoxicity and genotoxicity studies) was conducted.

Safety pharmacology studies indicate that ABL001 is not expected to cause effects on the vital functions of the CNS, and the respiratory systems. The IC50 for ABL001 in the hERG patch clamp is 11.4 µM (4498 ng/mL). No cardiovascular effects were observed in a single dose jacketed telemetry study in dogs at doses up to 200 mg/kg or the invasive telemetry

[redacted]

cardiovascular safety study up to 60 mg/kg. Furthermore, no ECG related findings were noted in the 4 week GLP dog toxicology study at the end of treatment or recovery.

ABL001 does not show mutagenic, clastogenic, or aneugenic potential in the *in vitro* assays or the MNT assessment *in vivo*; therefore, no potential risk for human is perceived.

As determined by the results of the phototoxicity assessment (*in vitro* and *in vivo*), phototoxic potential was identified in the mouse UV-LLNA assay. Given these data, patients should be advised to avoid prolonged exposure to sunlight (sunbathing) and to use sunscreen.

In the embryofetal development study in rats, results indicate a risk of fetal malformations and/or visceral and skeletal variants. In the fertility study, administration of ABL001 by daily oral gavage at doses of 10, 50 and 200 mg/kg/day to males and females there was no evidence of effects on reproductive function (mean day to mating, mating and fertility indices) at any dose. There was evidence of a slight effect on male sperm motility and/or sperm count in individual animals and an embryo-lethal effect at 200 mg/kg/day. Based on these results, the no-observed-adverse-effect level (NOAEL) for paternal and maternal toxicity was considered to be 200 mg/kg/day and the no-observed-effect level (NOEL) for reproductive function and early embryo-fetal development was considered to be 50 mg/kg/day.

Repeat dose toxicity studies have been performed in rats, dogs and monkeys up to 26, 4 and 13 weeks duration, respectively. Rat and dog toxicology studies identified pancreas, liver, adrenal and harderian gland as potential target tissues. The cynomolgus monkey did not recapitulate in short or long-term studies the pancreatic changes observed in the dog or the rat hepatic changes. All findings thus far have demonstrated a partial to complete reversibility during a 4-week recovery phase, and can be readily monitored in preclinical and clinical settings. The maximal doses evaluated in the 13/26-week general toxicity studies was 200 mg/kg in rats and 100 mg/kg in monkey and provide substantive safety margins over the 40 mg BID clinical dose exposures.

Please refer to the latest [ABL001 Investigator's Brochure] for more details.

Non-clinical pharmacokinetics and metabolism

The preclinical pharmacokinetic profile of ABL001 has been investigated in three species: mouse, rat and dog. In these species, ABL001 exhibited low to moderate clearance, a moderate volume of distribution and a short apparent terminal half-life. Bioavailability was found to be low in rodents and moderate to high in dog.

ABL001 displayed high plasma protein binding across all tested species (2-6% free fraction).

The metabolite profile of ABL001 has been examined in vitro using rat, dog, monkey and human hepatocytes. Interspecies differences were observed. Direct glucuronidation occurred more readily in human and dog than in monkey and was noticeably absent in rat. However, no unique, major metabolites were identified in human hepatocytes. The overall metabolic turnover was low.

The metabolite profile of ABL001 has also been examined in vivo in rats. Following intravenous and oral administration of [^{14}C-ABL001] to intact rats, ABL001 was found to be the predominant component of plasma, accounting for ~86 - 91% of radioactivity from 0 - 8 h. ABL001 was excreted primarily in the feces, with ~90% of radioactivity detected in the feces

[redacted]

from 0 - 48 h. Renal elimination represented a minor route, with ~2.4% of radioactivity detected in the urine from 0 - 72 h. In the feces, ~58% (intravenous) and ~71% (oral) of the dose was associated with unchanged ABL001, with several oxidative metabolites accounting for the remaining radioactivity. The metabolites formed in vivo were consistent with those observed in vitro. Similar observations were noted in bile-duct cannulated rats.

To assess for potential drug-drug interactions (DDI), studies have been conducted with cytochrome P450 (CYP) enzymes and several transporters in vitro.

In human liver microsomes, the major metabolic route of ABL001 was found to be glucuronidation, followed by oxidative metabolism, consistent with findings from human hepatocytes. Several UGT enzymes were found to be capable of ABL001 glucuronidation (UGT1A3, UGT1A4, UGT2B7, and UGT2B17). The oxidative metabolism of ABL001 was also catalyzed by several CYP enzymes. CYP3A4/5 appears to contribute the most, followed by CYP2C8, CYP4F12, and potentially CYP2D6. Though the DDI risk with inhibitors of these enzymes is likely to be minimal, inhibitors of CYP3A4/5 still have the potential to increase ABL001 concentration. Therefore, strong inhibitors of CYP3A4/5 should be avoided and are prohibited in this study. Strong inducers of CYP3A4/5 have the potential to reduce ABL001 concentrations. Therefore, the use of strong inducers of CYP3A4/5 or UGT1A/2B is prohibited in this trial.

Transporter phenotyping studies have identified ABL001 to be a substrate of Breast Cancer Resistant Protein (BCRP) and Permeability glycoprotein (P-gp). While inhibition of BCRP is not expected to result in any clinical relevant changes, inhibitors of P-gp may increase ABL001 concentrations significantly and are prohibited in this study.

There is a potential for DDIs with co-medications metabolized by CYP3A4/5, CYP2C8 and CYP2C9 at the anticipated human efficacious dose. Therefore, narrow therapeutic index substrates of CYP3A4/5, CYP2C8 and CYP2C9 are prohibited. All other substrates of CYP3A4/5, CYP2C8 and CYP2C9 should be used with caution.

Please refer to the latest [ABL001 Investigator Brochure] version for more details.

1.2.1.2 Clinical experience

ABL001 is undergoing evaluation in a first-in-human (FIH) phase I clinical study, study [CABL001X2101].

This study evaluates patients with 1) CML who have been treated with at least 2 prior TKIs, or 2) who have the T315I mutation and have been treated with at least 1 prior TKI, or 3) who have Acute Lymphoblastic Leukemia (ALL) and have been treated with at least 1 prior TKI. The study evaluates administration of ABL001 in a BID single agent dosing schedule, as well as in a QD single agent schedule, and in combination with nilotinib, imatinib, and dasatinib. In the present document, discussion will focus on data from CML patients treated with ABL001 BID single agent only.

In this study, 101 patients have been enrolled as of 2 May 2016, and recruitment is still ongoing. For the most recent data cut-off of 2 May 2016, 67 CML patients had been treated with twice-daily (BID) doses of ABL001 of 10 mg (1 patient), 20 mg (14 patients), 40 mg (26 patients), 80 mg (12 patients), 150 mg (9 patients), and 200 mg (5 patients). Of note, 66 of

[redacted]

those 67 patients had CML-CP, while one of the patients from the 40 mg cohort was in AP. This CML-AP patient discontinued after 20 days of treatment without any post screening efficacy assessment.

The dose of ABL001 40mg BID has been selected for the proposed Phase 3 study based on preliminary MMR and CCyR results from the ongoing FIH study [CABL001X2101], as well as overall ABL001 safety and pharmacokinetic information.

Efficacy:

Preliminary data from the ongoing Phase 1 FIH study [CABL001X2101] indicate that ABL001 has single-agent activity in patients with CML who have failed, relapsed, or are refractory or intolerant after at least two prior TKIs, as demonstrated by reduction in the BCR-ABL transcript. ABL001 resulted in molecular and cytogenetic responses at doses ≥10 mg BID. In reporting the activity of ABL001, the denominator at each time point represents the number of patients who, by that time point have either, achieved the endpoint, discontinued treatment, acquired an intra-patient dose escalation (ignoring assessments after escalation), or have sufficient exposure.

Overall at any dose of ABL001 BID, in patients without T315I mutation:

Molecular response:

In the subset of the n=47 patients treated at a dose level between 10mg - 200mg BID who were not in MMR at screening:

- 6 out of 42 (14.3%) patients achieved MMR by 3 months
- 10 out of 31 (32.3%) patients achieved MMR by 6 months
- 12 out of 31 (38.7%) patients achieved MMR by 9 months
- 13 out of 30 (43.3%) patients achieved MMR by 12 months
- At the dose of 40 mg BID, MMR was achieved in 1 out of 17 (5.9%) patients by 3 months, 4 out of 11 (36.4%) patients by 6 months, 5 out of 11 (45.5%) patients by 9 and 12 months

Cytogenetic response:

- 22 patients had >35% Ph+ metaphases at screening. Of these 22 patients, 5 patients were evaluable with 2 PCyR and 3 CCyR by 3 months. By 6, 9 and 12 months, 7 patients were evaluable with 1 minor cytogenetic response and 5 CCyR.
- 33 patients did not have CCyR at screening. Of these 33 patients, 7 patients were evaluable with 3 PCyR and 4 CCyR by 3 months. By 6, 9 and 12 months, 10 patients were evaluable with 1 minor cytogenetic response, 1 PCyR and 7 CCyR.
- 15 of the above 33 patients who did not have CCyR at screening were treated at the dose of 40mg BID. Of these 15 patients, 3 patients were evaluable and with PCyR by 3 months. By 6, 9 and 12 months 4 patients were evaluable with 1 PCyR and 2 CCyR.

Please refer to the latest [ABL001 Investigator's Brochure] for more details.

[redacted]

Safety:

ABL001 was generally well tolerated in heavily pre-treated CML patients resistant to or intolerant of prior TKIs. By data cutoff of 2 May 2016, 67 CML patients, including those with a T315I mutation (n=9), have been treated at any dose of the ABL001 BID regimen.

There were no study drug related deaths reported. One death was reported due to general physical health deterioration unrelated to the study drug. Overall, 43 SAEs were reported in 20 patients of the 67 patients. Six patients (9%) discontinued ABL001 due to adverse events Dose limiting toxicities in the study included acute cardiac syndrome, lipase increase, arthralgia/myalgia, and bronchospasm in 1 patient each.

Overall of 67 CML patients, almost all (94%) patients reported at least one AE, including 45% reported grade 3/4 AEs. The most common AEs (>10%), regardless of study drug-relationship, were headache, increased lipase (23.9%), rash (20.9), arthralgia, vomiting (both 19.4%), diarrhea, fatigue (both 17.9%), abdominal pain, pruritus (both 16.4%), constipation, myalgia, nausea, upper respiratory tract infection (all 14.9%), thrombocytopenia (13.4%), peripheral edema (11.9%), increased amylase, dizziness, musculoskeletal pain (all 10.4%).

At 40 mg BID dose (n=26), the most common adverse events (>10%), regardless of study drug-relationship, were: increased lipase (30.8%), rash (26.9%), abdominal pain, fatigue, vomiting (all 23.1%), arthralgia, diarrhea (both 19.2%), increased amylase, upper respiratory tract infection (both 15.4%), cough, bone pain, pruritus, increased weight, abdominal discomfort, anemia, constipation, dyspnea, ear pain, non-cardiac chest pain, and thrombocytopenia (all 11.5%).

Please refer to the latest [ABL001 Investigator's Brochure] for more details.

Pharmacokinetics:

PK data from 61 patients (1 in 10 mg BID; 14 in 20 mg BID; 20 in 40 mg BID; 12 in 80 mg BID; 9 in 150 mg BID; 5 in 200 mg BID) were available from the [CABL001X2101] study, as of 2 May 2016.

Based on the available PK data, ABL001, administered orally is rapidly absorbed with a median time to maximum plasma concentration (Tmax) of 2 to 3 hours, independent of dose. Systemic exposure of ABL001, following oral administration of single and multiple doses, as measured by Cmax and AUC, increased in an approximately dose proportional manner. The variability of exposure is low to moderate with inter-patient variability (geometric mean CV %) of 34 to 50% for Cycle 1 Day 1 AUC last and 36 to 60% for Cycle 1 Day 1 Cmax. With the twice daily dosing regimen, median plasma ABL001 accumulation ratios ranged from 1.4 to 2.4. The median accumulation half-life was estimated to be 7 to 15 hours.

The emerging data of the hADME study [CABL001A2102] show that the relative contribution of the glucuronidation pathway to the total clearance of ABL001 via metabolism is estimated to range from 30% to 61%, whereas the relative contribution of the oxidative pathway is estimated to range from 35% to 63%. CYP3A4 was the main contributor for the clearance of ABL001 via the oxidative pathway while UGT2B7 and UGT2B17 were responsible for the clearance of ABL001 via the glucuronidation pathway. There was no

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metabolite detected with mean contribution to plasma radioactivity AUC0-24hours ≥ 10%. ABL001 was the predominant drug-related component in plasma at all time points analyzed, ranging from 91.9 to 94.2% of the total radioactivity AUC0-24 hours AUC, with an average value of 92.7%.

Please refer to the latest [ABL001 Investigator's Brochure] for more details.

Exposure-response relationship:

Exposure-efficacy

A preliminary population PKPD model has been developed using data from the [CABL001X2101] study (cut-off 02May-2016). The time course of molecular response (change in BCR-ABL ratio % IS levels from baseline) was described using a semi-physiological model accounting for cell maturation, disease progression and existing resistance.

Simulations performed using an ABL001 population PK model revealed that a dose of 40 mg BID maintains Ctroughss above the clinical (0.07 to 61 ng/ml) threshold in >=95% of chronic phase CML patients without T315I mutation having failed ≥ 2 TKI or intolerant to TKIs. The estimates from this clinical study were found to be similar to the threshold trough concentration required for 90% inhibition of pSTAT5 derived from a preclinical PK-PD KCL-22 mouse xenograft model (free IC90: 30 to 121 ng/mL, after correction for protein binding) and *in vitro* gIC50 assessed in the KCL-22 cell line (1 ng/mL = 2.1 nM after correction for protein binding).

Simulations performed using ABL001 population PKPD model revealed that chronic phase CML patients having failed ≥ 2 TKI or intolerant to TKIs are likely to exhibit a 1 log10 reduction of (%) BCR-ABL mRNA transcript levels from baseline of ~33% (CI95%: 24-42%) at 6 months, and ~42% (CI95%: 32-52%) at 12 months at a dose of 20 mg BID and ~41% (CI95%: 31-51%) at 6 months, and ~53% (CI95%: 43-63%) at 12 months at a dose of 40 mg BID.

Additional preliminary exposure response analyses (i.e. exploring the relationship between PK and both safety and efficacy) support the selected dose.

Food effect

The effect of food on ABL001 PK was characterized in a Phase I study [CABL001A2101] in healthy volunteers. Food was found to influence the pharmacokinetics of ABL001. When administered with a low-fat meal, the exposure (AUC) decreased by approximately 30%. The overall exposure decreased by approximately 65% when administered with a high-fat meal. Therefore, ABL001 will be administered in a fasted state.

1.2.2 Overview of bosutinib

Bosutinib (Bosulif®) is indicated for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy [Bosulif® USPI], and in Europe for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive

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chronic myelogenous leukemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options [EU SmPC]. Bosutinib has been evaluated in patients treated with one or more prior TKIs.

For patients treated only with prior imatinib, the MMR rate is approximately 15% at 24 weeks overall, and approximately 10% in resistant patients and 20% in intolerant patients (Gambacorti-Passerini 2014). The cytogenetic, molecular, and hematological response rates did not appear to differ greatly between patients who were imatinib-resistant or imatinib-intolerant (Gambacorti-Passerini 2014).

When treated with bosutinib, the majority of patients with CML-CP previously treated with at least 2 TKIs did not achieve Major Cytogenetic Response (MCyR); there was a 27% MCyR rate by Week 24 [Bosulif® USPI]. For patients previously treated with imatinib and either dasatinib or nilotinib, after a median of 28.5 months follow-up, the cumulative rate of Major Molecular Response (MMR) is 15% (Khoury 2012). The cytogenetic, molecular, and hematological response rates appeared to be lower in patients who were resistant to dasatinib after imatinib treatment as compared to patients who were intolerant to dasatinib after imatinib treatment (Khoury 2012). In a small (30 patient) compassionate use trial of patients previously treated with imatinib, dasatinib and nilotinib, after a median duration of treatment of 9.3 months, the cumulative MMR rate was 14% (García-Gutiérrez 2015). Based on these data, the MMR rate at 6 month with bosutinib treatment in patients treated with at least 2 prior TKIs is estimated to be approximately 10-15%.

Bosutinib has no activity against the T315I and V299L mutant form of BCR-ABL. Accordingly, the pivotal trial leading to the registration in the 3rd line setting excluded patients with a known history of the T315I or V299L mutation [Bosulif® USPI].

2 Rationale

2.1 Study rationale and purpose

ABL001 is an agent intended to be evaluated for the treatment of patients with CML. In the ongoing study [CABL001X2101] study, ABL001 was found to produce clinically meaningful and durable responses in patients who have had treatment failure after a minimum of 2 prior ATP-binding site TKIs, with an acceptable safety and tolerability profile.

The purpose of this pivotal study is to compare the efficacy of ABL001 with that of bosutinib in the treatment of patients with CML-CP having previously been treated with a minimum of two prior ATP-binding site TKIs with BCR-ABL ratios ≥ 1% IS at screening.

Imatinib, nilotinib and dasatinib are indicated for the treatment of patients with newly diagnosed CML. Multiple agents, including nilotinib, dasatinib, ponatinib, bosutinib, radotinib (Korea) and omacetaxine (USA, Canada) are approved for patients with CML-CP previously treated with prior therapy. Imatinib is a first generation TKI; nilotinib, dasatinib, bosutinib, ponatinib and radotinib are considered second generation TKIs and have activity in patients previously treated with imatinib. The activity of nilotinib or dasatinib in patients previously treated with a second generation TKI is not known. All the currently approved

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BCR-ABL TKIs are enzymatic site inhibitors, in distinction to ABL001 which is an allosteric TKI. Omacetaxine is a cytotoxic chemotherapeutic agent.

2.2 Rationale for the study design

ABL001 is an orally bioavailable specific BCR-ABL1 inhibitor with a novel mechanism of action. In contrast to other TKIs that bind within the ATP-binding site of the ABL kinase domain, ABL001 inhibits ABL tyrosine kinase activity by binding to a particular allosteric site on the kinase domain that is utilized by a myristate group to auto-regulate the native ABL1 kinase. With allosteric inhibition of BCR-ABL being a novel mechanism of action, ABL001 produces clinically meaningful and durable responses in patients who have had treatment failure after a minimum of 2 prior ATP-binding site TKIs, with an acceptable safety and tolerability profile as demonstrated in study [CABL001X2101].

The development of ABL001, presents an opportunity to evaluate the beneficial effects of inhibition of BCR-ABL in the treatment of patients with CML. The proposed study design is expected to adequately allow an assessment of the efficacy, safety and tolerability of ABL001 in a population of patients with continuing medical need i.e., patients who have been treated with at least two prior TKIs and are in the need for further therapeutic intervention.

Bosutinib is one of the TKIs with proven clinical benefit in CP-CML patients previously treated with one or more tyrosine kinase inhibitor(s) and is currently approved for this indication in many countries, including the European Union. The proposed study will evaluate ABL001 in comparison to bosutinib at the approved doses in the targeted population.

This study is not being conducted as a blinded study; the conditions for drug administration being distinct for the two treatments arms makes blinding complex and increases the likelihood of dosing errors. Bosutinib needs to be taken with food, whereas ABL001 needs to be taken fasted. The difference in administration of the two treatments, requiring double dummy treatments, makes blinding difficult to put in place in practice and carries inherent risks of dosing errors and reduces patient compliance. Additionally, the characteristic adverse event profile of bosutinib (frequent gastrointestinal AEs of diarrhea and vomiting in 78.5% and 37.1% patients, respectively) further preclude effective blinding. Randomization and use of objective efficacy endpoints mitigate the risks of an open label study design.

The study design incorporates a 2:1 randomization, allocating more patients to the ABL001 arm in order to learn more about the safety profile of the experimental therapy, whereas the safety of bosutinib therapy is well documented.

Treatment duration for each patient in the present study is for up to 96 weeks after the last patient received the first dose, which should be adequate to address both the primary objective of the study, i.e. determination of the MMR rate at 24 weeks, as well as secondary efficacy and safety objectives. Blood Samples will be taken in this study from all patients randomized to ABL001 in order to describe the pharmacokinetics and possibly identify the sources of variabilities. Exploratory analysis may be performed to establish the relationship between exposure and efficacy or safety.

2.2.1 Rationale for Biomarker Assessment

The primary goal of the biomarker assessments for this study is to evaluate potential mechanisms of resistance to ABL001.

Exploratory endpoints involving biomarker assessments for patients treated with ABL001, in comparison to those treated with bosutinib, will focus on 1) the PK/PD relationship; 2) BCR-ABL1 gene mutations that could influence the outcome of treatment regimens; and 3) the underlying biology of CML.

In order to evaluate tumor kinetics on a molecular level and to explore the role of mutations with respect to response to treatment, exploratory endpoints include assessment of mutations in the BCR-ABL1 gene at baseline, upon loss of response and/or at end of treatment. Mutational status will be characterized in peripheral blood.

[redacted]

2.3 Rationale for dose and regimen selection

The dose and regimen of ABL001 selected for this study is 40 mg BID. This dose is supported by pharmacokinetic, efficacy and safety data available from the ongoing [CABL001X2101] study.

During escalating doses of ABL001 10mg to 200mg on a continuous BID schedule in study [CABL001X2101], the 40mg BID dose was shown to be active and well tolerated in CML-CP patients.

With respect to efficacy, no clear evidence of dose-response relationship was observed across dose levels when considering CCyR or MMR. However, as described below, PK-PD population modeling using change from baseline of BCR-ABL mRNA levels as a PD endpoint suggest a higher probability of achieving ≥1 log reduction at 6 and 12 months with 40 mg BID versus 20 mg BID.

With respect to safety, although no MTD (maximum tolerated dose) has been formally characterized, there is an increased toxicity observed at doses ≥80 mg BID (pancreatitis occurred at the dose of 80mg in two patients who had an intra-patient escalation to 80mg from 40mg, and in one patient at the dose of 150mg BID). Generally there is a trend for higher rates of discontinuation due to AE, DLT (dose limiting toxicity) and grade 3/4 AE with increasing doses.

[redacted]

With respect to overall exposure, the dose of 40 mg BID is expected to result in concentrations consistently above IC90 in-vitro concentrations. The estimates from study [CABL001X2101] were found to be above the threshold trough concentration required for 90% inhibition of pSTAT5 derived from a preclinical PK-PD KCL-22 mouse xenograft model (free IC90: 30 to 121 ng/mL, after correction for protein binding) and in vitro gIC50 assessed in the KCL-22 cell line (1 ng/mL = 2.1 nM after correction for protein binding).

A preliminary population PK-PD model has been developed using data from the [CABL001X2101] study (cut-off 2 May 2016). The time course of molecular response (change in BCR-ABL ratio % IS levels from baseline) was described using a semi-physiological model accounting for cell maturation, disease progression and existing resistance. Simulations performed (with 100 patients) using ABL001 population PK-PD model revealed that at a dose of 40 mg BID, ~41% (CI95%: 31-51%) of chronic phase CML patients having failed ≥ 2 TKI or intolerant to TKIs are likely to exhibit a 1 log10 reduction of (%) BCR-ABL mRNA transcript levels from baseline at 6 months, and 53% (CI95%: 43-63%) at 12 months, and predicting higher probability of achieving BCR-ABL mRNA ≥1 log reduction at 6 and 12 months with 40 mg BID versus 20 mg BID.

Additional preliminary PK-efficacy and PK-safety analyses to assess the exposure-response relationship for ABL001 were conducted (Section 1.2.1.2). The efficacy measure used was Molecular Response (MR) which is defined as a decline in BCR-ABL transcript levels in clinical blood samples of patients with Chronic Myeloid Leukemia (CML). MR was evaluated as both a continuous variable (BCR-ABL transcript levels) and categorical variable (whether or not adequate decline in BCR-ABL was achieved). The safety measures used were occurrence of Common Toxicity Criteria (CTC) grade 2, 3 or 4 laboratory values for lipase and amylase.

Reviewing the totality of the efficacy, safety, and pharmacokinetic data derived from the [CABL001X2101] study, the recommended dose for ABL001 in this phase 3 study is 40 mg BID. Of note, the dose of ABL001 single agent BID is further being evaluated in patients with the T315I mutation. At present the recommended dose of 40 mg BID is for patients without the T315I mutation. For this reason, patients with the T315I mutation are excluded from this study.

2.4 Rationale for choice of combination drugs

Not Applicable.

2.5 Rationale for choice of comparators drug bosutinib

The guidance provided by the NCCN and the ELN (Bacarrani 2013), recommends bosutinib as a treatment in CML-CP patients who fail first-line or second-line treatment with imatinib or nilotinib or dasatinib. Consistent with these recommendations and clinical practice, bosutinib was selected to be an appropriate comparator in a study of 3rd line CML-CP patients after failure of at least 2 prior TKIs, and is the comparator that will be used in the present study.

It is to be noted that bosutinib has no activity against the T315I and V299L mutant form of BCR-ABL. Patients who have the T315I or V299L mutations documented in their medical record will already be excluded from this study. Bosutinib is known to be active against

[redacted]

E255K/V, F317L/V/I/C, F359V/C/I, T315A, and Y253H and therefore, these mutations are not considered in the exclusion criteria for the current study.

Ponatinib is not selected as the comparator in the present clinical trial, because the comparator in this study needs to be an approved agent administered at the approved dose. Currently, the ponatinib dose is being evaluated in a randomized trial as a post-approval commitment due to the occurrence of vascular risks at the current approved dose of ponatinib. The dose of ponatinib that will be approved and will be used in practice at the completion of the present study may not be the approved dose at the time of initiation of the present study.

2.6 Risks and benefits

Appropriate eligibility criteria, as well as specific dose modification and stopping rules in the event of expected toxicities, are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events are provided in Section 6.3. Patients who have failed 2 prior TKIs are at increased risk of progression to more advanced phases of CML such as CML-AP and CML-BC. Currently available therapeutic agents in this setting are non-curative and patients remain at risk of progressing after short duration of remissions (Khoury 2012).

An important potential risk for patients enrolling on the experimental arm of the study with ABL001 will be that this agent may be ineffective. However, the evidence to date at the doses to be administered in a similar population of patients in the study [CABL001X2101] suggests that ABL001 is an active agent. Further, the adverse event profile of ABL001 is similar qualitatively to that observed with other TKIs targeting BCR-ABL1 (Section 1.2.1.2). The risk of ABL001 not being effective has been mitigated in that patients will be observed closely for evidence of efficacy, based on assessment of hematologic, cytogenetic and molecular response data, which will permit rapid decision making as to discontinuation of therapy if necessary.

Other risks to subjects in this trial will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, and adherence to dose modification and interruption guidance provided in the protocol.

The currently available information suggests that there is equivalence between the two arms with respect to benefit / risk to enable inclusion of patients in this study.

There may be unforeseen risks with ABL001 which could be serious. Refer to the latest [ABL001 Investigator's Brochure] for additional details.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To compare the MMR rate at 24 weeks of ABL001 versus bosutinib	Major Molecular Response (MMR) rate at 24 weeks	Refer to Section 10.4
Key secondary		
To compare additional parameters of the efficacy of ABL001 versus bosutinib	MMR rate at 96 weeks	Refer to Section 10.5.1
Other secondary		
To compare additional parameters of the efficacy of ABL001 versus bosutinib	• cytogenetic response rate (Complete, Partial, Major, Minor, Minimal, no response) at and by all scheduled data collection time points including 24, 48 and 96 weeks • MMR rate at all scheduled data collection time points (except 24 and 96 weeks which are already covered by primary and key secondary endpoints) • MMR rate by all scheduled data collection time points including 24, 48 and 96 weeks • Time to MMR • Duration of MMR • Time to CCyR • Duration of CCyR • Time to treatment failure • Progression free survival • Overall survival	Refer to Section 10.5.2
To compare the safety and tolerability profile of ABL001 versus bosutinib	Type, frequency and severity of adverse events, Changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG and other safety data (vital signs, physical examination)	
To characterize the PK of ABL001 in the CML-CP population	Trough plasma concentrations, PK parameters in full PK group: Cmax, Tmax, AUC0-12h, CL/F	

[redacted]

Objective	Endpoint	Analysis
Exploratory		
To evaluate the influence of factors such as cytogenetic response at baseline, failure/intolerance to prior TKIs, line of therapy, gender, race and age on the effect of ABL001 with respect to the primary efficacy endpoint	Major Molecular Response (MMR) rate at 24 weeks	Refer to Section 10.6
To explore the exposure-response relationships of ABL001; evaluate the effect of population covariates	Exposure-safety and exposure-PD analyses	
To characterize mutations in the BCR-ABL1 gene at baseline, upon loss of molecular response and at end of treatment and examine their association with molecular and cytogenetic response for ABL001 vs bosutinib	BCR-ABL1gene mutations pre-dose and at end of treatment as determined by Sanger Sequencing	
[redacted]	[redacted]	
[redacted]	[redacted]	
To assess clonal evolution during treatment with ABL001 vs. bosutinib	Low level BCR-ABL1 mutation profiles assessed by mass spectrometry pre dose and at EOT. Clonal evolution of several genes implicated in CML assessed by Next Generation Sequencing (NGS) methods	
[redacted]	[redacted]	
To compare the impact of treatment on patient reported outcomes (PRO) including CML-specific symptoms, patient quality of life, and impact on work productivity and activity impairment from baseline and EOT between treatment arms in all patients	Change in symptom burden and interference from baseline over time according to the MDASI-CML PRO instrument Change in patient's impression of CML symptoms according to PGIC Change in health utility from baseline over time according to EQ-5D-5L	
To compare the impact of treatment on health care resource utilization between treatment arms in all patients	Health care resource burden over time	

[redacted]

4 Study design

4.1 Description of study design

The study is a phase 3, multi-center, open-label randomized study of oral ABL001 versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors.

The trial is designed to compare the efficacy and safety of ABL001 with that of bosutinib in the treatment of patients with CML-CP having previously been treated with a minimum of two prior ATP-binding site TKIs with a BCR-ABL ratio-IS $\geq$ 1% at screening.

The study will also investigate secondary endpoints for efficacy, safety and PK of single-agent ABL001 compared to bosutinib. Tolerability, PK, PRO and exploratory biomarker activities will also be assessed.

Patients meeting all of the inclusion and none of the exclusion criteria will be randomized into one of the 2 treatment arms, based on a 2:1 randomization between the ABL001 arm and the bosutinib arm.

The randomization will be stratified to ensure the study population is balanced between the arms with respect to cytogenetic response status (See Section 7.2.1.2) at screening as follows:

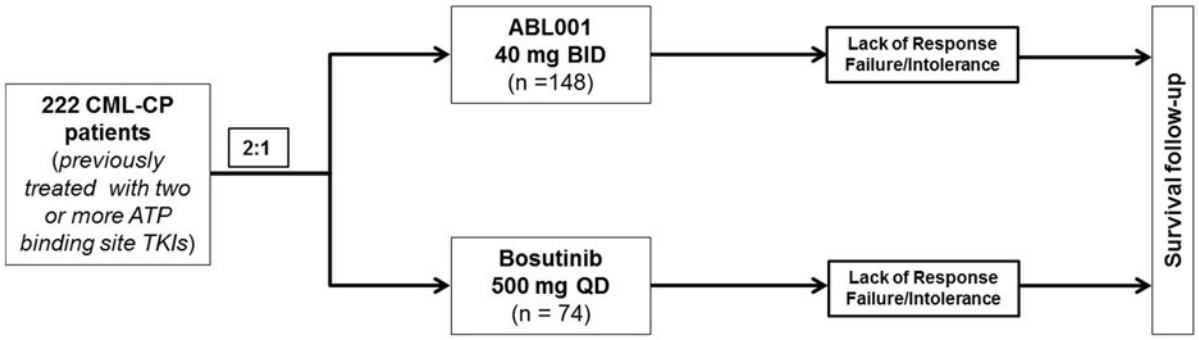
- Major Cytogenetic response (complete or partial)
- No major cytogenetic response (minor, minimal or none)

Patients will continue to receive the assigned study treatments (ABL001 or bosutinib) for up to 96 weeks after the last patient received the first study dose i.e., patients who are benefiting from their study treatment can continue to receive the treatment for up to a period of approximately 2 years following the completion of study enrollment. Patients who discontinue their study treatment at any time during the study will be followed up for survival and for progression to AP/BC for up to 5 years from the date the last patient received the first study dose.

Serial PK samples over 12 hours will be collected on Week 2 Day 1 from at least 20 CML-CP patients (full PK group) on the ABL001 arm, in addition to trough PK samples. These patients will be identified sequentially at selected sites that are capable of serial PK sampling over 12 hours. In the remaining patients in the ABL001 arm, sparse post-dose PK samples on Week 1 Day 1 and trough PK samples will be collected (sparse PK group).

[redacted]

Figure 4-1 Schematic of Study Design



4.2 Timing of interim analyses and design adaptations

Not applicable. There are no formal interim analyses or design adaptations planned for this study. See Section 8.6 for documentation of safety DMC.

4.3 Definition of end of study

The end of the study will occur 5 years from the date when the last patient enrolled into the study received the first dose of the randomized treatment.

The primary analysis (cut-off date) is defined as the date when all randomized patients have been on treatment for 24 weeks (Section 10.4) or discontinued early. Subsequent to this analysis, the primary clinical study report (CSR) will be developed. Following the cut-off date for the primary CSR, the study will remain open. Patients who are ongoing at the time of the primary analysis will continue to receive the assigned study treatments (ABL001 or bosutinib) for up to 96 weeks after the last patient received the first study dose i.e., patients who are benefiting from their study treatment can continue to receive the treatment for up to a period of approximately 2 years following the completion of study enrollment. The end of study treatment analysis will be conducted with a cut-off date 30 days after last patient receives the last study dose to ensure all available treatment data from all patients in the study is analyzed and summarized in a CSR.

After the end of the study treatment period the assigned study treatment will be made available to patients who in the opinion of the Investigator are still deriving clinical benefit. This may be outside of this study through alternative options including, but not limited to, an expanded access/compassionate use /managed access program or access to commercial supplies in applicable countries.

Patients will be followed up for survival and progression for up to 5 years from the date the last patient received the first study dose. Information on subsequent treatments will also be collected. An updated analysis of OS and PFS will be performed at the end of the follow-up period.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be contacted as soon as possible and instructed to stop taking study medication. The end of treatment visit should be scheduled and the same assessments should

[redacted]

be performed as described in Section 7 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

Two-hundred and twenty-two (222) patients with CML-CP who had prior treatment with two or more ATP binding site TKIs will be randomized in a 2:1 fashion to receive either ABL001 or bosutinib. No patients with a medical history of the T315I or V299L mutation at study entry will be included in the trial. Previous medical records should be used to confirm the patient's mutational status/history.

The definition of CML-CP will be according to the European Leukemia Network (ELN) criteria (Baccarani et al 2013), and is outlined below in the inclusion criteria.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Male or female patients with a diagnosis of CML-CP ≥ 18 years of age
2. Patients must meet all of the following laboratory values at the screening visit:
   - < 15% blasts in peripheral blood and bone marrow
   - < 30% blasts plus promyelocytes in peripheral blood and bone marrow
   - < 20% basophils in the peripheral blood
   - ≥ 50 x 10^9/L (≥ 50,000/mm3) platelets
   - Transient prior therapy related thrombocytopenia (< 50,000/mm3 for ≤ 30 days prior to screening) is acceptable
   - No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly
3. BCR-ABL ratio ≥ 1% IS according to central laboratory at the screening examination
4. Prior treatment with a minimum of 2 prior ATP-binding site TKIs (i.e. imatinib, nilotinib, dasatinib, radotinib or ponatinib)
5. Failure or intolerance to the last previous TKI therapy at the time of screening (adapted from the 2013 ELN Guidelines Bacarrani 2013)
   - Failure is defined for CML-CP patients (CP at the time of initiation of last therapy) as follows. Patients must meet at least 1 of the following criteria.
     - Three months after the initiation of therapy: No CHR or > 95% Ph+ metaphases
     - Six months after the initiation of therapy: BCR-ABL ratio > 10% IS and/or > 65% Ph+ metaphases

[redacted]

- Twelve months after initiation of therapy: BCR-ABL ratio > 10% IS and/or > 35% Ph+ metaphases
- At any time after the initiation of therapy, loss of CHR, CCyR or PCyR
- At any time after the initiation of therapy, the development of new BCR-ABL mutations
- At any time after the initiation of therapy, confirmed loss of MMR in 2 consecutive tests, of which one must have a BCR-ABL ratio ≥ 1% IS
- At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cells: CCA/Ph+

- Intolerance is defined as:
  - Non-hematologic intolerance: Patients with grade 3 or 4 toxicity while on therapy, or with persistent grade 2 toxicity, unresponsive to optimal management, including dose adjustments (unless dose reduction is not considered in the best interest of the patient if response is already suboptimal)
  - Hematologic intolerance: Patients with grade 3 or 4 toxicity (absolute neutrophil count [ANC] or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by manufacturer

6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2
7. Adequate end organ function as defined by (as per central laboratory tests):
   - Total bilirubin ≤ 1.5 x ULN except for patients with Gilbert's syndrome who may only be included if total bilirubin ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN
   - Aspartate transaminase (AST) ≤ 3.0 x ULN
   - Alanine transaminase (ALT) ≤ 3.0 x ULN
   - Serum amylase ≤ ULN
   - Serum lipase ≤ ULN
   - Alkaline phosphatase ≤ 2.5 x ULN
   - Creatinine clearance ≥ 50 mL/min as calculated using Cockcroft-Gault formula
8. Patients must avoid consumption of grapefruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.
9. Written informed consent obtained prior to any screening procedures.
10. Patients must have the following electrolyte values within normal limits (as per central laboratory tests) or corrected to be within normal limits with supplements prior to first dose of study medication:
    - Potassium
    - Magnesium
    - Total calcium (corrected for serum albumin)

[redacted]

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Known presence of the T315I or V299L mutation at any time prior to study entry
2. Known second chronic phase of CML after previous progression to AP/BC
3. Previous treatment with a hematopoietic stem-cell transplantation
4. Patient planning to undergo allogeneic hematopoietic stem cell transplantation
5. Cardiac or cardiac repolarization abnormality, including any of the following:
   - History within 6 months prior to starting study treatment of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG)
   - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)
   - QTcF at screening ≥450 ms (male patients), ≥460 ms (female patients)
   - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
     - Risk factors for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
     - Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointes that cannot be discontinued or replaced 7 days prior to starting study drug by safe alternative medication.
     - Inability to determine the QTcF interval
6. Severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol (e.g. uncontrolled diabetes, active or uncontrolled infection, pulmonary hypertension)
7. History of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis
8. History of elevation in amylase or lipase (> ULN) within 1 year other than that which may have occurred with gallstones, trauma, or medical procedures
9. History of acute or chronic liver disease
10. Known presence of significant congenital or acquired bleeding disorder unrelated to cancer
11. History of other active malignancy within 3 years prior to study entry with the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively
12. Known history of Human Immunodeficiency Virus (HIV), chronic Hepatitis B (HBV), or chronic Hepatitis C (HCV) infection. Testing for Hepatitis B surface antigen (HBs Ag) and Hepatitis B core antibody (HBcAb / anti HBc) will be performed at screening

13. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or gastric bypass surgery)
14. Treatment with medications that meet one of the following criteria and that cannot be discontinued at least one week prior to the start of treatment with study treatment
    - Moderate or strong inducers of CYP3A
    - Moderate or strong inhibitors of CYP3A and/or P-gp
    - Substrates of CYP3A4/5, CYP2C8, or CYP2C9 with narrow therapeutic index
15. Previous treatment with or known/ suspected hypersensitivity to ABL001 or any of its excipients.
16. Previous treatment with or known/ suspected hypersensitivity to bosutinib or any of its excipients.
17. Participation in a prior investigational study within 30 days prior to randomization or within 5 half-lives of the investigational product, whichever is longer
18. Pregnant or nursing (lactating) women
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 days after last dose of ABL001. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy) total hysterectomy or tubal ligation at least six weeks before taking study treatment). In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject.
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
    - In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
20. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

21. Sexually active males unless they use a condom during intercourse while taking the drug during treatment and for 3 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via semen.

6 Treatment

6.1 Study treatment

The investigational treatments for this study are ABL001 (40 mg BID) and bosutinib (500 mg QD). Novartis will supply ABL001 to the investigational site as 20 mg and 40 mg tablets. Bosutinib will be supplied to the investigational site as 100 mg and 500 mg tablets.

6.1.1 Dosing regimen

ABL001

ABL001 20 or 40 mg strength tablets will be administered orally twice-daily (BID), without food. ABL001 tablets should be ingested as follows:

- ABL001 should be administered in the fasted state at least 1 h before or 2 h after a meal. Water is permitted during this period.
- ABL001 should be taken with approximately 8 ounces (240 mL) of water.
- ABL001 should be swallowed whole and not chewed or crushed.
- If vomiting occurs within the first hour after taking the drug, re-dosing is allowed before the next scheduled dose
- If the patient does not take ABL001 within 6 hours after the approximate time of the usual dosing time, that dose should be skipped and treatment should continue with the next daily dose at the prescribed level

Bosutinib

Bosutinib 500 mg or 100 mg tablets will be administered orally once daily (QD) with food. If a dose is missed beyond 12 hours, the patient should skip the dose and take the usual dose on the following day.

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen	Fasting Condition
ABL001	Tablet for oral use	20 mg[a]	Twice-daily	Fasting
ABL001	Tablet for oral use	40 mg	Twice-daily	Fasting
Bosutinib	Tablet for oral use	100 mg[b]	Once-daily	Non-fasting
Bosutinib	Tablet for oral use	500 mg	Once-daily	Non-fasting

[a] 20 mg tablets will be dispensed to patients in the instance of dose reduction.
[b] 100 mg tablets will be dispensed to patients in the instance of dose modifications.

[redacted]

On days when serial blood samples are collected for ABL001 PK analysis, patients will be instructed to bring their drug supply to the site, and take the dose in the clinic, under supervision of the site personnel. The exact time for dose administration and meal intake must be recorded in the electronic Case Report Form (eCRF).

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.1.2 Ancillary treatments

Not applicable.

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

Not applicable. See Section 6.3.

6.1.5 Treatment duration

There is no fixed duration of treatment planned per patient. All patients will be given the opportunity to receive study treatment until the date that corresponds to 96 weeks after the last patient receives the first study dose. Patients may be discontinued from treatment with the study drug at any time due to unacceptable toxicity, disease progression and/or at the discretion of the investigator or the patient.

6.2 Dose escalation guidelines

Dose escalation beyond the standard doses of 40 mg BID for ABL001 is not permitted.

Dose escalation above 500 mg QD for bosutinib is permitted in this study. Bosutinib escalation guidelines are as follows:

Consider dose escalation to 600 mg once daily in patients who are currently taking 500 mg daily, did not have Grade 3 or higher adverse events and who:

- Did not reach complete hematological response (CHR) by week 8
- Did not reach complete cytogenetic response (CCyR) by week 12

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to allow the patient to continue the study treatment.

These dose modifications are summarized in Table 6-2. The dose reduction indicated as "recommendations" are provided to assist investigators in the event the patient experiences toxicity. However, deviations from "mandatory" dose interruptions and/or reductions are not

allowed and mandatory interruptions or reductions must be strictly followed. Re-escalation to ABL001 40mg BID is permitted if a change in the patient's individual benefit/risk assessment at the lower dose level is seen. Re-escalation will be allowed only once for any given patient on the ABL001 arm per protocol. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-2. Any dose changes must be recorded on the Dosage Administration Record eCRF.

A patient must discontinue treatment with either ABL001 or bosutinib if, after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity (See Table 6-2). If a patient requires a dose interruption of > 28 days, then the patient must be discontinued from the study treatment. Patients who discontinue the study treatment for an adverse event suspected to be related to study drug or an abnormal laboratory value suspected to be related to study drug must be followed as described in Section 8.

[redacted]

Table 6-2 Criteria for dose reduction/interruption and re-initiation of ABL001 and bosutinib treatment for adverse drug reactions

Dose modifications for both ABL001 and bosutinib		
Worst toxicity CTCAE Grade 4.03	**ABL001**	**bosutinib**
Investigations (Hematologic)		
Neutropenia (ANC)		
Grade 1 (ANC < LLN – 1.5 x 10^9/L)	**Recommendation**: Maintain dose level	**Recommendation**: Maintain dose level
Grade 2 (ANC < 1.5 – 1.0 x 10^9/L)	**Recommendation**: Maintain dose level	**Recommendation**: Maintain dose level
Grade 3 (ANC < 1.0 – 0.5 x 10^9/L)	**Mandatory**: Hold dose until resolved to ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, then reduce dose ↓ 1 dose level	**Mandatory**: Hold dose until resolved to ≤ Grade 2 and platelets ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, reduce dose ↓ 1 dose level
Grade 4 (ANC < 0.5 x 10^9/L)	**Mandatory**: Hold dose until resolved to ≤ Grade 2, (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved to ≤ Grade 2 and platelets ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level
Febrile neutropenia (ANC < 1.0 x 109/L, fever ≥ 38.5°C)	**Mandatory:** Hold dose until resolved, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved, then reduce dose ↓ 1 dose level
Thrombocytopenia		
Grade 1 (PLT < LLN – 75 X 10^9/L)	**Recommendation**: Maintain dose level	**Recommendation:** Maintain dose level
Grade 2 (PLT < 75 - 50 x 10^9/L)	**Recommendation**: Maintain dose level	**Recommendation:** Maintain dose level

[redacted]

Dose modifications for both ABL001 and bosutinib		
Worst toxicity CTCAE Grade 4.03	**ABL001**	**bosutinib**
Grade 3 (PLT < 50 - 25 x 10^9/L)	**Mandatory:** Hold dose until resolved to ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved to ≤ Grade 2 and neutrophils ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	**Mandatory:** Hold dose until resolved to ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved to ≤ Grade 2 and neutrophils ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level
Recurrence of all cytopenias	**Recommendation:** Hold dose until resolved to ≤ Grade 2, then maintain current dose level	**Recommendation:** Hold dose until resolved to ≤ Grade 2, then reduce dose ↓ 1 additional level
Non-hematologic adverse reactions except where further specified in individual sections		
Grade 1	**Recommendation**: Maintain dose level	**Recommendation:** Maintain dose level
Grade 2	**Recommendation:** Hold dose until resolved to ≤ Grade 1, then maintain dose level	**Recommendation:** Maintain dose level
Grade 3	**Mandatory:** Hold dose until resolved to ≤ Grade 1, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved to ≤ Grade 2, then reduce dose ↓ 1 dose level, If clinically appropriate, re-escalation of the dose back to baseline dose level (500 mg) should be considered
Grade 4	**Mandatory**: Permanently discontinue patient from study drug treatment.	**Mandatory:** Hold dose until resolved to ≤ Grade 2, then reduce dose ↓ 1 dose level; If clinically appropriate, re-escalation of the dose back to baseline dose level (500 mg) should be considered
Investigations (Renal)		
Serum creatinine		
Grade 1 (> ULN - 1.5 x ULN)	**Recommendation:** Maintain dose level	**Recommendation:** Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN)	**Recommendation:** Hold dose until resolved to ≤ Grade 1 or baseline, then maintain dose level	**Recommendation:** Hold dose until resolved to ≤ Grade 1 or baseline, then maintain dose level
Grade 3 (> 3.0 - 6.0 x ULN)	**Mandatory:** Permanently discontinue patient from study drug treatment.	**Mandatory:** Permanently discontinue patient from study drug treatment.
Grade 4 (> 6.0 x ULN)	**Mandatory:** Permanently discontinue patient from study drug treatment.	**Mandatory:** Permanently discontinue patient from study drug treatment.

[redacted]

Dose modifications for both ABL001 and bosutinib		
Worst toxicity CTCAE Grade 4.03	**ABL001**	**bosutinib**
Investigations (Hepatic)		
Isolated total Bilirubin elevation		
> ULN – 1.5 x ULN	**Recommendation:** Maintain dose level	**Recommendation:** Maintain dose level
> 1.5 - 3.0 x ULN	**Recommendation:** Hold dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level	**Recommendation:** Hold dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level
> 3.0 - 10.0 x ULN*	**Mandatory:** Hold dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: if resolved in ≤ 14 days, then reduce dose ↓ 1 dose level if resolved in > 14 days, then discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.	**Mandatory:** Hold dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: if resolved in ≤ 14 days, then reduce dose ↓ 1 dose level if resolved in > 14 days, then discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
> 10.0 x ULN*	**Mandatory:** Permanently discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.	**Mandatory:** Permanently discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
Isolated AST or ALT elevation		
> ULN - 3.0 x ULN	**Recommendation:** Maintain dose level	**Recommendation:** Maintain dose level
> 3.0 - 5.0 x ULN	**Recommendation:** Maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN	**Recommendation:** Maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN

[redacted]

Dose modifications for both ABL001 and bosutinib		
Worst toxicity CTCAE Grade 4.03	**ABL001**	**bosutinib**
> 5.0 - 10.0 x ULN	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN: Then If resolved in ≤ 14 days, maintain dose level If resolved in > 14 days, reduce dose ↓ 1 dose level	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 2.5 x ULN: Then **Recommendation:** If resolved in ≤ 28 days, reduce dose ↓ 1 dose level **Recommendation**: If resolved in > 28 days, Discontinue patient from study drug treatment
> 10.0 - 20.0 x ULN	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ baseline. Then reduce dose ↓ 1 dose level.	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 2.5 x ULN. Then **Recommendation:** If resolved in ≤ 28 days, reduce dose ↓ 1 dose level maintain dose level **Recommendation:** If resolved in > 28 days, Discontinue patient from study drug treatment.
> 20.0 x ULN	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3 x ULN (or ≤ 5 x ULN for patients with baseline value > 3.0 -5.0 x ULN), then resume treatment at reduce dose ↓ 1 dose level. Only 1 dose reduction is allowed; if reoccurs at > 5 x ULN, discontinue patient from study drug treatment.	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 2.5 x ULN (then **Recommendation:** If resolved in ≤ 28 days, reduce dose ↓ 1 dose level maintain dose level **Recommendation:** If resolved in > 28 days, Discontinue patient from study drug treatment

[redacted]

Dose modifications for both ABL001 and bosutinib		
Worst toxicity CTCAE Grade 4.03	**ABL001**	**bosutinib**
Combined [c] elevations of AST or ALT and total bilirubin		
For patients with normal baseline ALT and AST and total bilirubin value: AST or ALT >3.0 x ULN combined with total bilirubin >2.0 x ULN without evidence of cholestasis[d]	**Mandatory:** Permanently discontinue patient from study drug treatment.	**Mandatory:** Permanently discontinue patient from study drug treatment.
For patients with elevated baseline AST or ALT or total bilirubin value [AST or ALT>2 x baseline AND > 3.0 x ULN]	**Mandatory:** Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b]), or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Refer to Section 6.3.3.1 for additional follow-up evaluations as applicable.	**Mandatory:** Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTsb), or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Refer to Section 6.3.3.1 for additional follow-up evaluations as applicable.
Investigation (metabolic)		
Asymptomatic amylase and/or lipase elevation		
Grade 1 (> ULN - 1.5 x ULN)	**Recommendation:** Maintain dose level, measure 2x week	**Recommendation:** Maintain dose level, measure 2x week
Grade 2 (> 1.5 - 2.0 x ULN)	**Recommendation:** Maintain dose level, measure 2x week	**Recommendation:** Maintain dose level, measure 2x week
Grade 3 (> 2.0 - 5.0 x ULN)	**Mandatory:** Hold dose until resolved to Grade ≤ 1 or baseline, then: If resolved in ≤ 7 days, then reduce dose ↓ 1 dose level If resolved in > 7 days, then discontinue treatment and obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).	**Mandatory:** Hold dose until resolved to Grade ≤ 1 or baseline, then: If resolved in ≤ 7 days, then reduce dose ↓ 1 dose level If resolved in > 7 days, then discontinue treatment and obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).
Grade 4 (> 5.0 x ULN)	**Mandatory:** Permanently discontinue patient from study drug treatment. Obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).	**Mandatory:** Permanently discontinue patient from study drug treatment. Obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).

[redacted]

Dose modifications for both ABL001 and bosutinib		
Worst toxicity CTCAE Grade 4.03	**ABL001**	**bosutinib**
Vascular disorders		
Hypertension		
CTCAE Grade 3	**Mandatory:** Hold dose until resolved ≤ Grade 1, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved ≤ Grade 1, then reduce dose ↓ 1 dose level
CTCAE Grade 4	**Mandatory:** Permanently discontinue patient from study drug treatment.	**Mandatory:** Permanently discontinue patient from study drug treatment.
Gastro intestinal		
Pancreatitis		
Grade 2	**Mandatory:** If asymptomatic radiologic pancreatitis (Grade 2 pancreatitis), hold treatment until resolved to ≤ Grade 1 or baseline. If treatment delay is ≤ 7 days, then reduce dose ↓ 1 dose level. If treatment delay >7 days, discontinue treatment and obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).	**Mandatory**: If asymptomatic radiologic pancreatitis (Grade 2 pancreatitis), hold treatment until resolved to ≤ Grade 1 or baseline. If treatment delay is ≤ 7 days, then reduce dose ↓ 1 dose level. If treatment delay >7 days, discontinue treatment and obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).
Grade ≥ 3	**Mandatory:** Permanently discontinue patient from study drug treatment. Obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).	**Mandatory:** Permanently discontinue patient from study drug treatment. Obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).
Diarrhea***		
Grade 1	**Recommendation:** Maintain dose level but, initiate anti-diarrhea treatment	**Recommendation:** Maintain dose level but, initiate anti-diarrhea treatment
Grade 2	**Recommendation:** Hold dose until resolved to ≤ grade 1, then maintain dose level. If diarrhea returns as ≥ grade 2, then hold dose until resolved to ≤ grade 1, then reduce dose ↓ 1 dose level	**Recommendation:** Hold dose until resolved to ≤ grade 1, then maintain dose level. If diarrhea returns as ≥ grade 2, then hold dose until resolved to ≤ grade 1, then reduce dose ↓ 1 dose level
Grade 3	**Recommendation:** Hold dose and discontinue patient from study drug treatment	**Mandatory:** Hold dose until recovery to ≤ grade 1. **Recommendation:** Bosutinib may then be resumed at ↓ 1 dose level
Grade 4	**Mandatory:** Permanently discontinue patient from study drug treatment	**Mandatory**: Hold dose until recovery to ≤ grade 1. **Recommendation:** Bosutinib may then be resumed at ↓ 1 dose level

[redacted]

Dose modifications for both ABL001 and bosutinib		
Worst toxicity CTCAE Grade 4.03	**ABL001**	**bosutinib**
Skin and subcutaneous tissue disorders		
Rash/photosensitivity		
Grade 1	**Recommendation:** Maintain dose level. Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)	**Recommendation:** Maintain dose level. Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
Grade 2	**Recommendation**: Maintain dose level, but initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)	**Recommendation:** Maintain dose level, but initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
Grade 3, despite skin toxicity therapy	**Recommendation:** Hold dose until resolved to Grade ≤ 1, then: If resolved in ≤ 7 days, then reduce dose ↓ 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then discontinue patient from study drug treatment	**Recommendation:** Hold dose until resolved to Grade ≤ 1, then: If resolved in ≤ 7 days, then reduce dose ↓ 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then discontinue patient from study drug treatment
Grade 4, despite skin toxicity therapy	**Mandatory:** Permanently discontinue patient from study drug treatment.	**Mandatory:** Permanently discontinue patient from study drug treatment.
General disorders and administration site conditions		
Fatigue/ Asthenia		
Grade 1 or 2	**Recommendation:** Maintain dose level	**Recommendation:** Maintain dose level
Grade 3	**Recommendation:** Hold dose until resolved to ≤ grade 1, then : If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then reduce dose ↓ 1 dose level	**Recommendation:** Hold dose until resolved to ≤ grade 1, then : If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then reduce dose ↓ 1 dose level
Other adverse events		
Grade 1 or 2	**Recommendation**: Maintain dose level	**Recommendation:** Maintain dose level
Grade 3	**Mandatory:** Hold dose until resolved within 28 days to ≤ grade 1 then resume at ↓ 1 dose level	**Mandatory:** Hold dose until resolved 1 within 28 days to ≤ grade, then resume at ↓ 1 dose level
Grade 4	**Mandatory:** Hold dose and then discontinue from study drug treatment	**Mandatory:** Hold dose and then discontinue from study drug treatment

[redacted]

Dose modifications for both ABL001 and bosutinib		
Worst toxicity **CTCAE Grade 4.03**	**ABL001**	**bosutinib**
All dose modifications should be based on the worst preceding toxicity. [a] Common Toxicity Criteria for Adverse Events (CTCAE Version 4.03) [b] Core LFTs consist of ALT, AST, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.) [c] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when hold dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction [d] "Cholestasis" defined as ALP elevation (>2.0 x ULN and R value <2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury * Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator. ** Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study treatment. *** Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea		

[redacted]

Table 6-3 Dose reduction steps for ABL001 and bosutinib

Dose reduction*			
	Starting dose level – 0	Dose level - 1	
ABL001 BID	40 mg tablet BID (total daily dose 80 mg)	20 mg tablet BID (total daily dose 40 mg)	
*Dose reduction should be based on the worst toxicity demonstrated at the last dose.			
ABL001 dose reduction below total daily 40 mg is not allowed. 20 mg tablets will be dispensed to patients in the instance of dose reduction.			
Dose reduction*			
	Starting dose level – 0	Dose level - 1	Dose level – 2
Bosutinib QD	500 mg (1-500 mg tablet QD)	400 mg (4-100 mg tablets QD)	300 mg (3-100 mg tablets QD)
* Dose reduction should be based on the worst toxicity demonstrated at the last dose.			
Bosutinib dose reduction below total daily 300 mg is not allowed. 100 mg tablets will be dispensed to patients in the instance of dose reduction.			

6.3.2 Dose adjustments for QTcF prolongation

If QTcF >500 msec or QTcF prolongation >60 msec from baseline is observed at any point during study treatment, and confirmed, the below guidance must be followed:

1. Assess the quality of the ECG recording and the QT value and repeat if needed
2. Interrupt study treatment until confirmed resolution of QTcF and as per dose reduction guidelines for non-hematological AEs.
3. Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment.
4. Review concomitant medication use for other causes for QT prolongation (refer to qtdrugs.org for known QT prolonging drugs), and for drugs with the potential to increase the risk of drug exposure related QT prolongation (e.g., concomitant use of CYP3A4 inhibitors, if the study drug is a CYP3A4 substrate)
5. Check study drug dosing schedule and treatment compliance
6. Increased ECG safety monitoring is recommended during or in-between subsequent visits.

6.3.3 Follow-up for toxicities

Patients whose treatment is permanently discontinued due to a study drug related adverse event or clinically significant laboratory value, must be followed up at least once a week for 4 weeks, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary. All patients must be followed up for adverse events and serious adverse events for 30 days following the last dose of study treatment.

[redacted]

6.3.3.1 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatinine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

[redacted]

6.3.4 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e., hyperglycemia, skin toxicity and diarrhea are provided in Table 6-2. Refer to preclinical toxicity and or clinical data found in the [Investigator's Brochure].

6.4 Concomitant medications for patients on ABL001

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug and including over-the-counter treatment and nutritional or vitamin supplements) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the "Concomitant Medications/Significant non-drug therapies" section of the eCRF.

Chronic medication should be maintained at the same dose and schedule throughout the study period, as medically feasible.

All prior antineoplastic surgery, chemotherapy, biologic, immunologic and radiation therapy must be recorded in the "Prior antineoplastic therapy" section of the eCRF.

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records and on the appropriate case report form, including the medication's duration (start and end dates or if continuing at final exam). These include blood and platelet transfusions for patients with anemia and with thrombocytopenia.

6.4.1 Permitted concomitant therapy

Drugs that affect gastric pH

ABL001 does not have a pH-dependent solubility. Drugs that elevate gastric pH will not affect ABL001 absorption. All acid reducing agents are allowed.

6.4.2 Permitted concomitant therapy requiring caution and/or action

There is a potential for DDIs with co-medications metabolized by CYP3A4/5, CYP2C8 and CYP2C9 at the anticipated human efficacious dose. Therefore, substrates of CYP3A4/5, CYP2C8 and CYP2C9 should be used with caution (Section 14-Appendix).

Additionally, transporter phenotyping studies have identified ABL001 to be a substrate of Breast Cancer Resistant Protein (BCRP). While the effect on ABL001 exposure via BCRP interaction is not likely, BCRP inhibitors should be administered with caution.

6.4.3 Prohibited concomitant therapy

Strong CYP3A4/5 and P-gp inhibitors

Every effort should be made NOT to concomitantly administer strong CYP3A4/5 and P-gp inhibitors (e.g., erythromycin, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir, mibefradil). P-gp and CYP3A4/5 inhibitors may increase absorption or decrease the metabolism of ABL001 and resulting in increased serum concentrations and increased exposure. If administration of a strong CYP3A4/5 and P-gp inhibitor cannot be avoided during the study and cannot be switched to an alternative therapy that does not strongly inhibit CYP3A4/5 or P-gp, ABL001 must be stopped.

A list of cytochrome P450 isoenzymes and CYP3A4/5 and P-gp inhibitors may be found at http://medicine.iupui.edu/CLINPHARM/ddis/clinical-table.

A classification of CYP3A4/5 and P-gp inhibitors can be found in Section 14-Appendix.

Further information can also be found in the following reference (Venkatakrishnan et al 2001).

Strong CYP3A4/5, and UGT1A/2B inducers

Every effort should be made NOT to concomitantly administer strong CYP3A4 inducers during the study.

Additionally, the use of strong inducers of UGT1A/2B is prohibited during the study.

NTI substrates of CYP3A4/5, CYP2C8 and CYP2C9

Based on the in vitro results, there is a potential for DDIs with co-medications metabolized by CYP3A4/5, CYP2C8 and CYP2C9 at the anticipated human efficacious dose. Therefore, narrow therapeutic index substrates of CYP3A4/5, CYP2C8 and CYP2C9 are prohibited

QT prolonging agents

Every effort should be made NOT to administer a QT prolonging agent. If during the course of the study, concomitant administration of an agent known to prolong the QT interval is required and cannot be switched to an alternative therapy, ABL001 must be permanently discontinued.

Please see: http://www.torsades.org/medical-pros/drug-lists/printable-drug-list.cfmcrediblemeds.org/everyone/composite-list-all-qtdrugs/ for a list of agents that prolong the QT.

Herbal medications

Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

[redacted]

6.4.4 Other concomitant medications

Anti-emetics

Use of anti-emetics is allowed. Prophylactic anti-emetics should be started only once the patient experiences nausea or vomiting, at the discretion of the investigator. It is recommended that patients use drugs that do not cause QT prolongation. Please note that some anti-emetics have a known risk for Torsade de Pointes and are prohibited (refer to Section 6.4.2 and Section 14.1/Appendix 1).

Bisphosphonates

The use of bisphosphonates regardless of indication is allowed.

Contraceptives

Hormonal contraceptives are allowed as contraception methods. Highly effective contraception should be maintained throughout the study and for 3 days after study treatment discontinuation.

Anticoagulation agents

All anticoagulants or anti-aggregation agents may be administered under the discretion of the investigator.

Therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants should be used with caution and fully avoided whenever possible because of its known interaction with many commonly used medications and certain foods. As warfarin has a narrow therapeutic range, and ABL001 is possibly an inhibitor of CYP2C9, the major metabolizing enzyme of S-warfarin (R-warfarin is metabolized by multiple CYP enzymes), warfarin should be carefully monitored whenever used.

Caution is also advised when ABL001 is co-administered with anti-platelet pro-drugs such as clopidogrel, ticlopidine and prasugrel, which require metabolic activation by CYP3A4 and CYP2C9. While the weak reversible *in vitro* inhibition potential of ABL001 is unlikely to translate into clinical significance as the steady-state plasma concentrations at the maximum therapeutic doses are significantly lower than the experimentally determined inhibition constants, patients using anti-platelet pro-drugs should still be carefully monitored.

Direct Thrombin inhibitors (DTIs) and Factor Xa inhibitors are allowed as anticoagulants. Individual medications from each of the classes should be checked if they are not prohibited due to other drug-drug-interactions with ABL001. Alternatively, therapeutic anticoagulation may be accomplished using low-molecular weight heparin.

6.5 Concomitant medications for patients on Bosutinib

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug and including over-the-counter treatment and nutritional or vitamin supplements) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions)

[redacted]

administered during the study must be listed on the "Concomitant Medications/Significant non-drug therapies" section of the eCRF.

Chronic medication should be maintained at the same dose and schedule throughout the study period, as medically feasible.

All prior antineoplastic surgery, chemotherapy, biologic, immunologic and radiation therapy must be recorded in the "Prior antineoplastic therapy" section of the eCRF.

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records and on the appropriate case report form, including the medication's duration (start and end dates or if continuing at final exam). These include blood and platelet transfusions for patients with anemia and with thrombocytopenia

6.5.1 Prohibited concomitant medications

Concomitant use with CYP3A inhibitors

Avoid the concomitant use of strong or moderate CYP3A inhibitors as an increase in bosutinib plasma concentration is expected. Strong CYP3A inhibitors include boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole.

Moderate CYP3A inhibitors include amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit products, imatinib and verapamil) [Bosulif® USPI]. If administration of a strong or moderate CYP3A4/5 inhibitor cannot be avoided during the study and cannot be switched to an alternative therapy, bosutinib must be stopped.

Concomitant use with CYP3A inducers

Avoid the concomitant use of strong or moderate CYP3A inducers as a large reduction in exposure is expected (strong CYP3A inducers include carbamazepine, phenytoin, rifampin and St. John's Wort. Moderate CYP3A inducers include bosentan, efavirenz, etravirine, modafinil and nafcillin) [Bosulif® USPI]. If administration of a strong or moderate CYP3A4/5 inducer cannot be avoided during the study and cannot be switched to an alternative therapy, bosutinib must be stopped.

P-gp Inhibitors

Avoid the concomitant use of P-gp inhibitors with BOSULIF as an increase in bosutinib plasma concentration is expected [Bosulif® USPI].

pH Altering Medications

Bosutinib displays pH-dependent aqueous solubility, in vitro. In a cross-over trial in 23 healthy volunteers, a single oral dose of 400 mg of bosutinib was either administered alone or in combination with multiple-oral doses of 60 mg of lansoprazole (PPI) under fasting conditions. Lansoprazole decreased bosutinib Cmax and AUC by 46% and 26%, respectively.

[redacted]

Concomitant administration with PPIs is not allowed.

Consider using short-acting antacids or H2 blockers instead of PPIs to avoid a reduction in bosutinib exposure. Separate antacid or H2 blocker dosing by more than 2 hours [Bosulif® USPI].

6.6 Patient numbering, treatment assignment or randomization

6.6.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Screening Disposition page. IRT must be notified within 2 days that the patient was not randomized.

6.6.2 Treatment assignment or randomization

Patients will be assigned to one of the 2 treatment arms (Section 4.1 and Section 6.1) in a ratio of 2:1. Randomization will be stratified by cytogenetic response status at screening.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

[redacted]

6.6.3 Treatment blinding

Not applicable.

6.7 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.7.1 Study treatment packaging and labeling

Study treatment, ABL001 and bosutinib tablets, will be provided as global clinical open-label supply and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

Study treatment labels will comply with the legal requirements of each country and will include storage conditions, a unique medication number (corresponding to study treatment and strength). Responsible site personnel will identify the study treatment package(s) to dispense by the medication number(s) assigned by IRT to the patient. Site personnel will add the patient number on the label. If the label has 2-parts (base plus tear-off label), immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document.

Table 6-4 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
ABL001 (20 mg and 40 mg)	Tablets in bottle	Labeled as 'ABL001 20 mg/ABL001 40 mg'(BID)
bosutinib (100 mg or 500 mg)	Tablets in bottle or tablets in blister	Labeled as 'bosutinib 100 mg or bosutinib 500 mg'(QD)

6.7.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the ABL001 and bosutinib should be stored according to the instructions specified on the drug labels.

6.7.3 Study drug compliance and accountability

6.7.3.1 Study drug compliance

Total daily dose of study treatment administered with start and end date will be collected on the Dose Administration Record eCRF page. Name, start and end dates of any Concomitant Medications and Surgical and Medical procedures will be collected on the Prior and Concomitant medications and Surgical and Medical procedures eCRFs respectively.

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug

[redacted]

Accountability Form. This information must be captured in the source document at each patient visit.

6.7.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.3.3 Handling of other study treatment

Not applicable.

6.7.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, or at the site only if permitted by local regulations and authorized by Novartis in a prior agreement.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. Patients can be consented for study participation prior to study day -21.

No eCRF will be used as a source document.

(S) is defined as "Source"

(D) is defined as "Data Based"

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section 7	Screening Phase	Treatment Phase																	
Visit name			Screening/ Baseline (Day -21 to -1)	Week 1 D1	Week 2 D1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Obtain Informed Consent	D		X (Screening window -42 days)																		
IRT																					
Eligibility checklist/registration	D		X																		
Randomization	D			X																	
Demography	D	7.1.2.3	X																		
Inclusion/exclusion criteria	D		X																		
Medical History	D	7.1.2.3	X																		
Disease History	D	7.1.2.3	X																		
Mutation status	D	7.1.2.3	X																		
Prior antineoplastic therapy	D	7.1.2.3	X																		
Prior TKI therapy	D	7.1.2.3	X																		
Prior/concomitant medications	D	7.1.2.3	X	continuous																	
Physical examination	S	7.2.2.1	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Extramedullary Involvement	D	7.2.2.1	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

	Category	Protocol Section 7	Screening Phase	Treatment Phase																
Visit name			Screening/ Baseline (Day -21 to -1)	Week 1 D1	Week 2 D1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
ECOG Performance status	D	7.2.2.4	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	D	7.2.2.3	X																		
Weight	D	7.2.2.3	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	D	7.2.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments		7.2.2.5																			
Hematology	D	7.2.2.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	D	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry-Hemoglobin A1c	D	7.2.2.5.2	X	Week 12 and as clinically indicated																	
Coagulation	D	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy test (if applicable)	D	7.2.2.5.3	X			X		X		X		X	X	X	X	X	X	X	X	X	X
Hepatitis markers	D	7.2.2.5.2	X																		
Liver assessments	D			as clinically indicated																	
Efficacy assessments		7.2.1																			
Blood collection for BCR-ABL quantification by RQ-PCR	D	7.2.1.1	X			X		X		X		X		X			X			X	
Blood collection for exploratory BCR-ABL mutation analysis by Sanger Sequencing	D	7.2.1.1		X																	

[redacted]

	Category	Protocol Section 7	Screening Phase	Treatment Phase																	
Visit name			Screening/ Baseline (Day -21 to -1)	Week 1 D1	Week 2 D1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Blood collection for exploratory BCR-ABL mutation analysis (Sanger Sequencing) for patients with mutations at Baseline	D	7.2.1.1								X				X			X			X	
Bone Marrow Aspirate/Cytogenetics -scheduled	D	7.2.1.2	X (Screening window -42 days)											X						X	
Cardiac Assessments		7.2.2.6																			
ECG	D	7.2.2.6.1	X	X	X	X				X				X							
Cardiovascular risk factor assessments (including Family History)	D	7.2.2.6.2	X																		
Echocardiogram	D	7.2.2.6.3	X										X								
Pulmonary Function Test	D	7.2.2.6.4	X										X								
Adverse events / SAE	D		X	Continuous																	

[redacted]

	Category	Protocol Section 7	Screening Phase	Treatment Phase																	
Visit name			Screening/ Baseline (Day -21 to -1)	Week 1 D1	Week 2 D1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Biomarker Assessments		7.2.4																			
[redacted]	D	7.2.4.1	X (Screening window -42 days)											X							
[redacted]	D	7.2.4.1	X (Screening window -42 days)																		
[redacted]	D	7.2.4.2		X																	
Blood collection for Low level mutation analysis	D	7.2.4.2		X																	
[redacted]	D	7.2.4.2		X		X		X		X				X			X			X	
[redacted]	D	7.2.4.2		X																X	
[redacted]	D	7.2.4.2		X																	

[redacted]

	Category	Protocol Section 7	Screening Phase	Treatment Phase																	
Visit name			Screening/ Baseline (Day -21 to -1)	Week 1 D1	Week 2 D1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Patient reported Outcomes		7.2.6																			
MDASI-CML	D	7.2.6	X			X		X		X		X		X			X			X	
EQ 5D 5L	D	7.2.6	X			X		X		X		X		X			X			X	
PGIC	D	7.2.6	X			X		X		X		X		X			X			X	
WPAI	D	7.2.6	X			X				X				X						X	
Resource Utilization Assessments	D	7.2.5	X	Continuous																	
ABL001 Drug administration	D			Continuous																	
Bosutinib Drug administration	D			Continuous																	
PK sampling (ABL001 arm only)		7.2.3																			
Sparse PK blood collection	D	7.2.3		X	X	X				X				X							
Full PK blood collection (at least 20 patients)	D	7.2.3		X	X	X				X				X							
Meal record	D			X	X	X				X				X							

[redacted]

	Category	Protocol Section 7	Treatment Phase											EOT/Early Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	**Week 76**	**Week 80**	**Week 84**	**Week 88**	**Week 92**	**Week 96**	**W108, W120, W132, W144, W156, W168**			
Prior/concomitant medications	D		Continuous													
Physical examination	S	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X		
Extramedullary Involvement	D	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance status	D	7.2.2.4	X	X	X	X	X	X	X	X	X	X	X	X	X		
Weight	D	7.2.2.3	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs	D	7.2.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory assessments		7.2.2.5															
Hematology	D	7.2.2.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry	D	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry-Hemoglobin A1c	D	7.2.2.5.2	as clinically indicated														
Coagulation	D	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum Pregnancy test (if applicable)	D	7.2.2.5.3	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urine Pregnancy test (if applicable	D	7.2.2.5.3											Monthly between visits				
Liver assessments	D		as clinically indicated														

[redacted]

	Category	Protocol Section 7	Treatment Phase												EOT/Early Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	**Week 76**	**Week 80**	**Week 84**	**Week 88**	**Week 92**	**Week 96**	**W108, W120, W132, W144, W156, W168**			
Efficacy assessments		7.2.1															
Blood collection for BCR-ABL quantification by RQ-PCR	D	7.2.1.1		X			X			X			X	X	X		
Blood collection for BCR-ABL Mutation analysis by Sanger sequencing	D	7.2.1.1													X		
Blood collection for BCR-ABL Mutation analysis for patients with mutations at Baseline	D	7.2.1.1		X			X			X			X	X			
Bone Marrow Aspirate/Cytogenetics - scheduled	D	7.2.1.2					X						X		X		
Cardiac Assessments		7.2.2.6															
ECG	D	7.2.2.6.1											X				
Cardiovascular risk factor assessments (including Family History)	D	7.2.2.6.2													X		
Echocardiogram	D	7.2.2.6.3													X		
Pulmonary Function Test	D	7.2.2.6.4													X		

[redacted]

	Category	Protocol Section 7	Treatment Phase											EOT/Early Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	**Week 76**	**Week 80**	**Week 84**	**Week 88**	**Week 92**	**Week 96**	**W108, W120, W132, W144, W156, W168**			
Adverse events / SAE	D		Continuous													
Biomarker Assessments		7.2.4														
[redacted]	D	7.2.4.2												X		
[redacted]	D	7.2.4.2												X		
[redacted]	D	7.2.4.2		X			X			X			X	X		
[redacted]	D	7.2.4.2												X		
[redacted]	D	7.2.4.1												X		
[redacted]	D	7.2.4.1												X		
Patient reported Outcomes		7.2.6														
MDASI-CML	D	7.2.6											X			
EQ 5D 5L	D	7.2.6											X			

[redacted]

	Category	Protocol Section 7	Treatment Phase											EOT/Early Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	**Week 76**	**Week 80**	**Week 84**	**Week 88**	**Week 92**	**Week 96**	**W108, W120, W132, W144, W156, W168**			
PGIC	D	7.2.6											X				
WPAI	D	7.2.6											X				
Resource Utilization Assessments	D	7.2.5	Continuous														
ABL001 Drug administration	D		Continuous														
Bosutinib Drug administration	D		Continuous														
PK sampling (ABL001 arm only)		7.2.3															
Sparse PK blood collection	D	7.2.3											X				
Full PK blood collection (at least 20 patients)	D	7.2.3											X				
Survival follow-up	D																X
Antineoplastic therapies since discontinuation of study treatment	D															X	X
Stem Cell Transplant status	D																X
Progression status	D																X
Meal Record	D												X				

[redacted]

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 Screening

Written informed consent must be obtained before any study specific medical procedures are performed (Day -42). All screening/baseline assessments (with the exception of Bone Marrow Aspirates) should occur within 21 days before randomization.

The screening visit window for bone marrow assessments is 42 days prior to randomization. During the screening visit, inclusion and exclusion criteria will be assessed. Screening assessments to confirm eligibility must be performed prior to randomization. The results of the RQ-PCR and the bone marrow aspirate must be available prior to randomization and first dose of study treatment

For details of assessments required during screening please refer to Table 7-1.

Laboratory baseline assessments (including hematology, chemistry, coagulation and serum pregnancy test), physical examination including extramedullary involvement, performance status, ECG, height, weight and vital signs, evaluation of all relevant medical history including cardiovascular risk factors, CML disease history, including prior TKI therapy and antineoplastic medication and prior and concomitant medication must be performed prior to the first dose of study treatment. Patients with potassium, and/or magnesium and/or total calcium levels that are < LLN at screening, must have their potassium, and/or magnesium, and/or calcium replenished through supplementation and the levels must be within normal limits prior to the first dose of study drug.

A patient who has a laboratory test (peripheral blood test) results that do not satisfy the entrance criteria may have the tests repeated. These tests may be repeated as soon as the investigator believes the re-test results are likely to be within the acceptable range to satisfy the entrance criteria, but should be completed within approximately 2 weeks of the original screening visit date. In this case, the subject will not be required to sign another ICF, and the original patient ID number assigned by the investigator will be used. In the event that the laboratory tests cannot be performed within the screening visit window, or the re-tests do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the patient is considered a screen failure, and must be discontinued from the study.

A new ICF will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed, however, the patient ID number will remain the same. All required screening activities must be performed when the patient is re-screened for participation in the study. An individual patient may only be re-screened once for the study. Once the number of patients screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the patients who screen failed will not be permitted to re-screen.

[redacted]

7.1.2.1 Eligibility screening

Following registering in the IRT for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be managed via IRT system. Please refer and comply with detailed guidelines in the IRT manual.

7.1.2.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details). If the patient fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

7.1.2.3 Patient demographics and other baseline characteristics

Patient demographics and baseline characteristics collected will include the following: date of birth, gender (and child bearing potential for female), race and ethnicity, height, weight, all relevant medical history including cardiovascular disease history, CML disease history, including mutation status, and prior and concomitant medication including prior TKI therapy and antineoplastic medication.

Physical examination including extramedullary involvement, performance status, vital signs, ECGs, and laboratory assessments will be performed at screening.

Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the subject's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the patient's eCRF.

The central reading of the screening ECGs as well as the results of the RQ-PCR and the bone marrow aspirate must be available prior to randomization and first dose of study treatment to evaluate eligibility and to stratify the patient.

7.1.2.4 Local recruitment procedures-Japan

Given the limited safety data available in Japanese patients, specific recruitment and data monitoring procedures will be put in place for Japanese patients randomized to ABL001. Randomization of these patients will be staggered to avoid enrollment of more than one patient on the same day. Safety parameters from a minimum of 2 patients treated on the ABL001 arm will be reviewed for determining the appropriateness of continuing patient enrollment in Japan.

7.1.3 Run-in period

Not applicable.

[redacted]

7.1.4 Treatment period

There is no fixed duration of treatment planned per patient. All patients will be given the opportunity to receive study treatment until the date that corresponds to 96 weeks after the last patient receives the first study dose.

During the treatment phase, the patients will receive either ABL001 treatment 40 mg BID or bosutinib 500mg QD according to randomization. The dose can be modified, if required from the perspective of tolerance, following the guidance in Section 6.2 and Section 6.3. Treatment is ongoing until patient experiences unacceptable toxicity, disease progression, death, lost to follow-up and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent.

The patients are advised to adhere to the food restrictions during the treatment (fasting status regarding study treatment administration, avoidance of prohibited concomitant medication).

7.1.5 Visit windows

Study visits from Day 1 to Week 16 should be completed every 2 weeks on the designated date [with an allowed "visit window" of +/- 1 day]

Study visits from Week 16 to Week 96 should be completed every 4 weeks on the designated date [with an allowed "visit window" of +/- 2 days]

Study visits from Week 96 to EOT should be completed every 12 weeks on the designated date [with an allowed "visit window" of +/- 7 days]

A delayed visit will have no impact on the next planned visit. The next visit should be completed as scheduled in order to avoid accumulation of additional weeks.

7.1.6 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate eCRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if, he/she believes that continuation would be detrimental to the patient's well-being. Patients who discontinue study treatment should undergo an end of study visit.

For patients who discontinue treatment for reasons other than death, lost to follow-up, or withdrawal of consent, the patient should enter the survival follow-up phase. Survival visit assessments (survival, antineoplastic therapies, stem cell transplant and progression) should be performed every 12 weeks until documented death, lost to follow-up, or withdrawal of consent.

Patients who discontinue the study treatment for an adverse event suspected to be related to study drug or an abnormal laboratory value suspected to be related to study drug must be followed as described in Section 8.

[redacted]

Patients may also be discontinued from the study treatment if any of the following occurs:

- discovery of patient ineligibility
- errors in treatment compliance [study treatment, other prescribed or non-prescribed medications]
- missed/unscheduled/off schedule/incomplete/incorrect assessments
- major protocol deviation
- pregnancy during treatment phase
- use of prohibited treatment refer to Appendix 1.
- any other protocol deviation that results in a significant risk to the patient's safety

In addition to the general discontinuation criteria, the following study specific criteria will also require discontinuation of study treatment:

In the event of treatment failure the patient must be discontinued from the study treatment. The following events will constitute 'treatment failure', and are based on the ELN criteria (Bacarrani 2013) defining failure of a second line treatment:

- No CHR or > 95% Ph+ metaphases at three months after randomization or thereafter
- BCR-ABL ratio > 10% IS and/or > 65% Ph+ metaphases at six months after randomization or thereafter
- BCR-ABL ratio > 10% IS and/or > 35% Ph+ metaphases at 12 months after randomization or thereafter
- Loss of CHR, CCyR or PCyR at any time after randomization
- Detection of new BCR-ABL mutations at any time after randomization
- Confirmed loss of MMR in 2 consecutive tests, of which one must have a BCR-ABL ratio ≥ 1% IS 6 months after randomization
- New clonal chromosome abnormalities in Ph+ cells: CCA/Ph+: at any time after randomization

In the event of disease progression the patient must be discontinued from the study treatment. The following events are considered disease progression.

1. CML-related death (any death during treatment or follow-up if the principal cause of death is marked as "study indication" in the eCRF by the investigator, or if the death occurred subsequent to documented progression to AP/BC and the cause of death is reported as "unknown" or not reported by the investigator)
2. Accelerated phase (AP) as defined by any of the following:
    - ≥ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate
    - ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate
    - ≥ 20% basophils in the peripheral blood
    - Thrombocytopenia (<100 x 10^9/L) that is unrelated to therapy

[redacted]

3. Blast crisis (BC) as defined by any of the following:
   - ≥ 30% blasts in peripheral blood or bone marrow aspirate
   - Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma).

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 Molecular response

Molecular response (MR) will be assessed in all patients randomized to each treatment arm.

Levels of BCR-ABL transcripts will be determined by real-time quantitative PCR (RQ-PCR) testing of peripheral blood and analyzed at a central testing laboratory. Log reduction in BCR-ABL transcripts levels from the standardized baseline value, or the percent ratio of BCR-ABL transcripts versus control gene (ABL) transcripts converted to a reference standard, international scale (Hughes and Branford 2006), will be calculated for each sample.

Major molecular response and related variables are defined as the following:

- Rate of Major Molecular Response (MMR) where MMR is defined as a ≥ 3.0 log reduction in BCR-ABL transcripts compared to the standardized baseline equivalent to ≤ 0.1 % BCR-ABL/ABL % by international scale as measured by RQ-PCR, confirmed by duplicate analysis of the same sample
- Time to MMR defined as the time from the date of randomization to the date of the first documented MMR,
- Duration of MMR defined as the time from the date of first documented MMR to the earliest date of loss of MMR, progression to AP or BC, or CML-related death.

Loss of MMR is defined as confirmed loss of a greater than or equal to 3.0 log reduction in BCR-ABL transcript levels compared to the standardized baseline value, or confirmed loss of a less than or equal to 0.1% BCR-ABL/ABL by international scale in association with a ≥ 5-fold rise in BCR-ABL from the lowest value achieved on study treatment confirmed by a duplicate analysis of the same sample. This result has to be confirmed by a subsequent sample within 4-6 weeks unless it is associated with confirmed loss of CHR or loss of CCyR or progression to AP/BC or CML-related death.

Mutational analysis will be performed at a Novartis designated laboratory by Sanger sequencing at baseline and at end of treatment. If the result at baseline is positive for a mutation, analysis will be performed every 12 weeks.

The blood samples will be taken as described in Table 7-1 and Table 7-2.

[redacted]

Table 7-2 Blood samples (efficacy primary endpoint)

Sample Type	Volume	Visit	Time point
Blood for BCR-ABL quantification by RQ-PCR	20 mL	Screening/Baseline	Pre-dose
	20 mL	Week 4	Pre-dose
	20 mL	Week 8	Pre-dose
	20 mL	Week 12	Pre-dose
	20 mL	Week 16	Pre-dose
	20 mL	Week 24	Pre-dose
	20 mL	Week 36	Pre-dose
	20 mL	Week 48	Pre-dose
	20 mL	Week 60	Pre-dose
	20 mL	Week 72	Pre-dose
	20 mL	Week 84	Pre-dose
	20 mL	Week 96	Pre-dose
	20 mL	Every 12 weeks thereafter (W108,W120,W132, W144,W156,W168)	Pre-dose
	20 mL	End of Treatment	Anytime
Blood for BCR-ABL Mutation analysis by Sanger Sequencing	2.5 ml	Week 1 Day 1	Pre-dose
	2.5 ml	End of Treatment	Anytime
Blood for BCR-ABL Mutation analysis **only** for patients with mutations at W1D1	2.5 ml	Week 12	Anytime
	2.5 ml	Week 24	Anytime
	2.5 ml	Week 36	Anytime
	2.5 ml	Week 48	Anytime
	2.5 ml	Week 60	Anytime
	2.5 ml	Week 72	Anytime
	2.5 ml	Week 84	Anytime
	2.5 ml	Week 96	Anytime
	2.5 ml	Every 12 weeks thereafter (W108,W120,W132, W144,W156,W168)	Anytime

During the study, peripheral blood samples will be collected into PAXgene™ Blood RNA tubes for all RQ-PCR assessments. Detailed instructions for the collection, handling, and shipment of RQ-PCR and mutation samples are outlined in the [CABL001A2301 Laboratory Manual].

7.2.1.2 Bone marrow analysis and cytogenetics

Cytogenetic response will be assessed as the percentage of Ph+ metaphases in the bone marrow and is defined as the following (a review of a minimum of 20 metaphases is required):

- Complete (CCyR) - 0% Ph+ metaphases
- Partial (PCyR) - >0 to 35% Ph+ metaphases
- Major (MCyR) - 0 to 35% Ph+ metaphases

[redacted]

- Minor (mCyR) - >35 to 65% Ph+ metaphases
- Minimal - >65 to 95% Ph+ metaphases
- None - >95 to 100% Ph+ metaphases.

Bone marrow aspirate for cytogenetic analyses will be performed at screening/baseline (performed up to 42 days prior to randomization), at week 24, 48, 72, 96 and at end of treatment. For patients on the bosutinib arm an unscheduled bone marrow assessment at week 12 may be performed to evaluate cytogenetic response in consideration for potential dose escalation.

Quantification of the percentage of Ph+ chromosome metaphases, number of metaphases, number positive for Ph chromosome, additional chromosomal abnormalities as well as data from cytologic evaluation (microscopic analysis) of percentage of blasts and promyelocytes will be recorded on the Bone Marrow eCRF. These exams will be performed and analyzed locally. Fluorescent In-situ hybridization (FISH) analysis will not be accepted.

7.2.1.3 Hematologic response

A complete hematologic response (CHR) is defined as all of the following present for ≥ 4 weeks:

- WBC count <10 x 109/L
- Platelet count <450 x 109/L
- Basophils <5%
- No blasts and promyelocytes in peripheral blood
- Myelocytes + metamyelocytes < 5% in peripheral blood
- No evidence of extramedullary disease, including spleen and liver

7.2.2 Safety and tolerability assessments

Safety will be monitored by the assessments described below as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8. Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the patient's eCRF.

7.2.2.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. Information about the physical examination must be present in the source documentation at the study center and will be collected on the following visits:

- Screening
- Day 1
- Every 2 weeks from Week 4 to Week 16

[redacted]

- Every 4 weeks from Week 16 to Week 96
- Every 12 weeks from Week 96 to EOT
- End of treatment visit or early discontinuation visit in case of premature discontinuation.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF. Presence of extramedullary leukemic involvement will be checked with each physical examination as outlined above. Findings on physical examination consistent with extra-medullary leukemic involvement will be recorded (e.g. liver and spleen size, any other organ involvement)..

7.2.2.2 Vital signs

Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature and must be performed at the following visits:

- Screening
- Day 1
- Every 2 weeks from Week 2 to Week 16
- Every 4 weeks from Week 16 to Week 96
- Every 12 weeks from Week 96 to EOT
- End of treatment visit or early discontinuation visit in case of premature discontinuation.

7.2.2.3 Height and weight

Height in centimeters (cm) will be measured at screening only.

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1:

- Screening
- Every 2 weeks from Week 4 to Week 16
- Every 4 weeks from Week 16 to Week 96
- Every 12 weeks from Week 96 to EOT
- End of treatment visit or early discontinuation visit in case of premature discontinuation.

7.2.2.4 Performance status

ECOG Performance status scale (Table 7-2) will be used as described in the Table 7-1.

- Screening
- Day 1
- Every 2 weeks from Week 4 to Week 16
- Every 4 weeks from Week 16 to Week 96
- Every 12 weeks from Week 96 to EOT
- End of treatment visit or early discontinuation visit in case of premature discontinuation.

[redacted]

More frequent examinations may be performed at the investigator's discretion, if medically indicated.

Table 7-3 ECOG Performance status scale

Description	Grade
Fully active, able to carry on all pre-disease activities without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light housework, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead.	5

7.2.2.5 Laboratory evaluations

Central laboratory will be used for analysis of hematology, biochemistry, coagulation, serum pregnancy and hepatitis marker specimens collected (safety monitoring). Details on the collections, shipment of the samples and reporting of results by the central laboratory are provided to investigators in the [CABL001A2301 Laboratory Manual]. The time windows granted for laboratory evaluations are identical with the corresponding visit time windows for each visit (see Section 7.1.5).

Table 7-4 Central clinical laboratory parameters collection plan

Test Category	Test Name	Frequency
Hematology	Hemoglobin, Platelets, Red blood cells, White blood cells, WBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Promyelocytes, Myelocytes, Metamyelocytes, Blast and Other)	Screening/Baseline, week 1 Day 1, week 2 Day 1, every 2 weeks from week 4 up to week 16, every 4 weeks up to week 96, and every 12 weeks thereafter, EOT and as clinically indicated
Chemistry	Hemoglobin A1c	Screening/Baseline, Week 12 and as clinically indicated
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Total Calcium, Creatinine, Creatinine kinase, Potassium, Magnesium, Sodium, Phosphorus, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea or Nitrogen (BUN), Uric Acid, Amylase, Lipase, Glucose (fasting)	Screening/Baseline, week 1 Day 1, week 2 Day 1, every 2 weeks from week 4 up to week 16, every 4 weeks up to week 96, and every 12 weeks thereafter, EOT, and as clinically indicated
Coagulation	International normalized ratio (INR)	
Hepatitis markers	HbsAg, HbcAb /anti-Hbc	Screening/Baseline
Serum Pregnancy test (if applicable)	Serum ß-HCG testing	Screening/Baseline, every 4 weeks up to week 96, and every 12 weeks thereafter, EOT, unscheduled

[redacted]

7.2.2.5.1 Hematology

Hematology labs are to be analyzed at each scheduled visit by a central laboratory. Hematology includes assessment of hemoglobin, platelets count, red blood cells, total white blood cell count (WBC) and a full manual differential count including basophils, eosinophils, lymphocytes, monocytes, neutrophils, promyelocytes, myelocytes, metamyelocytes, blast and other cells (Table 7-4).

7.2.2.5.2 Clinical chemistry

Blood chemistry labs are to be analyzed at each scheduled visits by a central laboratory. Chemistry includes albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), total calcium, creatinine, creatinine kinase, potassium, magnesium, sodium, phosphorus, direct bilirubin, indirect bilirubin, total bilirubin, total cholesterol, LDL, HDL, total protein, triglycerides, blood urea or nitrogen (BUN), uric acid, amylase, lipase and fasting glucose. In addition the coagulation parameter INR is analyzed at each scheduled visit.

HbA1c is analyzed at screening/baseline, week 12 and as clinically indicated.

The hepatitis markers HbsAg, HbcAb/anti-Hbc are analyzed at screening/baseline (Table 7-4).

7.2.2.5.3 Pregnancy and assessments of fertility

All women of childbearing potential have to complete a serum pregnancy test at the screening visit, at every monthly visit until end of treatment visit. Pregnancy testing is not required for patients who are determined to be post-menopausal. The time windows granted for pregnancy testing are identical with the corresponding visit time windows for each visit. Refer to Table 7-1 of the Visit evaluation schedule. Serum pregnancy test will be performed by a central laboratory.

After Week 96 monthly urine pregnancy test must be performed by all women of child-bearing potential between the three monthly visits (beginning at Week 100). Urine pregnancy tests may be performed at the investigational site or at home. Test results performed at home should be recorded onto a patient diary and brought to each scheduled visit for the site to review. If a test result indicates a pregnancy, the patient must contact the investigator immediately.

All pregnancies (including female partners of male patients) should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the Oncology Novartis Drug Safety and Epidemiology Department (DS&E).

During the whole study, women of childbearing potential should employ the use of highly effective contraception. Highly effective contraception methods are defined in Section 5.3.

Sexually active males must use a condom during intercourse while taking the drug and for at least 3 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

[redacted]

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

After the subject has rested approximately 10 minutes in a semi-supine position, standard 12-lead ECGs must be obtained in triplicate with a recommended minimal interval of 5 minutes between each ECG at the time points specified in Table 7-5 and Table 7-6. Blood samples for PK scheduled at the same time point should be taken after the ECGs are completed.

Table 7-5 Central ECG collection (all patients)

Week (or Day)	Number of ECGs (per visit)	Time of ECG
Day -21 to -1	3	3 serial ECGs at the screening visit
Week 1 Day 1	3	3 serial ECGs at 2 h post dose
Week 2 Day 1	12	3 serial ECGs pre-dose and at 2, 3, 4 h post-dose
Week 4	3	3 serial ECGs pre-dose
Week 12	3	3 serial ECGs pre-dose
Week 24	3	3 serial ECGs pre-dose
Week 96	3	3 serial ECGs 30 min* post-dose
Unscheduled	3	3 serial ECGs 30 min* post-dose
* 30 min +/- 5min allowed		

Table 7-6 Central ECG collection plan for patients in full PK ABL001 group

Week (or Day)	Number of ECGs (per visit)	Time of ECG
Day -21 to -1	3	3 serial ECGs at the screening visit
Week 1 Day 1	3	3 serial ECGs at 2 h post dose
Week 2 Day 1	24	3 serial ECGs pre-dose and at 1, 2, 3, 4, 6, 8, 12 h post-dose
Week 4	3	3 serial ECGs pre-dose
Week 12	3	3 serial ECGs pre-dose
Week 24	3	3 serial ECGs pre-dose
Week 96	3	3 serial ECGs 30 min post-dose
Unscheduled	3	3 serial ECGs 30 min post-dose
* 30 min +/- 5min allowed		

All ECGs performed will be independently reviewed. Instructions for the collection and transmission of these ECGs to the independent central reader (eRT) will be provided in the [CABL001A2301 ECG Manual].

Three serial ECGs (triplicate) should be performed ½ hour prior to dosing for pre-dose assessment. The serial ECGs should be taken approximately 5 minutes apart. All 3 ECGs for each time point should be sent to eRT. Readings for QTc prolongation will be based on the average seen in the scans for each time point. The enrollment of patients has to be based on centrally assessed QTcF time. If one of the 3 serial ECGs prior to dosing on day 1 shows a QTcF ≥ 450msec (male) or ≥ 460msec (female) by automated reading, an immediate manual central reading must be requested by calling eRT. The patient may not be dosed if the average of the manually read ECGs confirms a QTcF ≥ 450msec (male) or ≥460msec (female).

[redacted]

Dose adjustments in case of QT prolongation should be performed per Section 6.3.2.

Additional unscheduled ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator.

All ECGs, including unscheduled triplicate safety ECGs with clinically relevant findings, collected during the study should be transmitted to the central core ECG laboratory for review.

The results of the centrally assessed ECGs are automatically transferred into the clinical database.

Clinically significant ECG abnormalities present at screening should be reported on the Medical History eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

7.2.2.6.2 Cardiovascular risk factor assessment

Cardiovascular events (CVE) including ischemic heart disease, peripheral arterial occlusive disease and ischemic cerebrovascular events have been reported in CML patients receiving TKI therapies. As both study treatments in the trial are TKIs (ABL001 and bosutinib), the cardiovascular risk factors (hypertension, tobacco use, raised blood glucose (diabetes), physical inactivity, unhealthy diet, cholesterol/lipids, overweight and obesity) of each patient will be collected prior to randomization and end of treatment. This will also include the patient's Family History.

7.2.2.6.3 Echocardiogram

Echocardiograms will be performed to monitor cardiac safety. Assessments are scheduled at screening/baseline, Week 20 and end of treatment visits. The echocardiogram will be performed and evaluated locally to assess the left ventricular ejection fraction. Any clinically significant findings will be collected and reported in the database (i.e. reported as adverse events).

7.2.2.6.4 Pulmonary function test

Pulmonary function test will be performed to monitor cardio-pulmonary safety. Assessments are scheduled at screening/baseline, Week 20 and end of treatment visits. The pulmonary function test with the plethysmograph includes the assessment of the lung volumes FEV1, FVC, FEV1/FVC, TLC and VC. In addition the DLCO to evaluate the gas exchange will be assessed at the same time points. Any clinically significant findings will be collected and reported in the database (i.e. reported as adverse events).

7.2.3 Pharmacokinetics

Blood samples for ABL001 pharmacokinetics will be collected on all study subjects allocated to the ABL001 treatment arm. Blood samples for full PK profiles will be collected from at least 20 patients. These patients will be identified sequentially at selected sites that are capable of serial PK sampling over 12 hours. ABL001 should be taken for at least 3 consecutive days without interruption or dose modification prior to full PK day.

[redacted]

For the assessment of ABL001 pharmacokinetics in plasma, serial blood samples will be collected following ABL001 administration at several time-points (see Table 7-7 and Table 7-8 below for further details). Remaining plasma samples may be used for identification and/or measurement of metabolites of ABL001.

Refer to the [CABL001A2301 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

Table 7-7 Pharmacokinetic blood collection log (Sparse PK-group-ABL001 arm)

Week	Day	Scheduled Time Point	Dose Reference ID	PK Sample No	Blood Volume (mL)
1	1	2 h (± 10 min)	101	101	2
2	1	0 h (Pre-dose)[a]	102/2001[b]	102	2
	1	2 h (± 10 min)	102	103	2
	1	3 h (± 15 min)	102	104	2
	1	4 h (± 15 min)	102	105	2
4	Any	0 h (Pre-dose)[a]	103/3001[b]	106	2
12	Any	0 h (Pre-dose)[a]	104/4001[b]	107	2
24	Any	0 h (Pre-dose)[a]	105/5001[b]	108	2
96	Any	0 h (Pre-dose)[a]	106/6001 [b]	109	2
		Unscheduled		1001+	

[a] Pre-dose PK sample should be taken immediately prior to the next administration of ABL001. PK samples on Week 2 Day 1 should be taken before and after the morning dose (i.e. 1st dose of the day). PK samples on other weeks may be taken immediately prior to the morning dose (i.e. 1st dose of the day) or the evening dose (i.e. 2nd dose of the day).
[b] The first dose reference ID refers to the first dose administered after PK sampling and the second dose reference ID refers to the last dose administered prior to the PK sampling.

[redacted]

Table 7-8 Pharmacokinetic blood collection log (Full PK group-ABL001 arm)

Week	Day	Scheduled Time Point	Dose Reference ID	PK Sample No	Blood Volume (mL)
1	1	2 h (± 10 min)	1	1	2
2	1	0 h (Pre-dose)[a]	2/201[b]	2	2
	1	0.5 h (± 10 min)	2	3	2
	1	1 h (± 10 min)	2	4	2
	1	2 h (± 10 min)	2	5	2
	1	3 h (± 15 min)	2	6	2
	1	4 h (± 15 min)	2	7	2
	1	6 h (± 30 min)	2	8	2
	1	8 h (± 60 min)	2	9	2
	1	12 h (± 60 min) (Pre-dose)[a]	3/2[b]	10	2
4	Any	0 h (Pre-dose)[a]	4/401[b]	11	2
12	Any	0 h (Pre-dose)[a]	5/501[b]	12	2
24	Any	0 h (Pre-dose)[a]	6/601[b]	13	2
96	Any	0 h (Pre-dose)[a]	7/701[b]	14	2
		Unscheduled		2001+	

[a] Pre-dose PK sample should be taken immediately prior to the next administration of ABL001. PK samples on Week 2 Day 1 should be taken before and after the morning dose (i.e. 1st dose of the day). PK samples on other weeks may be taken immediately prior to the morning dose (i.e. 1st dose of the day) or the evening dose (i.e. 2nd dose of the day).
[b] The first dose reference ID refers to the first dose administered after PK sampling and the second dose reference ID refers to the last dose administered prior to the PK sampling.

7.2.3.1 Analytical method

Plasma ABL001 concentrations will be measured at the designated laboratory using a validated high-performance liquid chromatography/tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) was 1.00 ng/mL.

7.2.4 Biomarkers

Exploratory biomarker analysis will be performed to identify mechanisms of resistance to ABL001 treatment. Using multiple approaches we plan to study both mature and stem leukemic cells. [redacted]

7.2.4.1 Biomarker assessment of bone marrow

[redacted]

[redacted]

7.2.4.2 Biomarker assessments in blood samples

Blood samples will be requested from all patients participating in the study.

[redacted]

Characterization of low level mutation in BCR-ABL

A 10 ml blood sample to be collected at W1D1 pre-dose and end of treatment to assess whether there are low level mutations undetected by Sanger Sequencing or NGS in BCR-ABL gene at baseline or new mutations appearing during treatment and at time of progression which potentially cause resistance to ABL001 or bosutinib treatment.

[redacted]

[redacted]

Table 7-9 Biomarker sample collection plan

Sample Type	Volume	Visit	Time point
Bone marrow samples(exploratory)			
[redacted]			
Blood samples (exploratory)			
[redacted]			
Blood for low level mutation analysis	10ml	Week 1 D1	Pre-dose
	10ml	End of Treatment	Anytime
[redacted]			

[redacted]

7.2.5 Resource utilization

The measures of healthcare Resource Utilization (RU) to be collected include: hospitalization (H), emergency room (ER) visit, general practitioner (GP) visits, specialist (Sp) visit and urgent care (UC) visit. These measures will be used to derive the economic impact of ABL001 and bosutinib.

Hospitalization visits will also record the number of days in ward and the type of ward (hospital unit) and the discharge status. At each RU collection, the reason for the visit (i.e. related to CML, AE or other reason) will be collected in order to quantify the impact of ABL001 and bosutinib on healthcare resources.

The RU assessment will be completed at each scheduled clinical trial visit; the RU will be completed by the investigator however information with respect to the number of GP, UC, Sp or ER visits will be ascertained from the patient.

All attempts to collect as much information from the patient as possible should be made in order to minimize selection bias.

7.2.6 Patient reported outcomes

The MDASI CML, PGIC, WPAI along with EQ-5D-5L (EuroQol Group (1990), Brooks (1996), Herdman et al (2011)) will be used to compare data on the patient's disease-related symptoms and health-related quality of life from baseline to EOT between the treatment arms. The WPAI will be used to assess work productivity and activity impairment related to the patient's CML. All measures will assess differences between the treatment arms. All tools require patient's direct completion and will be administered utilizing electronic device for data collection.

Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses. Missing data items in a scale will be handled according to the manual for each instrument. No imputation will be applied if the total or subscale scores are missing at a visit.

The patient should be given the questionnaire(s) to be completed at the scheduled visit before any clinical assessments are conducted. Patient's refusal to complete all or any part of a questionnaire should be documented in the study data capture system and should not be captured as a protocol deviation. Patient questionnaires should be completed in the language most familiar to the patient.

The patient should be given sufficient space and time to complete the questionnaires and the administered questionnaire should be reviewed for completeness. If missing responses are noted, patients should be encouraged to complete any missing responses.

Completed questionnaire(s) and any unsolicited comments written by the patient should be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the patient to change responses reported in the completed questionnaires. Study investigators

must follow reporting instructions outlined in Section 8 (e.g. reference "Adverse Events" Section) of the study protocol.

MDASI-CML

The M.D. Anderson Symptom Inventory – Chronic Myeloid Leukemia (MDASI-CML) is a 26 item self-administered questionnaire for adult CML patients. Twenty of the items measure the severity of disease-related symptoms and are scored from 0 (Not present) to 10 (As Bad as you can imagine) and 6 items that measure symptom interference with daily life scored from 0 (Did not interfere) to 10 (Interfered completely). Descriptive statistics will be provided for the MDASI-CML symptom score and interference score, and the change in the MDASI-CML symptom score and interference score from baseline to all available time points to the end of study. Additional analysis may be performed and details will be described in the analysis plan.

EQ-5D-5L

EQ-5D-5L is a two-part standardized instrument for measuring health outcomes in a wide range of health conditions and treatments. It consists of a descriptive system and a visual analogue scale (EQ VAS). The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems (or unable to perform the activity). The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'worst imaginable health state'. The health states derived from the descriptive system can be summarized into a single index score that provides a simple measure of health for clinical and economic appraisal. Descriptive statistics will be provided for EQ-5D-5L health index score and for the EQ VAS, at each scheduled assessment time point. There should be only ONE response for each dimension. Missing values can be coded as '9'. Ambiguous values (e.g. 2 boxes are ticked for a single dimension) should be treated as missing values. Additional analysis may be performed and details will be described in a separate analysis plan.

WPAI

The Work Productivity and Activity Impairment Questionnaire (WPAI) is a four-item questionnaire which is intended to measure work and activity impairment associated with CML for those who self-identify as currently employed for pay. This questionnaire measures self-reported productivity loss associated with CML during the past seven days. It consists of questions about absence from work due to CML, hours spent at work, the reduction in productivity at work attributed to CML, and the reduction in productivity while performing regular activities. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, Scoring will be done according to WPAI instrument guidance resulting in four scores including: Percent work time missed due to problem; percent impairment while working due to problem; Percent overall work impairment due to problem; and, percent activity impairment due to problem. Change from baseline in WPAI at each visit, where measured, will be done for each of the four derived scores.

[redacted]

PGIC

The Patient Global Impression of Change is comprised of a single question intended to measure a patient's perspective of improvement or deterioration over time relative to treatment. The PGIC uses a seven-point scale where one (1) equals very much improved and seven (7) equals very much worse. A summary of Patient Global Impression of Change (PGIC) at each visit, where measured will be provided.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

[redacted]

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)

If the event worsens the event should be reported a second time in the eCRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the eCRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Natural progression or deterioration of the malignancy under treatment (including loss of response, progression to accelerated phase or blast crisis and death due to disease progression), will be recorded as part of the efficacy evaluation and should NOT be reported as an AE/SAE.

Signs and symptoms clearly associated with the disease under study should NOT be reported as AEs unless they are newly emergent (i.e. not previously observed in the patient), judged by the Investigator to be unusually severe or accelerated, or if the Investigator considers deterioration of disease-related signs and symptoms to be caused directly by the study drug. If there is any uncertainty about an AE being due solely to the disease under study, it should be reported as an AE or SAE as appropriate.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a

[redacted]

sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the [Investigator Brochure].

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

[redacted]

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

[redacted]

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes until delivery must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

This study will institute a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will be constituted prior to the randomization of the first patient. The DMC will be responsible to review safety data at approximately 6 months after the first randomized patient has started study treatment. Subsequent reviews will be conducted approximately every 6 months on an as and when needed basis thereafter (ie. if significant safety findings are noted). This includes but does not limit the role of the DMC to evaluate these data and to provide recommendations to the sponsor to continue, modify or stop the study early. The DMC will be in place at least until the conduct of the primary analysis.

It is expected that the DMC will consist at a minimum of two physicians with appropriate disease area qualifications and one statistician. There will be a meeting with the DMC describing their roles and responsibilities and discussing potential data format and process issues prior to the finalization of DMC charter.

It is envisioned that the DMC may make certain types of recommendations, namely:

- No safety concerns, ethical to continue the study as planned
- Serious safety concerns precluding further study treatment, regardless of efficacy
- Recommendation to continue the study but proposing an amendment to the protocol (e.g., incorporate an additional safety assessments)

8.7 Steering Committee

In order to monitor study conduct, a Steering Committee (SC) will be established comprising investigators participating in the trial. Additionally two sponsor representatives (a physician and a statistician) will be active members of this committee.

[redacted]

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. Novartis will make final decisions on trial conduct based on SC recommendations. Together with the clinical trial team, the SC will review protocol amendments as appropriate, and also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study

[redacted]

treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Data collected by third parties (biochemistry, PCR assessments, biomarkers, PK) will be sent electronically to Novartis.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using the Novartis Interactive Response Technology.

[redacted]

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

The data will be analyzed by Novartis and/or designated CRO. It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis.

Study data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant PK and PD measurements.

The cut-off date for the primary analysis is defined as the date when all patients have been on study for 24 weeks or early discontinued. The cut-off date for the final treatment phase analysis is defined as 30 days after last patient last study drug to ensure that all available treatment phase data from all patients up to the last dose of study drug taken in this study, will be analyzed and summarized in a final treatment phase CSR. Patients will be further followed up for survival and progression for up to 5 years from the date the last patient received the first study dose. An update analysis of OS and PFS will be performed at the end of the follow-up period.

10.1 Analysis sets

10.1.1 Full Analysis Set

The **Full Analysis Set (FAS)** comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment and stratum they have been assigned to during the randomization procedure.

10.1.2 Safety set

The **Safety Set** includes all patients who received at least one dose of study treatment. Patients will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

10.1.3 Per-Protocol set

The **Per-Protocol Set (PPS)** consists of a subset of the patients in the FAS who are compliant with requirements of the CSP. The PPS will be used for sensitivity analyses on the primary endpoint only.

Oncology standards for protocol deviations potentially leading to exclusion from the PPS are:

- Type of indication different from those required by the CSP
- If prior therapy does not match with CSP requirements in terms of number and types of previous therapy regimens

[redacted]

- Another anti-neoplastic therapy administered after start of study treatment and prior to first efficacy assessment
- Study treatment received different from treatment assigned by randomization

10.1.4 Dose-determining analysis set

Not applicable.

10.1.5 Pharmacokinetic analysis set

The **Pharmacokinetic analysis set (PAS)** includes all patients who provide at least one evaluable PK concentration. For a concentration to be evaluable, patients are required to:

- Take a dose of ABL001 prior to sampling,
- Take the same dose of ABL001 for at least 3 consecutive days without dose interruption or dose modification prior to sampling,
- For post-dose samples, do not vomit within 4 hours after the dosing of ABL001; For pre-dose samples do not vomit within 4 hours after the dosing of ABL001 prior to sampling,
- Have the pre-dose sample collected before the next dose administration

10.1.6 Other analysis sets

For duration of MMR and time to MMR, the MMR Responder Set will be used that includes patients who achieve MMR at any time.

For CCyR rates at and by scheduled time points, the CCyR Analysis Set will be used that includes patients who are not in CCyR at baseline.

For duration of CCyR and time to CCyR, the Cytogenetic Responder Set will be use that includes patients who do not have CCyR at baseline and achieve CCyR at any time.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the FAS or the Safety Set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, by treatment group.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The Safety set will be used for the analyses below.

Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in days to ABL001 and bosutinib, as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure)

[redacted]

and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics.

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized by treatment group and all dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

10.4 Primary objective

The primary objective of the study is to evaluate the efficacy of ABL001 at the recommended dose in CML patients in chronic phase, previously treated with 2 or more tyrosine kinase inhibitors and to compare this efficacy profile in this population with that achieved by patients receiving bosutinib.

10.4.1 Variable

The primary efficacy variable of the study is the Major Molecular Response (MMR) rate at 24 weeks. A patient will be counted as having achieved MMR at 24 weeks if he meets the MMR criteria (BCR-ABL ratio $\leq$0.1%) at 24 weeks.

10.4.2 Statistical hypothesis, model, and method of analysis

The MMR rate at 24 weeks will be calculated based on the FAS and according to the Intent To Treat (ITT) principle. MMR rate and its 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. The confidence interval for the difference in MMR rate between treatment groups will be provided using the Wald method.

The null hypothesis is that there is no difference between the treatment groups with respect to MMR rate at 24 weeks. The Cochrane-Mantel-Haenszel chi-square test, stratified by the randomization stratification factor, i.e. major cytogenetic response status (PCyR or CCyR vs others) at screening, will be used to compare MMR rate between the two treatment groups, at the two-sided 5% level of significance. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

10.4.3 Handling of missing values/censoring/discontinuations

Only patients with MMR at 24 weeks are considered responders. In other words, any patient who achieves MMR before 24 weeks, but is no longer in MMR at 24 weeks, will be considered as a non-responder in this primary analysis. Patients discontinuing the randomized treatment prior to 24 weeks due to any reason will be considered as non-responders.

One exception to the rule above is if the 24-week PCR evaluation is missing, but both a PCR evaluation at 16 weeks and a PCR evaluation at 36 weeks indicate MMR, the 24-week assessment is imputed as a ‘Response’.

[redacted]

10.4.4 Supportive and Sensitivity analyses

The analysis of the primary endpoint will also be repeated on the PPS if the PPS is different from the FAS.

Subgroup analyses and a logistic regression analysis will be employed. Refer to the exploratory objectives Section 10.6.1 for further details.

10.5 Secondary objectives

The secondary objectives in this study are as follows:

- To compare additional parameters of the efficacy of ABL001 versus bosutinib, defined as:

Key secondary endpoints

- MMR rate at 96 weeks

Other efficacy endpoints

- Cytogenetic response (Complete, Partial, Major, Minor, Minimal, no response) rate at all scheduled data collection time points including24, 48 and 96 weeks.
- Cytogenetic response (Complete, Partial, Major, Minor, Minimal, no response) rate by all scheduled data collection time points including, 24, 48 and 96 weeks.
- MMR rate at all scheduled data collection time points (except 24 and 96 weeks which are already covered by primary and key secondary endpoints)
- MMR rate by all scheduled data collection time points including 24, 48 and 96 weeks.
- Time to MMR
- Duration of MMR
- Time to CCyR
- Duration of CCyR
- Time to treatment failure
- Progression free survival
- Overall survival

- To compare the safety and tolerability profile of ABL001 versus bosutinib
- To characterize the PK of ABL001 in the CML-CP population

10.5.1 Key secondary objective(s)

The key secondary endpoint to be evaluated is MMR rate at 96 weeks, which is defined as the proportion of patients with MMR at 96 weeks and derived in a similar fashion to MMR rate at 24 weeks.

[redacted]

10.5.1.1 Analysis for key secondary objectives

The null hypothesis is that there is no difference between the treatment groups with respect to MMR rate at 96 weeks. Formal statistical testing of the key secondary endpoint will be performed with $\alpha = 0.05$ (two-sided) only if the primary endpoint is significant by means of a gatekeeping procedure to control the overall alpha level.

MMR rate at 96 weeks will be evaluated in a similar fashion to the primary analysis of MMR rate at 24 weeks. The rate and the associated 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. Confidence interval for the difference between treatment groups will be provided using the Wald method.

Statistical testing will be performed via CMH chi-square test stratified by the randomization strata. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

10.5.2 Other secondary efficacy objectives

Unless otherwise stated the FAS will be used for the analysis of all other secondary efficacy endpoints. The exceptions are using the Molecular Responder Set for duration of MMR and time to MMR, the CCyR Analysis Set for CCyR rates, and the Cytogenetic Responder Set for duration of CCyR and time to CCyR.

No statistical testing of non-key secondary efficacy endpoints will be performed, however a nominal p-value will be presented for exploratory purposes.

Molecular Response

MMR rates at scheduled time points (except 24 and 96 weeks which have been specified as primary and key secondary endpoints) will be evaluated in a similar fashion to the primary analysis of MMR rate at 24 weeks. Patients discontinuing the randomized treatment prior to a specific time point due to any reason will be considered as non-responders for that time point.

MMR rates by scheduled time points are defined as the proportion of patients who achieve MMR at or before the specified visit, i.e. if a patient achieves an MMR but then loses it before or at the visit, he/she will still be classed as achieving MMR by that time point.

For each endpoint the rate and the associated 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. Confidence intervals for the differences in any response rates between treatment groups will be provided using the Wald method.

Statistical testing will be performed via CMH chi-square tests stratified by the randomization strata. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

Duration of MMR is defined in Section 7.2.1.1 as the time between the date of the first documented MMR and the earliest date of loss of MMR, progression to AP/BC, or CML-related death for patients in the Molecular Responder Set. The time will be censored at the last molecular assessment (PCR) date on treatment for patients who have not experienced any of the above events.

[redacted]

Duration of MMR will be analyzed by K-M method and presented by K-M plots. The estimated rates of patients who are still responding at various time points will also be provided using K-M method.

The cumulative incidence of MMR will be graphically displayed by an increasing step function. This curve will increase each time (after randomization) at which a new responder is observed and thus will increase up to the best observed response rate (e.g. up to 50% if half of the patients in the analysis population are able to achieve response).

Time to MMR is defined in Section 7.2.1.1 as: date of first MMR - date of randomization +1, for patients in the Molecular Responder Set. Descriptive statistics (range, median, quartiles, mean, sd) of time to MMR will be provided for the two treatment groups separately.

Cytogenetic Response

Patients in FAS will be categorized with counts and percentages provided for cytogenetic response (Complete, Partial, Major, Minor, Minimal, No Response) at and by (i.e. best response up to a specified time point) scheduled time points. Shift tables will also be employed to examine the changes in cytogenetic response category from baseline.

Since there are expected to be only very limited numbers who are actually in CCyR at baseline (due to the inclusion criteria requiring BCR-ABL ratio $\geq$ 1%) the analysis of CCyR rate at and by scheduled time points will only include patients who are not in CCyR at baseline, i.e. the CCyR Analysis Set.

CCyR rates at and by scheduled time points etc. and the associated 95% confidence intervals based on the Pearson-Clopper method will be presented by treatment group with the analysis of these endpoints only including patients who are not in CCyR at baseline.

Confidence intervals for the differences in any response rates between treatment groups will be provided using the Wald method.

Statistical testing will be performed via CMH chi-square tests stratified by the randomization strata. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

Time to CCyR is defined for patients in the Cytogenetic Responder Set as: date of first CCyR - date of randomization +1. Descriptive statistics (range, median, quartiles, mean, sd) of time to CCyR will be provided for the two treatment groups separately.

The cumulative incidence of CCyR will also be graphically displayed by an increasing step function. This curve will increase each time (after randomization) at which a new responder is observed and thus will increase up to the best observed response rate.

Duration of CCyR is defined as the time between date of first documented CCyR and the earliest date of loss of CCyR, progression to AP/BC, or CML-related death for patients in the Cytogenetic Responder Set. The time will be censored at the last cytogenetic assessment date on treatment for patients for whom none of the above events is reported or last PCR evaluation on treatment indicating MMR.

Duration of CCyR response will be analyzed by K-M method and presented by K-M plots. The estimated rates of patients who are still responding at various time points will also be provided using K-M method.

Treatment failure, disease progression and survival

Time to treatment failure (TTF) is defined as the time from date of randomization to an event of treatment failure. The following events will constitute 'treatment failure', and are based on the ELN criteria (Bacarrani 2013) defining failure of a second line treatment adapted to include discontinuation of randomized treatment as an event:

- No CHR or > 95% Ph+ metaphases at three months after randomization or thereafter
- BCR-ABL ratio > 10% IS and/or > 65% Ph+ metaphases at six months after randomization or thereafter
- BCR-ABL ratio > 10% IS and/or > 35% Ph+ metaphases at 12 months after randomization or thereafter
- Loss of CHR, CCyR or PCyR at any time after randomization
- Detection of new BCR-ABL mutations at any time after randomization
- Confirmed loss of MMR in 2 consecutive tests, of which one must have a BCR-ABL ratio ≥ 1% IS 6 months after randomization
- New clonal chromosome abnormalities in Ph+ cells: CCA/Ph+: at any time after randomization
- Discontinuation from randomized treatment for any reason

For patients who have not reach treatment failure, their TTFs will be censored at the time of last study assessment (PCR, cytogenetic, hematologic or extramedullary).

Progression-Free-Survival (PFS) is defined as the time from the date of randomization to the earliest occurrence of documented disease progression to AP/BC or the date of death from any cause (including progressions and deaths observed during the survival follow-up period).

The time will be censored at the date of last study assessment (PCR, cytogenetic, hematologic or extramedullary) or last post-treatment follow-up for patients without event.

Overall survival (OS) is defined as the time from the date of randomization to the date of death (including the survival follow-up period). Patients who are alive at the time of the analysis data cutoff date will be censored at the date of last contact before the cut-off date.

TTF, PFS and OS will be estimated and graphically displayed using the K-M approach. The estimated rates by K-M method at various time points will be provided and the endpoints will be compared between the two treatment groups using stratified log-rank test stratified by the randomization strata. The hazard ratio and 95% confidence intervals will be computed from a stratified Cox model.

[redacted]

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

The overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of subject's first informed consent to the day before first administration of study treatment
2. on-treatment period: from day of first administration of study treatment to 30 days after last actual administration of the same study treatment (including start and stop date)
3. post-treatment period: starting at day 31 after last administration of any study treatment

Summary tables for safety data will be presented for the on-treatment period. Comparative analysis will be performed only for the on-treatment period. Listings of safety data will include pre-treatment, on-treatment, and post-treatment periods, with a flag to indicate data collected before or after the on-treatment period.

10.5.3.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and serious adverse events (including those from the pre-treatment, on-treatment and post-treatment periods) will be listed and those collected before or after the on-treatment period will be flagged.

10.5.3.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following listings and summaries will be generated separately for hematology, and biochemistry tests:

[redacted]

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v4.03

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline in the on-treatment period.
- Shift tables using CTCAE grades to compare respective baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v4.03,

- Shift tables using the low/normal/high/ (low and high) classification to compare respective baseline to the worst on-treatment value.

10.5.3.4 Other safety data

ECG

ECGs (12-lead) including PR, QRS, QT, QTcF, and HR intervals will be obtained for each subject during the study. ECG data will be read and interpreted centrally.

Categorical analysis of QT/QTc interval data based on the number of patients meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these patients will be produced by treatment group.

Vital signs

Data on vital signs will be tabulated and listed, notable values will be flagged.

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

10.5.3.6 Tolerability

Tolerability of each study treatment will be assessed by summarizing the number of subjects with dose interruptions and dose reductions. Reasons for dose interruptions and dose reductions will be listed by subject and summarized.

10.5.4 Secondary PK objectives

The PK objective is to characterize the PK of ABL001 in CML population.

Using PAS, summary statistics (n, mean, SD, coefficient of variation (CV) for mean, geometric mean, CV for geometric mean, median, minimum and maximum) will be presented for plasma concentration at each scheduled time point. The geometric mean with mean (SD) and individual plasma concentration versus time profiles of ABL001 will be displayed graphically.

Using Safety set, concentration data will be listed. Concentration values below the limit of quantification (BLQ) will be set to zero by the Bioanalyst and displayed in listings as zero

[redacted]

with a flag. BLQ values will be handled as zero in any calculations of summary statistics, but handled as missing for the calculation of the geometric means and CVs.

Pharmacokinetic parameters will be determined by non-compartmental method(s) using the pharmacokinetic profile of ABL001 in patients with full PK sampling. PK parameters listed in Table 10-1 will be derived and reported, when feasible.

Population PK modeling may be performed and the results may be reported in a separate population PK report. Data from this study may be combined with data from other studies for this analysis.

Table 10-1 Non compartmental pharmacokinetic parameters in full PK group

AUC0-12h	The area under the plasma concentration-time curve from time zero to 12 h (mass x time x volume-1)[a]
Cmax	The maximum (peak) observed plasma drug concentration after dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma drug concentration after dose administration (time)
CL/F	The total body clearance of drug from the plasma after oral administration (volume x time-1)

10.6 Exploratory objectives

10.6.1 Exploratory efficacy objectives

- To evaluate the influence of factors such as major cytogenetic status at baseline, failure/intolerance to prior TKIs, line of therapy, gender, race and age on the effect of ABL001 with respect to the primary efficacy endpoint.
- To characterize mutations in the BCR-ABL1 gene at baseline and at end of treatment and examine their association with molecular and cytogenetic response for ABL001 vs bosutinib

10.6.1.1 Data analysis of exploratory efficacy objectives

Subgroup analyses will be performed to evaluate the influence of factors such as baseline major cytogenetic response status, baseline BCR-ABL ATP-binding site mutation status (from local historical record and from Sanger Sequencing), failure/intolerance to prior TKIs, line of therapy, gender, race and age on the primary efficacy endpoint. In addition, a logistic regression analysis will incorporate the key baseline variables into the model to further evaluate the impact of these variables on the primary endpoint and to provide a treatment effect estimate which is adjusted for imbalances in the treatment groups. An adjusted odds ratio for the treatment effect with associated 95% confidence intervals will be presented. Mantel-Haenszel estimates of the common odds ratio and the corresponding 95% confidence interval will also be provided.

[redacted]

10.6.2 Exploratory PK objectives

The potential relationship between ABL001 exposure (e.g. trough concentration) and efficacy or safety endpoints may be assessed by graphic exploration and/or statistical modeling as appropriate. The details will be further specified in the SAP. Additional exposure-response analyses for ECG may be conducted and reported separately.

10.6.3 Exploratory biomarker objectives

The study is not powered to assess specific biomarker-related hypotheses, thus the statistical analyses of these data should be considered exploratory in nature. Analytical results from such analyses may be used to generate additional hypotheses that must then be verified with data derived from subsequent clinical trials. Furthermore, additional post hoc exploratory assessments may be performed.

While the goal of the biomarker analyses is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a sample collection, or not perform/ discontinue the analysis of blood and bone marrow (e.g. issues related to the quality and or quantity of samples, or issues related to the assay that preclude the analysis of samples). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed.

Unless otherwise specified, all statistical analyses of biomarker data will be performed on subjects with valid biomarker samples.

The exploratory biomarker objectives are:

- To characterize mutations in the BCR-ABL1 gene at baseline, upon loss of molecular response and at end of treatment and examine their association with molecular and cytogenetic response for ABL001 vs. bosutinib
- [redacted]
- To assess clonal evolution of pre-existing mutations versus mutations acquired during treatment with ABL001 vs. bosutinib

[redacted]

[redacted]

- Explore the relationship between BCR-ABL1 mutations at baseline and efficacy outcomes for the primary endpoint and key secondary endpoints. The association between loss of response and BCR-ABL1 mutations will also be explored descriptively.
- Explore the influence of early molecular response levels on long term molecular response

[redacted]

Additional exploratory biomarker analyses may be performed depending on the data. All patients with evaluable biomarker measurements in the FAS will be included in the analysis and will be reported in a separate biomarker report.

10.6.4 Exploratory Patient Reported Outcomes objectives

The exploratory patient reported outcomes objectives are:

- To compare the impact of treatment on health care resource utilization between treatment arms in all patients
- To compare the impact of treatment on patient reported outcomes (PRO) including CML-specific symptoms, patient quality of life, and impact on work productivity and activity impairment from baseline through end of treatment between treatment arms in all patients

10.6.4.1 Resource Utilization

Data relating to Resource Utilization from the FAS will be used for the purpose of economic evaluation. Descriptive statistics of the levels of resource utilization over time will be done for each treatment arm. The measures of healthcare Resource Utilization (RU) include: hospitalization (H), Emergency Room (ER) visit, general practitioner (GP) visits, specialist (Sp) visit and urgent care (UC) visit. Medical resource utilization (MRU) will be assessed as follows: frequency and duration of hospitalization from Baseline up to End of Study; frequency of emergency room visits from Baseline up to End of Study; frequency of

[redacted]

additional outpatient office visits general practitioner, specialist, and urgent care visits from Baseline up to End of Study. Hospitalization visits will also record the number of days on ward and the type of ward (hospital unit) and the discharge status. At each RU collected, the reason for the visit, i.e. related to CML, AE or other reason, will be collected, in order to quantify the impact of treatment on healthcare resources.

10.6.4.2 Patient Reported Outcomes

The MDASI CML, PGIC along with EQ-5D-5L will be used to compare data on the patient's disease-related symptoms and health-related quality of life from baseline to EOT between the treatment arms. The WPAI will be used to assess work productivity and activity impairment related to the patient's CML. All measures will assess differences between the treatment arms.

Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses. Missing data items in a scale will be handled according to the manual for each instrument. No imputation will be applied if the total or subscale scores are missing at a visit.

10.7 Interim analysis

No formal interim analysis is planned for this trial. As described in Section 10, three formal analyses are planned: the primary at week 24, another at the 96-week end of study treatment and a PFS/OS update at year 5.

- 24-week primary analysis: Formal testing of the primary endpoint with full alpha will be performed. Analyses of other efficacy endpoints at and by 24 weeks will also be performed.
- 96-week end of study treatment analysis: Formal statistical testing of the key secondary endpoint will be performed with $\alpha = 0.05$ (two-sided) only if the primary endpoint is significant. Analyses of other efficacy endpoints (including MMR rate at 48 weeks) will also be performed.
- 5-year PFS/OS update analysis: PFS and OS

In addition DMC safety analyses will be conducted as described in Section 8.6.

10.8 Sample size calculation

To test the null hypothesis that the response rate is equal in the two groups, based on two-sided 5% level of significance and with 90% power, 222 patients will be needed in total (i.e. 148 patients in the ABL001 arm and 74 patients in the bosutinib arm based on 2:1 randomization allocation). This assumes that ABL001 leads to a 20% improvement in the MMR rate at 24 weeks over bosutinib from 15% to 35% which corresponds to an odds ratio of 3.05.

The assumed bosutinib MMR rate of 15% at 24 weeks is based on previous trials evaluating bosutinib therapy (Khoury 2012, Gambacorti-Passerini 2014, García-Gutiérrez 2015).

[redacted]

10.9 Power for analysis of key secondary variables

If the primary analysis of MMR rate at 24 weeks is statistically significant, then the key secondary endpoint MMR rate at 96 weeks will be tested, with the overall alpha controlled at the 5% two-sided level. The testing will use a gatekeeping strategy. Full details of the testing strategy are provided in Section 10.5.1.

Table 10-2 below summarizes the treatment effects of the key secondary endpoint which can be detected with 80% and 90% power, based on the specified assumptions regarding the bosutinib effect. The calculations were made using the software package PASS (2008).

Table 10-2 Detectable effect sizes for key secondary endpoint

Endpoint	Anticipated effect with bosutinib	2-sided alpha	Power	Detectable effect size§
MMR rate at 96 weeks	30%*	0.05	90% 80%	≥ 23% ≥ 20%

*: Gambacorti-Passerini et al. 2014, Figure 1D.
§: Absolute difference from the anticipated effect with bosutinib.

For MMR rate at 96 weeks, if the anticipated effect with bosutinib is 30%, then the given sample size with 2-sided alpha=0.05 would allow to detect an absolute difference of at least 23% (i.e. MMR rate at 96 weeks with ABL001 is at least 53%) for 90% power and of at least 20% (i.e. MMR rate at 96 weeks with ABL001 is at least 50%) for 80% power.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

[redacted]

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Additional consent form

Not applicable.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. www.clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

[redacted]

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study electronic case report form (eCRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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[redacted]

14 Appendices

14.1 Appendix 1 List of CYP3A4 inducers, inhibitors and substrates

Table 14-1 CYP3A4 inducers

Category	Drug Names
Strong inducers of CYP3A4[1]	avasimibe, carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort (HYPERICUM PERFORATUM)[5]
Moderate inducers of CYP3A4[2]	bosentan, efavirenz, etravirine, lersivirine, lopinavir, modafinil, nafcillin, ritonavir/tipranavir, semagacestat[4], talviraline[4], thioridazine
Weak inducers of CYP3A43	amprenavir, aprepitant, armodafinil bexarotene, boceprevir, brivacetam, clobazam, danshen[5], dexamethasone, echinacea[5], eslicarbazepine, gingko (ginkgo biloba)[5], ginseng[5], glycyrrhizin[5], honey[6], quercetin[6], methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, pleconaril[4], prednisone, primidone, raltegravir, ritonavir, rufinamide, sorafenib, Stribild (combo of elvitegravir, cobicistat, emtricitabine, and tenofovir), sulfinpyrazone, telaprevir, terbinafine, ticagleror, ticlopidine, topiramate, troglitazone[4], vemurafenib, vicriviroc/ritonavir, vinblastine, yin zhi huang[5]

[1] A strong inducer for a specific CYP is defined as an inducer that decreases the AUC of a sensitive substrate for that CYP by equal or more than 80%.

[2] A moderate inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 50-80%.

[3] A weak inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 20-50%.

[4] Drugs not available in the US Market.

[5] Herbal product.

[6] Food product.

This list was based on information from the FDA's "Guidance for Industry, Drug Interaction Studies", from the Indiana University School of Medicine's "Clinically Relevant" Table, from the University of Washington's Drug Interaction Database. This list may not be comprehensive and may be updated periodically. Refer to Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated 2016) for update or more details.

[redacted]

Table 14-2 CYP3A4 inhibitors

Category	Drug Names
Strong inhibitors of CYP3A41	boceprevir, cobicistat (GS-9350), conivaptan, clarithromycin, danoprevir/ritonavir[12], delalisib, darunavir/ritonavir[12], elvitegravir/ritonavir[12], grapefruit product[11], indinavir, indinavir/ritonavir[12], itraconazole, ketoconazole, LCL161, lopinavir/ritonavir[12], mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir12, telaprevir, telithromycin, tipranavir/ritonavir[12], troleandomycin, VIEKIRA PAK[2], voriconazole
Moderate inhibitors of CYP3A42	ACT-178882, amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporine, Erythromycin, darunavir, diltiazem, dronedarone, FK1706Ferula asafetida resin (Ferula assa-foetida)[4], faldaprevir, fluconazole[7], imatinib, isavuconazole, netupitant, nilotinib, schisandra, sphenanthera, tofisopam, verapamil
Weak inhibitors of CYP3A43	almorexant, alprazolam, AMD070, amiodarone, amlodipine, atorvastatin, AZD2327, azithromycin, berberine, bicalutamide, blueberry juice[5], chlorzoxazone, cilostazol, clotrimazole, cranberry juice[5], daclatasvir, delavirdine, evacetrapid, everolimus, fosaprepitant (IV), fluvoxamine[8], fostamatinib, Garden Cress seeds (Lepidium sativum)[5], ginkgo[4], goldenseal[4], Guan Mai Ning[13], GSK1292263, GSK2248761, isoniazid, ivacaftor, lacidipine, linagliptin, lomitapide, M100240, oral contraceptives, palbociclib, pazopanib, peppermint oil, propiverine, ranitidine, ranolazine, resveratrol, roxithromycin, Seville orange juice[5], simeprevir, sitaxentan, suvorexant, tabimorelin, tacrolimus, teriflunomide, ticagrelor, tolvaptan, Tong Xin Luo[13]

[1] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by equal or more than 5-fold.

[2] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.

[3] A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-foldbut equal to or more than 1.25-fold.

[4] Herbal product.

[5] Food product.

[6] Gemfibrozil also inhibits OATP1B1. Applicable for another class of CYP inhibitor.

[7] Fluconazole is listed as a strong CYP2C19 inhibitor based on the AUC ratio of omeprazole, which is also metabolized by CYP3A; fluconazole is a moderate CYP3A inhibitor.

[8] Fluvoxamine strongly inhibits CYP1A2 and CYP2C19, but also inhibits CYP2C8/2C9 and CYP3A.

[9] Ticlopidine strongly inhibits CYP2C19, but also inhibits CYP3A, CYP2B6, and CYP1A2. The inhibition of CYP3A4 by ticlopidine is not strong although the actual class of its inhibition on CYP3A4 (moderate vs weak) has yet to be defined.

[10] Effect seems to be due to CYP2C19 inhibition by ethinyl estradiol. Applicable for another class of CYP inhibitor.

[11] The effect of grapefruit product varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength).

[12] Combination therapy.(in some cases combinations with ritonavir have been listed as moderate inhibitors of CYP3A in the UW database, the have all been listed as strong in the DDI guide to avoid any potential confusion).

[13] Traditional Chinese medicine.

This list is based on information from the FDA’s “Guidance for Industry, Drug Interaction Studies”, from the Indiana University School of Medicine’s “Clinically Relevant” Table and from the University of Washington’s Drug Interaction Database. Please note that this is not an exhaustive list. Please refer to footnotes. Refer to Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated 2016) for update or more details.

[redacted]

Table 14-3 CYP3A4 substrates: Narrow therapeutic index, sensitive, and others

Category	Drug Names
Narrow Therapeutic index substrates of CYP3A41	alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfanadine, thioridazine
Sensitive substrates of CYP3A42	alpha-dihydroergocryptine, alfentanil, almorexant, alisoporivir, aplaviroc, aprepitant, atazanavir, atorvastatin, avanafil, bosutinib, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, conivaptan, danoprevir, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, elvitegravir, eplerenone, everolimus, felodipine, fluticasone, ibrutinib, indinavir, ivacaftor, levomethadyl, lomitapide, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simeprevir, simvastatin, tacrolimus, terfenadine, ticagrelor, tilidine,tipranavir, tolvaptan, triazolam, ulipristal, vardenafil, vicriviroc, voclosporin.
Other Substrates of CYP3A43	alprazolam, ambrisentan, amlodipine, antipyrine, aripiprazole, artemether, avosentan, boceprevir, bosentan, buprenorphine, carbamazepine, dexloxiglumide, dextromethorphan, diazepam, docetaxel, enzalutamide, gemigliptin, halofantrine, imipramine, lansoprazole, lidocaine, linagliptin, loperamide, loratadine, losartan, lurasidone, macitentan, methadone, mirodenafil, montelukast, morphine, nelfinavir, netupitant, nevirapine, nifedipine, nilotinib, nitrendipine, omeprazole, ospemifene, oxycodone, paclitaxel, pazopanib, pioglitazone, quinine, ranolazine, repaglinide, rifabutin, ritonavir, roflumilast, saxagliptin, selegiline, sertraline, sibutramine, sotrastaurine, telaprevir, theophylline, tirilazad, tolterodine, udenafil, ulipristal, vincristine, voriconazole
Narrow Therapeutic index substrates of CYP2C9	warfarin (also sensitive), phenytoin
Narrow Therapeutic index substrates of CYP2C8	paclitaxel

[1] Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.

[2] Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

[3] Other substrates are these that have shown an *in vivo* ≥2-fold increase in AUC with co-administration of an inhibitor based on the UW database.

This list of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; from the FDA's "Guidance for Industry, Drug Interaction Studies" and from the University of Washington's Drug Interaction Database. This list may not be comprehensive and may be updated periodically. Refer to Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated 2016) for update or more details.

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NOVARTIS

Clinical Development

Asciminib/ABL001

Oncology Clinical Trial Protocol CABL001A2301

A phase 3, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors

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List of abbreviations

ABL	Abelson proto-oncogene
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute neutrophil count
AP	Accelerated phase
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATP	Adenosine triphosphate
AUC	Area under the curve
AV block	Atrioventricular block
BC	Blast crisis
BCR	Breakpoint Cluster Region gene
BCR-ABL	BCR-ABL fusion gene (also called the Philadelphia chromosome)
BCRP	Breast Cancer Resistant Protein
BID	*bis in diem*/twice a day
BMA	Bone marrow aspirate
BUN	Blood urea nitrogen
CBC	Complete Blood Count
CCA	Clonal chromosome abnormalities
CCyR	Complete Cytogenetic Response
CD8	Cluster of differentiation 8
CD34	Cluster of differentiation 34
CHR	Complete Hematological Response
CI	Confidence Interval
CMH	Cochran–Mantel–Haenszel
CML	Chronic Myelogenous Leukemia
CML-AP	Chronic Myelogenous Leukemia-Accelerated Phase
CMO&PS	Chief Medical Office and Patient Safety
CP	Chronic phase
CRO	Contract Research Organization
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP3A4	Cytochrome P450 3A4
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DLCO	Carbon monoxide diffusing capacity
DMC	Data Monitoring Committee
DNA	Desoxyribonucleic acid
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram

[redacted]

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ELN	European Leukemia Network
EOT	End of Treatment
ERT	Electronic Research Technology, Inc
EU	European Union
FAS	Full Analysis Set
FIH	First In Human
GDPR	General Data Protection Regulation
GFR	Glomerular Filtration Rate
hADME	Human ADME study (Absorption, Distribution, Metabolism and Excretion)
HDL	High density lipoprotein
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
[redacted]	[redacted]
INN	International Nonproprietary Name
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
K-M	Kaplan-Meyer
Km	Michaelis-Menten constant
LDL	Low density lipoprotein
LFT	Liver function test
LLN	Lower limit of normal
[redacted]	[redacted]
MCyR	Major Cytogenetic Response
mCyR	Minor Cytogenetic Response
MDASI-CML	MD Anderson Symptom Inventory – Chronic Myelogenous Leukemia
MMR	Major Molecular Response
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NGS	Next Generation Sequencing
NTI	Narrow Therapeutic Index
OS	Overall survival
PAS	Pharmacokinetic analysis set
PBPK	Physiologically based pharmacokinetic
PCR	Polymerase Chain Reaction
PCyR	Partial Cytogenetic Response
PD	Pharmacodynamic
[redacted]	[redacted]
[redacted]	[redacted]
PGIC	Patient Global Impression of Change
P-gp	Permeability glycoprotein

[redacted]

Ph+	Philadelphia chromosome positive
PHI	Protected Health Information
PK	Pharmacokinetics
PLT	Platelets
PPS	Per-protocol set
QD	Quaque die/once a day
QT	Q to T interval (ECG)
QTcF	QTc Fredericia
REB	Research Ethics Board
RNA	Ribonucleic acid
RQ-PCR	Real time quantitative polymerase chain reaction
RU	Resource Utilization
SAE	Serious Adverse Event
SAP	The Statistical Analysis Plan (SAP) is a regulatory document which provides evidence of preplanned analyses
SC	Steering committee
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TBIL	Total bilirubin
TdP	Torsades de Pointes
TKI	Tyrosine Kinase Inhibitor
TTF	Time to treatment failure
UGT	Uridin diPhospho-glucuronosyltransferase
ULN	Upper limit of normal
US	United States
USPI	US prescribing information
WBC	White blood cell count
WPAI	Work Productivity and Activity Impairment

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g. q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

[redacted]

Protocol summary:

Title	A phase 3, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors
Brief title	Study of efficacy of CML-CP patients treated with asciminib versus bosutinib, previously treated with 2 or more TKIs
Sponsor and Clinical Phase	Novartis Phase 3
Investigation type	Drug
Study type	Interventional
Purpose and rationale	**Purpose:** The purpose of this pivotal study is to compare the efficacy of asciminib with that of bosutinib in the treatment of patients with CML-CP having previously been treated with a minimum of two prior ATP-binding site TKIs with BCR-ABL1 ratios ≥ 1% IS at screening. Patients intolerant to the most recent TKI therapy must have BCR-ABL1 ratio > 0.1% IS at screening and patients failing their most recent TKI therapy must meet the definition of treatment failure as per the 2013 ELN guidelines (Baccarani et al 2013). No more than 66 patients (approximately 30% of the overall trial population) that are intolerant to their most recent TKI therapy with BCR-ABL1< 1% will be recruited in order to ensure that the CML third line patient population is adequately represented. **Rationale:** There remains an unmet need for new compounds in patients with CML who have failed at least two prior TKIs. Current practice suggests that a second generation TKI will have been used for first line therapy for about one half of patients with CML, meaning that most patients who have failed at least two prior TKIs will have failed at least one if not two second generation TKIs (such as dasatinib and/or nilotinib). Potentially, such patients may also have failed bosutinib and/or ponatinib (Soverini 2014). Patients having failed at least two TKIs may have limited sensitivity to the remaining available agents and, thus, there exists a need for new safe and effective therapy. In addition, mutations will have developed in 21 to 33% of patients that prevent the use of specific TKIs, increasing the need for a better and alternative compound (Soverini 2014). Omacetaxine, a chemotherapeutic agent, is available for patients who have failed at least two prior TKIs under these conditions but only in the US and Canada. This agent is not available for most patients globally, where a bigger unmet medical need is present. Thus, there remains an unmet need for patients with CML who have failed at least two prior TKIs despite the existence of multiple agents.
Primary Objective and Key Secondary Objective	**Primary Objective:** To compare the Major Molecular Response (MMR) rate at 24 weeks of asciminib versus bosutinib **Key Secondary Objective:** To compare MMR rate at 96 weeks of asciminib versus bosutinib
Secondary Objectives	● To compare additional efficacy parameters of asciminib versus bosutinib: ● cytogenetic response rate (Complete, Partial, Major, Minor, Minimal, no response) at and by all scheduled data collection time points, including 24, 48 and 96 weeks ● MMR rate at all scheduled data collection time points (except 24 and 96 weeks which are already covered by primary and key secondary endpoints) ● MMR rate by all scheduled data collection time points, including 24, 48 and 96 weeks ● Time to MMR ● Duration of MMR ● Time to CCyR ● Duration of CCyR ● Time to treatment failure

[redacted]

	● Progression free survival ● Overall survival ● To compare the safety and tolerability profile of asciminib versus bosutinib by type, frequency and severity of adverse events, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG and other safety data (vital signs, physical examination) ● To characterize the PK of asciminib in the CML-CP population (Trough plasma concentrations, PK parameters in full PK group: Cmax, Tmax, AUC0-12h, CL/F) ● To assess the safety of asciminib when administered as treatment after bosutinib failure according to the 2013 ELN Guidelines
Study design	This study is a randomized, phase 3, open-label, active-controlled multi-center study. Patients will be randomized to the novel BCR-ABL1 TKI asciminib and bosutinib in a 2:1 ratio. The randomization is to be stratified to ensure the study population is balanced between the arms with respect to the patient's cytogenetic response status at baseline (Major Cytogenetic response (complete or partial) vs. No major cytogenetic response (minor, minimal or none)). The study design incorporates a 2:1 randomization, allocating more patients to the asciminib arm in order to learn more about the safety profile of the experimental therapy, whereas the safety of bosutinib therapy is well documented. Treatment duration for each patient in the present study is for up to 96 weeks after the last randomized patient receives the first dose, or up to 48 weeks after the last patient has switched from bosutinib to asciminib whichever is longer unless patients have discontinued treatment earlier, which should be adequate to address both the primary objective of the study, i.e. determination of the MMR rate at 24 weeks, as well as secondary efficacy and safety objectives. Patients on bosutinib will be able to switch to asciminib treatment up to 96 weeks after the last patient has been randomized. If patients in the bosutinib arm have documented treatment failure according to the 2013 ELN Guidelines (Baccarani et al 2013), they will have the option to receive asciminib. Each patient who switches to asciminib after bosutinib failure can remain on asciminib treatment for up to 48 weeks after the last bosutinib failure patient has switched to asciminib during the treatment period unless patients have discontinued treatment earlier.
Population	Two-hundred and twenty-two (222) patients with CML-CP who had prior treatment with two or more ATP binding site TKIs will be randomized on a 2:1 basis to receive either asciminib or bosutinib. Patients with known history of T315I and/or V299L mutations at study entry will be excluded from the trial since bosutinib, the comparator, is not approved for these patients.
Inclusion criteria	Patients eligible for inclusion in this study have to meet **all** of the following criteria: 1. Male or female patients with a diagnosis of CML-CP ≥ 18 years of age 2. Patients must meet all of the following laboratory values at the screening visit: ● < 15% blasts in peripheral blood and bone marrow ● < 30% blasts plus promyelocytes in peripheral blood and bone marrow ● < 20% basophils in the peripheral blood ● ≥ 50 x 10^9/L (≥ 50,000/mm^3) platelets ● Transient prior therapy related thrombocytopenia (< 50,000/mm^3 for ≤30 days prior to screening) is acceptable ● No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly 3a. Patients intolerant to the most recent TKI therapy, BCR-ABL1 ratio > 0.1% IS according to central laboratory at the screening examination 4. Prior treatment with a minimum of 2 prior ATP-binding site TKIs (i.e. imatinib, nilotinib, dasatinib, radotinib or ponatinib) 5. Failure (adapted from the 2013 ELN Guidelines; Baccarani et al 2013) or intolerance to the most recent TKI therapy at the time of screening

[redacted]

	● Failure is defined for CML-CP patients (CP at the time of initiation of last therapy) as follows. Patients must meet at least 1 of the following criteria. ● Three months after the initiation of therapy: No CHR or > 95% Ph+ metaphases ● Six months after the initiation of therapy: BCR-ABL1 ratio > 10% IS and/or > 65% Ph+ metaphases ● Twelve months after initiation of therapy: BCR-ABL1 ratio > 10% IS and/or > 35% Ph+ metaphases ● At any time after the initiation of therapy, loss of CHR, CCyR or PCyR ● At any time after the initiation of therapy, the development of new BCR-ABL1 mutations which potentially cause resistance to study treatment ● At any time after the initiation of therapy, confirmed loss of MMR in 2 consecutive tests, of which one must have a BCR-ABL1 ratio ≥ 1% IS ● At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cells: CCA/Ph+ ● Intolerance is defined as: ● Non-hematologic intolerance: Patients with grade 3 or 4 toxicity while on therapy, or with persistent grade 2 toxicity, unresponsive to optimal management, including dose adjustments (unless dose reduction is not considered in the best interest of the patient if response is already suboptimal) ● Hematologic intolerance: Patients with grade 3 or 4 toxicity (absolute neutrophil count [ANC] or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by manufacturer 6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2 7. Adequate end organ function as defined by (as per central laboratory tests): ● Total bilirubin ≤ 1.5 x ULN) except for patients with Gilbert's syndrome who may only be included if total bilirubin ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN ● Aspartate transaminase (AST) ≤ 3.0 x ULN ● Alanine transaminase (ALT) ≤ 3.0 x ULN ● Serum lipase ≤ 1.5 x ULN. For serum lipase > ULN - ≤ 1.5 x ULN, value must be considered not clinically significant and not associated with risk factors for acute pancreatitis ● Alkaline phosphatase ≤ 2.5 x ULN ● Creatinine clearance ≥ 50mL/min as calculated using Cockcroft-Gault formula 8. Patients must avoid consumption of grapefruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed. 9. Written informed consent obtained prior to any screening procedures. 10a. Patients must have the following electrolyte values (as per central laboratory tests) within normal limits or corrected to be within normal limits with supplements prior to first dose of study medication: • Potassium (potassium increase of up to 6.0 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits) • Total calcium (corrected for serum albumin); (calcium increase of up to 12.5 mg/dl or 3.1 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits) • Magnesium, with the exception of magnesium increase > ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L associated with creatinine clearance (calculated using Cockcroft-Gault formula) within normal limits 11. Evidence of typical BCR-ABL1 transcript [e14a2 and/or e13a2] at the time of screening which are amenable to standardized RQ-PCR quantification.
Exclusion criteria	Patients eligible for this study must not meet **any** of the following criteria: 1. Known presence of the T315I or V299L mutation at any time prior to study entry 2. Known second chronic phase of CML after previous progression to AP/BC

[redacted]

	3. Previous treatment with a hematopoietic stem-cell transplantation 4. Patient planning to undergo allogeneic hematopoietic stem cell transplantation 5. Cardiac or cardiac repolarization abnormality, including any of the following: ● History within 6 months prior to starting study treatment of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG) ● Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block) ● QTcF at screening ≥450 msec (male patients), ≥460 msec (female patients) ● Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following: ● Risk factors for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia ● Concomitant medication(s) with a "known risk of TdP" per wwwcrediblemeds.org/ that cannot be discontinued or replaced 7 days prior to starting study drug by safe alternative medication. ● Inability to determine the QTcF interval 6. Severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol (e.g. uncontrolled diabetes, active or uncontrolled infection, pulmonary hypertension) 7. History of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis 9. History of acute or chronic liver disease 10. Known presence of significant congenital or acquired bleeding disorder unrelated to cancer 11. History of other active malignancy within 3 years prior to study entry with the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively 12. Known history of Human Immunodeficiency Virus (HIV), chronic Hepatitis B (HBV), or chronic Hepatitis C (HCV) infection. Testing for Hepatitis B surface antigen (HBs Ag) and Hepatitis B core antibody (HBcAb / anti HBc) will be performed at screening 13. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or gastric bypass surgery) 14a. Treatment with medications that meet one of the following criteria and that cannot be discontinued at least one week prior to the start of treatment with study treatment ● Moderate or strong inducers of CYP3A ● Moderate or strong inhibitors of CYP3A 15. Previous treatment with or known/ suspected hypersensitivity to asciminib or any of its excipients. 16. Previous treatment with or known/ suspected hypersensitivity to bosutinib or any of its excipients. 17. Participation in a prior investigational study within 30 days prior to randomization or within 5 half-lives of the investigational product, whichever is longer 18. Pregnant or nursing (lactating) women 19a. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 days after last dose of asciminib and one month after last dose of bosutinib. Highly effective contraception methods include: ● Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

	● Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy) total hysterectomy or bilateral tubal ligation at least six weeks before taking study treatment). In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment ● Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject. ● Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. ● In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. ● Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking study medication. In the case of oophorectomy alone, women are considered post-menopausal and not of child bearing potential only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

Conditions to be fulfilled for asciminib switch	1. Failure to bosutinib treatment up to 96 weeks after the last patient received the first dose (adapted from the 2013 ELN Guidelines; Baccarani et al 2013). Patients must meet at least 1 of the following criteria. Failure is defined as follows:
	• Three months after the initiation of therapy or thereafter: No CHR or > 95% Ph+ metaphases.
	• Six months after the initiation of therapy or thereafter: BCR-ABL1 ratio > 10% IS and/or > 65% Ph+ metaphases.
	• Twelve months after initiation of therapy or thereafter: BCR-ABL1 ratio > 10% IS and/or > 35% Ph+ metaphases.
	• At any time after the initiation of therapy, loss of CHR, CCyR or PCyR.
	• At any time after the initiation of therapy, detection of new BCR-ABL1 mutations which potentially cause resistance to study treatment (asciminib or bosutinib).
	• At any time after the initiation of therapy, confirmed loss of MMR in 2 consecutive tests.
	• At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cells: CCA/Ph+.
	
	<u>Conditions preventing patients to switch to asciminib:</u>
	• Any Grade 3 or 4 toxicity which has not resolved to Grade 2 or lower within 28 days and before starting asciminib treatment.
	• Asymptomatic (Grade 2) pancreatitis if not resolved within 28 days
	• Disease progression while on bosutinib treatment. The following events are considered disease progression:
	  • Accelerated phase (AP) as defined by any of the following:
	  • ≥ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate.
	  • ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate.
	  • ≥ 20% basophils in the peripheral blood.
	  • Thrombocytopenia (< 100 x 10^9/L) that is unrelated to therapy.
	  • Blast crisis (BC) as defined by any of the following:
	  • ≥ 30% blasts in peripheral blood or bone marrow aspirate

	• Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma). • QTcF at time of switch > 480 msec or inability to determine QTc interval
Investigational and reference therapy	Asciminib 40 mg BID Bosutinib 500 mg QD
Efficacy assessments	Molecular response (RQ-PCR, mutational analysis) Cytogenetic response (Bone Marrow Aspirate)
Safety assessments	● Physical examination ● Vital Sign ● Height and weight ● ECOG performance status ● Laboratory chemistry and hematology ● Serology ● Electrocardiogram (ECG) ● Echocardiogram ● Pulmonary function tests with DLCO
Other assessments	● PK sampling (full/sparse) ● Bone Marrow Biopsy ● Patient Report Outcomes (MDASI-CML, PGIC, WPAI, EQ--5D-5L, resource utilization)
Data analysis	The primary efficacy variable of the study is the Major Molecular Response (MMR) rate at 24 weeks. A patient will be counted as having achieved MMR at 24 weeks if he meets the MMR criteria (BCR-ABL1 ratio ≤0.1%) at 24 weeks. The MMR rate at 24 weeks will be calculated based on the FAS and according to the Intention To Treat (ITT) principle. MMR rate and its 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. Confidence interval for the difference in MMR rate between treatment groups will be provided using the Wald method. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided. The key secondary endpoint is MMR rate at 96 weeks. Formal statistical testing of the key secondary endpoint will be performed only if the primary endpoint is significant by means of a gatekeeping procedure to control the overall alpha level.
Key words	Phase III, open-label, randomized trial, asciminib, bosutinib, CML-CP, prior treatment with 2 or more TKIs

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Amendment 3 (14-Dec-2018)

Amendment rationale

As of 21-Nov-2018, 137 patients were screened and 86 patients were randomized in the study, the study is currently ongoing.

The primary purpose of the amendment is:

Modification of the inclusion criterion of BCR-ABL1 transcript threshold required at study entry from a BCR-ABL1 ratio ≥ 1% IS to BCR-ABL1 ratio > 0.1% IS (i.e. not in MMR) for patients with intolerance to most recent TKI treatment. The threshold presented in this inclusion criteria affects only patients who are intolerant to prior treatment, since patients failing prior treatment must fulfill the criteria defined by ELN guidelines (Baccarani et al 2013). Although the number of treatment options is increasing, especially for patients with imatinib intolerance, alternatives for patients with resistance and/or intolerance to at least two previous TKIs are limited (NCCN 2018, ELN 2013). The reason of reducing the BCR-ABL1 ratio is that in routine clinical practice, physicians do not wait to observe increased BCR-ABL1 levels to switch treatment in patients with intolerance, which may increase the risk of disease progression, especially in patients with only limited further treatment options. This is in line with current CML treatment guidelines where the switch to an alternative therapy in intolerant patients is not linked to a BCR-ABL1 threshold (NCCN 2018, Baccarani et al 2013 and Hochhaus et al 2017).

Therefore, the threshold of ≥ 1% BCR-ABL1 in the current trial is reduced to BCR-ABL1 ratio > 0.1% IS for patients with intolerance to most recent TKI treatment. No more than 66 patients (approximately 30% of the overall trial population) that are intolerant to their most recent TKI therapy with BCR-ABL1 < 1% will be recruited in order to ensure that the CML third line patient population is adequately represented. As the primary endpoint is the rate of MMR at 24 weeks a baseline molecular response level > 0.1 % BCR-ABL1 is needed.

Patients experiencing documented treatment failure on bosutinib treatment will be allowed to switch to asciminib. Patients failing bosutinib treatment will have failed at least their third TKI treatment, with limited remaining treatment options. With this amendment patients who have failed bosutinib will be offered the possibility to continue in the study by receiving asciminib, if investigators consider that this treatment option is in the best interest of the patient. As of 15-Oct-2018, 4 patients could have potentially benefited from this option. Treatment failure during study treatment is assessed by measureable and pre-specified milestones defined by ELN criteria (Baccarani et al 2013), which are also used to define treatment failure as entry criteria for the study. Only documented treatment failure in the bosutinib arm will be considered for a treatment switch. For the purpose of the primary and secondary endpoint analyses, any patient meeting the ELN failure criteria while receiving study treatment, (either before or by the time of conducting the analysis and irrespective of treatment arm), will be considered as non-responders for the specific time point and for any subsequent time point. The switch to asciminib in case of bosutinib treatment failure is not expected to introduce bias as those patients will be regarded as non-responders irrespective of treatment switch and the disease burden will certainly not improve without further treatment. There is no option to switch patients failing on the asciminib treatment arm, as those patients can be offered approved

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therapies outside of the context of the study. The efficacy data collected after the switch from patients switching to asciminib following bosutinib failure will be analyzed separately as exploratory endpoints and will not be included for primary and secondary study endpoints. In addition, safety data from patients receiving asciminib after bosutinib failure will be collected to further characterize asciminib's safety profile.

Potassium increase of up to 6.0 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits. Grade 2 increase of potassium is acceptable in case of normal creatinine clearance as this is not considered to be a risk factor for QTc prolongation. Total calcium (corrected for serum albumin) increase of up to 12.5 mg/dl or 3.1 mmol/L (Grade 2) is acceptable at study entry if associated with creatinine clearance within normal limits as this is not considered to be a risk factor for QTc prolongation.

A change to creatinine clearance instead of GFR is being made in relation to the magnesium inclusion requirement as GFR in this study is expressed by creatinine clearance.

Exclusion criteria #19 is being modified under this amendment in order to define the duration of the use of highly effective methods of contraception after the last dose of bosutinib under this study (one month after last dose of bosutinib). This is being done in order to align with the latest Bosulif® USPI.

Exclusion criteria #21 has also been removed under this amendment. In embryofetal development studies with asciminib, fetal malformations (cardiac malformations) and increased visceral and skeletal variants were observed in rats and increased incidence of resorptions indicative of embryo-fetal mortality and a low incidence of cardiac malformations indicative of dysmorphogenesis were observed in rabbits. Asciminib is not genotoxic. As published in the literature, small molecules can distribute to seminal fluid and the seminal accumulation suggested is semen/plasma ratios up to 11.3 (Klemmt and Scialli 2005). According to the FDA guidance, in general, there is increased concern for reproductive or developmental toxicity in humans for relative exposure ratios (animal: human) that are < 10 and decreased concern for exposure ratios > 25 (FDA Guidance for Industry 2011). The calculations for the asciminib safety margin were done based on Cmax (plasma) seen in patients at a dose of 200 mg BID (Cmax 6843 ng/ml). Safety margin calculation based on the embryo-fetal development study in rats was 768 and safety margin calculation based on the embryo-fetal development study in rabbits was 894. In conclusion, for asciminib, as outlined above, the safety margins are well above 25 and therefore no embryo- and fetotoxicity effects can be anticipated via seminal fluid. Removal of male contraception is in line with the Bosutinib USPI and SmPC.

In addition, patients can be re-screened up to three times for the study, instead of once. The patient population being investigated in this study is heavily pre-treated and patients might not have other treatment options outside the trial. There can be many intolerance-related temporary conditions resulting in ineligibility for the trial.

Recruitment period extension has been reflected in the VES table. Study length has changed with introduction of switch option for patients failing bosutinib treatment.

Patients enrolling in this trial will present a high disease burden after failure of previous therapies. Myelosuppression during TKI targeted treatment is a very common effect observed due to the suppression of the leukemic clone; this effect is also extended to hematopoiesis of

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stem cells and progenitors (Steegmann et al 2016). For this reason, the recovery period for cytopenias has been extended from 28 to 42 days in order to allow for sufficient time to recover from suppression and to re-populate the bone marrow.

The biomarker sampling profile has been revised to remove the gene expression profile in leukemic stem cells in both blood and bone marrow due to technical limitations. In addition, there is currently no validated assay available.

A clarification has been made to how the tests for blood urea and Blood Urea Nitrogen (BUN) are noted. The text "blood urea, Blood Urea Nitrogen (BUN)" has been revised to “blood urea or Blood Urea Nitrogen (BUN)” in order to note that either test is permitted.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Change of the purpose of the study by decreasing the requirement of BCR-ABL1 ratio ≥ 1% IS to BCR-ABL1 ratio > 0.1% IS at the time of screening for patients with intolerance:
  - Protocol summary.
  - Section 2.1 Study rationale and purpose.
  - Section 4.1 Description of study.
  - Section 5.2 Inclusion criteria.
  - Section 10.5.2 Other secondary efficacy objectives.
- Change of the study design by introducing the switch to asciminib option for patients experiencing treatment failure on bosutinib treatment:
  - Protocol summary.
  - Section 2.2 Rationale for the study design.
  - Section 4.1 Description of study.
  - Figure 4-1 Schematic of Study Design.
  - Addition of Section 4.1.1 Study treatment switch from bosutinib to asciminib
  - Section 4.3 Definition of end of study.
  - Section 6.1.5 Treatment duration
  - Section 6.7.3.2 Study drug accountability.
  - Section 7 Visit schedule and assessments:
    - Addition of Table 7-2 Visit evaluation schedule (study treatment switch phase).
    - Addition of Section 7.1.2.2 Conditions to be fulfilled for asciminib switch.
    - Section 7.1.5 Visit windows.
    - Section 7.1.6 Discontinuation of study treatment.
    - Section 7.2.1.1 Molecular response.
    - Section 7.2.1.2 Bone marrow analysis and cytogenetics
    - Section 7.2.2.1 Physical examination.

[redacted]

    - Section 7.2.2.2 Vital signs.
    - Section 7.2.2.3 Height and weight.
    - Section 7.2.2.4 Performance status.
    - Section 7.2.2.5 Laboratory evaluations.
    - Section 7.2.2.6 Cardiac assessments.
    - Section 7.2.3 Pharmacokinetics.
    - Section 7.2.4 Biomarkers.
  - Section 10.1.6 Other analysis sets.
  - Section 10.5.3.1 Analysis set and grouping for the analysis
- Addition of new exploratory measure for patients that switch from bosutinib to asciminib:
  - Table 3-1 Objectives and related endpoints.
  - Section 10.1.6 Other analysis sets.
  - Section 10.6 Exploratory objectives:
    - Section 10.6.1 Exploratory efficacy objectives.
    - Section 10.6.1.1 Data analysis of exploratory efficacy objectives.
- Reference for concomitant medications with a "known risk of TdP" has been updated to wwwcrediblemeds.org/
  - Protocol summary
  - Section 5.3 Exclusion criteria
  - Section 6.3.2 Dose adjustments for QTcF prolongation
  - Section 6.4.3 Prohibited concomitant therapy
- [redacted]
- Section 5.2 Inclusion criteria and protocol summary: updated inclusion criteria to reflect the changes below:
  - Inclusion Criteria #3: As referenced above, the requirement of BCR-ABL1 ratio ≥ 1% IS has been decreased to BCR-ABL1 ratio > 0.1% IS at the time of screening for patients intolerant to previous TKI.
  - Inclusion Criteria #10: Potassium increase of up to 6.0 mmol/L is accepted at study entry if associated with creatine clearance within normal limits. Calcium increase of up to 12.5 mg/dl or 3.1 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits. GFR replaced by Creatinine clearance (calculated using Cockcroft-Gault formula) in order to maintain consistency throughout the protocol as creatinine clearance is already calculated based on inclusion criteria #7.
  - Inclusion Criteria #11: As study eligibility is assessed during screening with BCR-ABL1 PCR quantification via international scale this requirement was added as

[redacted]

clarification. Measurement according to international scale is only possible for typical BCR-ABL1 transcripts.

- Section 5.3 Exclusion Criteria and Protocol summary: updated exclusion criteria to reflect the following changes:
  - Exclusion Criteria #14: Removal of P-gp as a moderate or strong inhibitor of CYP3A as P-gp inhibitors are no longer prohibited per updated USPI, and SmPC
  - Exclusion Criteria #19: Duration of the use of highly effective methods of contraception after the last dose of bosutinib has been defined to align with the latest bosutinib USPI.
  - Exclusion Criteria #21 Removal of this criteria in order to align with updated pre-clinical data.
- Section 6.3.1 Dose modification and dose delay: The recovery period for cytopenias has been extended from 28 to 42 days in order to allow for sufficient time to recover from suppression and to re-populate the bone marrow.
- Table 7-1 Visit evaluation schedule: updates due to inadvertent omissions in previous protocols and to reflect extension of study treatment period
  - ECOG Performance status: X has been replaced by “If needed” under Week 6, Week 10 and Week 14.
  - Vital signs: added “If needed” under Week 6, Week 10 and Week 14.
  - Visit name: “W108, W120, W132, W144, W156” has been changed to “Every 12 weeks up to end of study treatment” to align with new extended recruitment timelines.
- Section 7.1.2 Change of patient re-screening allowance from once to up to three times.
- Section 7.1.2.2 Addition of new section with screening eligibility criteria for patients switching from bosutinib to asciminib.
- Section 7.1.4 Change of treatment duration for patients including those patients that switch to asciminib after failure on bosutinib. Patients can remain on asciminib treatment for up to 96 weeks after the last patient received the first dose in the study or up to 48 weeks after the last patient has switched to asciminib whichever is longer.
- Section 7.1.6 Discontinuation of study treatment: updated to specify that the safety follow-up visit can be conducted by telephone and replacement of “after randomization” by “after initiation of therapy” in the event that constitutes a treatment failure.
- Section 7.2.2.5.3 Pregnancy and assessments of fertility: Change in requirement for reporting pregnancies under this study. Pregnancies diagnosed in female partners of male participants are no longer required to be reported to CMO&PS. Contraception use by sexually active males while on study treatment is no longer required.
- Table 7-5 Central clinical laboratory parameters collection plan: Clarification on blood urea and Blood Urea Nitrogen (BUN). The text "blood urea, Blood Urea Nitrogen (BUN)" has been revised to “blood urea or Blood Urea Nitrogen (BUN)”.
- Section 8.4 Pregnancies: removal of male contraception requirement due to new information of asciminib embryo and fetotoxicity.
- Section 10.4.3 Handling of missing values/censoring/discontinuations: imputation rules updated to take in account unscheduled visits close to visit Week 24.

[redacted]

- Section 10.5.1.1. Analysis for key secondary endpoints: imputation rules updated to take in account unscheduled visits close to visit Week 96.
- Section 14 Appendices: updates to reflect that P-gp inhibitors are no longer prohibited
  - Section 14.2 Appendix List of concomitant medications for patients on bosutinib:
    - Removal of P-gp inhibitors from Table 14-3 Prohibited concomitant medications for bosutinib arm.
    - Addition of new medications to Category Torsade de pointe (TdP) TdP/QT risk: Known.
    - Addition of new category, TdP/QT risk: Possible.
    - Addition of new category, TdP/QT risk: Conditional.

IRBs/IECs

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The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 2 (13-Jul-2018)

Amendment rationale

As of 29-Jun-2018, this study has been submitted in 25 and approved in 24 countries. Eighty five (85) sites were initiated, 67 patients were screened and 38 patients were randomized in the study.

The primary purposes of the amendment are:

The frequency of bone marrow aspirate (BMA) to perform cytogenetic analysis has been decreased in accordance with treatment guidelines (European Leukemia Network (ELN) Guidelines (Baccarani et al 2013), National Comprehensive Cancer Network (NCCN) (Clinical Practice Guidelines in Oncology-Chronic Myeloid Leukemia v4.2018). Initially BMAs were foreseen at screening, every 24 weeks thereafter and at end of treatment. With the protocol amendment BMA is no longer needed for patients that have achieved MMR during study, however BMA assessment is requested at the time of end of treatment for biomarker analysis.

Toxicity studies performed in rats, dogs and cynomolgus monkeys identified the pancreas as potential target tissues. Therefore the assessment for laboratory parameters that are associated with pancreatitis were part of the inclusion criteria (amylase, lipase). Serum lipase is the preferred test due to its improved sensitivity, and a threshold concentration of 2-3 x ULN is recommended for the diagnosis of pancreatitis. There are a number of other conditions that can elevate lipase, including TKI pretreatment, thus the screening threshold for lipase is increased from ≤ ULN to ≤ 1.5 x ULN (CTCAE v4.03 grade 1), as patients with history of acute pancreatitis within 1 year of study and history of chronic pancreatitis are excluded. Amylase is not a specific marker for pancreatitis, as up to 60% of total serum amylase originates from non-pancreatic sources. Its short half-life reduces its value as a diagnostic test in the early clinical course. Lipase has replaced amylase as the biochemical test of choice for acute pancreatitis due to its higher specificity (Basnayake 2015), therefore the requirement of amylase ≤ ULN at screening has been removed.

Assessments for visits at weeks 6, 10 and 14 will be limited to the monitoring of the bone marrow function to allow for adjustments of study treatment. Assessments will comprise a complete blood count to detect neutropenia and thrombocytopenia which are among the most frequent adverse reactions [Asciminib Investigator's Brochure, Bosutinib label]. The physical examination must be done at site only in case of previous or newly occurring adverse events.

The concomitant medication section has been updated to reflect the most recent clinical updates on asciminib as well to align with the Bosutinib label.

In addition some minor inconsistencies (discrepancies between sections, typos) have been corrected.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- ABL001 has been replaced by International Nonproprietary Name (INN) asciminib throughout the protocol amendment.

[redacted]

- Protocol Summary and Section 5.2 Inclusion criteria:
  - Inclusion criterion 5: rewording of the reference to previous TKI therapy for more clarity.
  - Inclusion criterion 7: Criteria for amylase removed. Threshold for lipase increased to CTCAEv4.03 grade 1.
  - Inclusion criterion 10: grade 1 increase of magnesium is acceptable in case of normal Glomerular Filtration Rate (GFR) as this is not considered to be a risk factor for QTc prolongation.
- Protocol Summary and Section 5.3 Exclusion criteria:
  - Exclusion criterion 5: adapting the exclusion criteria concerning QT prolonging agents for clarification regarding known, possible or conditional risk for TdP, and adding the external web link to qtdrugs.org.
  - Exclusion criterion 8: deleted to avoid redundancy with inclusion and exclusion criteria 7.
  - Exclusion criterion 14: removal of substrates of CYP3A4/5, CYP2C8, or CYP2C9 with narrow therapeutic index based on most updated PBPK modeling predicting a negligible risk for sensitive CYP3A4/5, CYP2C8, or CYP2C9 substrates. These substrates will be moved under requiring caution and/or action section.
  - Exclusion criteria 19: changed from tubal ligation to bilateral tubal ligation,
  - Exclusion criterion 20: definition of menopausal women should be part of exclusion criterion 19.
- Section 1.2.1 Overview of asciminib (ABL001): updated.
- Section 1.2.1.1 Non-clinical experience/ Non-clinical pharmacokinetics and metabolism:
  - Rephrased to add more clarity on interspecies differences observed and recommendation about sunlight protection.
  - Updated with current available information.
- Section 1.2.1.2 Clinical experience: updated with current available information.
- Section 2.2.1 Rational for biomarker assessment: harmonization of time points for BCR-ABL1 gene mutation analysis.
- [redacted] Addition of the following endpoint: Change in work productivity and activity impairment over time according to WPAI.
- Section 4.3 Definition of end of study: rephrased to add more clarity.
- Section 6.1.1 Dosing regimen: precision on patient fasted state for asciminib dosing.

[redacted]

- Section 6.3.1 Dose modification and dose delay: clarification made on treatment discontinuation.
- Table 6-2 Criteria for dose reduction/interruption and re-initiation of asciminib and bosutinib treatment for adverse drug reactions:
  - Gastro intestinal/ Pancreatitis/Grade 2: precisions provided and treatment delay changed from 7 to 21 days to give investigators sufficient time for re-assessment.
  - Removal of "other adverse event" section which was redundant with the section "non-hematological adverse event reaction except where further specified in individual section".
  - Mandatory instructions for grade 3 and 4 "Non-hematological adverse event reaction except where further specified in individual section" for bosutinib have been aligned with those of asciminib: dose hold until resolved to ≤ grade 1, to handle the patients identically independent of the treatment assigned.
- Section 6.3.2 Dose adjustments for QTcF prolongation: adapting the dose adjustment concerning QT prolonging agents to the classification known, possible or conditional risk for TdP, and adding the external web link to qtdrugs.org.
- Section 6.4.2 Permitted concomitant therapy requiring caution and/or action: updated with the most clinical data available.
- Section 6.4.3 Prohibited concomitant therapy (asciminib):
  - Section on other anticancer agent added,
  - Sections on strong CYP3A4/5 inhibitors and P-gp inhibitors: prohibition on P-gp inhibitors has been removed and moved under requiring caution and/or action section based on CABL001A2102 ADME study,
  - Section on strong CYP3A4/5, UGT1A/2B inducers updated to provide instructions on action to be taken in case these inducers are taken,
  - Section on NTI substrates of CYP3A4/5, CYP2C8 and CYP2C9 removed based on a most updated PBPK modeling predicting a negligible risk for sensitive CYP3A4/5, CYP2C8, or CYP2C9 substrates and moved under requiring caution and/or action section,
  - Section on QT prolonging agents updated to change agents known to prolong QT interval to agents with "known", "possible" or "conditional" risk of Torsades de Pointes.
- Section 6.5.1 Permitted concomitant therapy requiring caution (bosutinib): has been updated to reflect the bosutinib label information regarding the use of QT prolonging agents.
- Section 6.5.2 Prohibited concomitant therapy (bosutinib):
  - Section on other anticancer agent added,
  - Concomitant use with CYP3A4/5 inhibitors/inducers: further clarifications on necessary actions.
- Table 7-1 Visit evaluation schedule:
  - Exploratory BCR-ABL1 mutation analysis (Sanger Sequencing) for patients with mutations at Week 1 Day 1: rephrased to indicate that this assessment will be performed without any dedicated blood collection.

[redacted]

  - [redacted]
  - Removal of PGIC questionnaire at screening: the question should only be completed for patients on treatment.
  - Week 6, 10 and 14: physical examination and extramedullary involvement to be performed only if new or ongoing adverse event since last visit. Chemistry and coagulation testings removed.
- Section 7.1.2 Screening, section 7.2.1.2 Bone marrow analysis and cytogenetics and Table 7-1 Visit evaluation schedule: timeframe for performing bone marrow aspirate and biopsy changed from 42 to 56 days. Historical bone marrow assessments performed before main informed consent form signature allowed if within 56 days of Week 1 Day 1.
- Section 7.1.2.2 Information to be collected on screening failures: correction of screening failure definition.
- Section 7.1.4 Treatment period: treatment failure added as a reason for stopping study treatment.
- Section 7.1.5 Visit windows: correction of the start of visit scheduled every two weeks.
- Section 7.1.6 Discontinuation of study treatment:
  - Has been made mandatory in case of pregnancy.
  - Confirmed loss of MMR in 2 consecutives tests rephrased for consistency with the efficacy assessments.
  - Ineligibility of patient due to detection of T315I or V299L mutations at any time has been added under the section describing the cases when a patient MUST be discontinued to remove any ambiguity.
- Section 7.1.7 Withdrawal of consent and Glossary of terms: these sections were added/updated to incorporate and reflect the European Economic Area (EEA) General Data Protection Regulation (GDPR) requirements.
- Section 7.2.1.1 Molecular response: definition of loss of MMR rephrased and harmonization of time points for BCR-ABL1 gene mutation analysis.
- Table 7.2 Blood samples (efficacy primary endpoint): updated to reflect:
  - Removal of blood sample collection for the assessment of asciminib mode of action via flow cytometry analysis
  - Exploratory BCR-ABL1 mutation analysis (Sanger Sequencing) for patients with mutations at Week 1 Day 1 will be performed without any dedicated blood collection.
- Section 7.2.1.2 Bone marrow analysis and cytogenetics: bone marrow aspirate for cytogenetic analysis at week 24, 48, 72 and 96 has been limited to patients who have not achieved MMR.
- Section 7.2.2.1 Physical examination: week 6, 10 and 14 assessments must be performed only if new or ongoing adverse event since last visit.
- Section 7.2.2.3 Height and weight and Table 7-1 Visit evaluation schedule: weight to be collected at Week 1 Day 1 and thereafter every 12 weeks.

[redacted]

- Section 7.2.2.5 Laboratory evaluations: was updated to allow on exceptional basis local laboratory evaluations.
- Section 7.2.2.5.1 Hematology: the week 6, 10 and 14 assessments can be performed at site or at any peripheral local laboratory.
- Table 7-4 Central clinical laboratory parameters collection plan and Section 7.2.2.5.2 Clinical chemistry: clarification added for some of the parameters. Parameter naming clarified and total calcium (corrected for albumin) added.
- Table 7-5 Central ECG collection (all patients): clarification for ECG on Week 2 Day 1 for patients treated with bosutinib.
- Section 7.2.4.2 Biomarker assessments in blood samples:
  - Characterization of low level mutations in BCR-ABL1: clarification of time points for Sanger mutation testing.
  - [redacted]
- Table 7-9 Biomarker sample collection plan:
  - Bone marrow samples (exploratory): clarifications added.
  - [redacted]
  - Addition of one time point collection for low level mutation analysis to be consistent with text in Section 7.2.4.2 Biomarker assessment in blood sample.
- Section 7.2.2.5.3 updated to reflect the change of name of the Novartis Drug Safety and Epidemiology (DS&E) department to the present name, Chief Medical Office and Patient Safety (CMO&PS).
- Section 7.2.2.6.1 Electrocardiogram (ECG): additional instruction given if ECG and blood samples for PK scheduled at the same time point.
- Section 7.2.5 Resource utilization and Section 10.6.4.1 Resource Utilization: precision of the reasons for resource utilization.
- Section 7.2.6 Patient reported outcome: precision that completion of questionnaires is mandatory.
- Section 8.4 Pregnancies: updated to reflect the change of name of the Novartis Drug Safety and Epidemiology (DS&E) department to the present name, Chief Medical Office and Patient Safety (CMO&PS) and the change in collection of pregnancy outcomes from "must" to "should".
- Section 10 Statistical methods and data analysis: precisions provided regarding the cut-off dates for the primary and end of study treatment phase analysis.
- Section 10.1.5 Pharmacokinetic analysis set: precision provided on the post and pre-dose samples and vomiting.
- Section 10.1.6 Other analysis sets: precision of MMR and CCyR responder sets.
- Section 10.5.1.1 Analysis of key secondary objectives: adding an imputation rule for the secondary objective at 96 weeks and clarification concerning the analysis of the key secondary endpoint at week 96 if statistical significance is not reached for primary endpoint at week 24.

[redacted]

- Section 10.5.2 Other secondary efficacy objectives: update of descriptive statistics definition and removal of presentation of p value as no formal statistical testing will be performed.
- Section 10.6.1 Exploratory efficacy objectives and Section 10.6.3 Exploratory biomarker objectives:
  - Correction of time points for BCR-ABL1 mutation characterization (baseline corrected to Week 1 Day 1, adding "upon confirmed loss of MMR, and changed "and" to "and/or" End of treatment).
  - [redacted]
- Section 10.6.4.1 Resource utilization: correction on duration of resource utilization reporting.
- Section 10.7 Interim analysis: clarification concerning the analysis of the key secondary endpoint at week 96 if statistical significance is not reached for primary endpoint at week 24.
- Section 14 Appendices: the lists of concomitant medications for patients on asciminib and bosutinib have been updated based on the internal Pharmacokinetic Sciences memorandum on Drug-Drug Interaction (release date: January 2018).
- Some minor inconsistencies (discrepancies between sections, typos) have been corrected.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 1 (10-Apr-2017)

Amendment rationale

This study is currently in the protocol submission phase. The protocol was submitted to the FDA only. The submissions to the other HA and IRB/EC will be performed once the amended protocol is available. As of 30 Mar 2017, no sites were initiated nor any patients screened for this study.

The primary purpose of this amendment is:

Patients with a mutation V299L are excluded from the study, due to the known inactivity of the comparator drug bosutinib. The designation of the mutation was inadvertently identified incorrectly throughout the protocol as V229L instead of V299L. The purpose of this amendment is to correctly identify the exclusionary mutation as "V299L" throughout the document.

In addition some inconsistencies that were discovered after the finalization of the initial protocol are corrected.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Protocol summary: The wrongly designated mutation V229L was corrected to V299L
- Protocol summary: The missing exclusion criteria number 18 "Pregnant or nursing (lactating) women" was added, to be consistent with Section 5.3.
- Section 1.2.2- Overview of bosutinib: The wrongly designated mutation V229L was corrected to V299L
- Section 2.5- Rationale for choice of comparators drug bosutinib: The wrongly designated mutation V229L was corrected to V299L
- [redacted]
- Section 5.1- Patient population: The wrongly designated mutation V229L was corrected to V299L
- Section 5.3- Exclusion criteria: The wrongly designated mutation V229L was corrected to V299L
- Section 6.4.4- Other concomitant medications: The duration of contraception was corrected to "3 days" after treatment discontinuation. Highly effective contraception needs to be continued until 3 days post-treatment discontinuation.
- Table 7-1-Visit evaluation schedule: X for weight removed from Visit Week 1 Day 1, to be consistent with Section 7.2.2.3.
- Table 7-1-Visit evaluation schedule: X for antineoplastic therapies since discontinuation of study treatment added to survival follow-up phase to be consistent with Section 7.1.6.

[redacted]

- Section 7.1.6- Discontinuation of study treatment: The criteria for study treatment discontinuation "documented lack of efficacy, disease progression" was removed. All patients (excluding patients that died, withdrew consent or are lost to follow-up), are followed up for survival after the treatment phase.
- Section 7.1.6- Discontinuation of study treatment: clarification added to distinguish between discontinuation of study treatment versus discontinuation of study.
- Section 7.2.2.1- Physical examination: clarification of methodology to assess extramedullary involvement.
- [redacted]
- Section 7.2.6- Patient reported outcomes: The statement "The original questionnaire will be kept with the patient's file as the source document." was removed. Questionnaires will be completed electronically; no paper copies will be kept in the source documents.
- Section 10.1.5- Pharmacokinetic analysis set: The number of consecutive days required for PK concentration evaluability was corrected to "3" days. ABL001 should be taken at least 3 consecutive days without interruption or dose modification prior to full PK day.

IRBs/IECs

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[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Chronic myeloid leukemia (CML) is a hematological stem cell disorder characterized by a specific chromosomal translocation leading to the Philadelphia (Ph) chromosome which is detected in 95% of patients (Nowell and Hungerford 1960; Rowley 1973). The molecular consequence of the translocation is the fusion of the *ABL1* proto-oncogene to the *BCR* gene resulting in the production of an activated form of the ABL1 protein tyrosine kinase (TK) (Bartram et al 1983; Heisterkamp et al 1983). BCR-ABL1 drives the growth factor independence, increased proliferation, genomic instability, suppression of apoptosis and alteration of the adhesive properties of CML cells (Hochhaus 2009) and the expression of BCR-ABL1 in mice results in the development of a CML-like disease (Daley et al 1990; Kelliher et al 1990). This evidence that BCR-ABL1 is a genetic driver of CML was subsequently confirmed by the clinical efficacy of imatinib in patients [IRIS Study STI571A0106].

Clinically, CML is characterized by overproduction of immature myeloid cells and mature granulocytes in the spleen, bone marrow and peripheral blood. Most patients, however, present in the CP, characterized by splenomegaly and leukocytosis with generally few symptoms. CML progresses through three distinct phases of increasing refractoriness to therapy: chronic phase (CP), accelerated phase (AP), and blast crisis (BC). With conventional chemotherapy, such as busulfan or hydroxyurea, the median survival time commonly reported for CML was about 4 years, but progression to AP and BP was only slightly delayed. Interferon-alfa delayed progression significantly, with a median survival of approximately 6 years. However, during the last decade, TK inhibitor (TKI) therapy became the standard treatment for most patients with CML, with complete cytogenetic response rates of 70% to 90% and 5-year progression-free survival and overall survival of 80% to 95% commonly reported (Vardiman 2009).

The National Comprehensive Cancer Network (NCCN) guideline on CML (NCCN guideline v 1.2014) and the European Leukemia Net (ELN) (Baccarani et al 2013) recommend continuing TKI treatment indefinitely in all responding patients. The first TKI, imatinib mesylate (imatinib, STI571, Gleevec™/Glivec™), an adenosine triphosphate (ATP)-competitive TKI with selectivity towards BCR-ABL1, revolutionized treatment of CML and significantly improved the prognosis of patients since its approval in 2001. It is effective in most patients with CML at well-tolerated doses, and is indicated as frontline therapy for Ph+ CML-CP and in patients with Ph+ CML in blast crisis (BC), accelerated phase (AP), or in CP after failure of interferon-alpha therapy. However, despite the remarkable efficacy of imatinib, some patients are either intolerant to the drug or can develop resistance (O'Hare 2006). Imatinib resistance is primarily due to nucleotide substitutions in BCR-ABL1, which encode mutant forms of protein's tyrosine kinase domain that impair imatinib binding. Over-expression of the BCR-ABL1 protein may also cause resistance. Rates of resistance increase with each stage of progression of CML (CP < AP < BC) (Branford 2003).

Multiple agents, including nilotinib, dasatinib, ponatinib, bosutinib, radotinib (Korea) and omacetaxine (USA, Canada) are able to combat various forms of imatinib-resistant CML and are currently approved for patients with CML-CP previously treated with prior therapy. With the exception of omacetaxine, which is a cytotoxic chemotherapeutic agent, all of these drugs

[redacted]

are ATP-competitive TKIs. Like imatinib, nilotinib, dasatinib and most recently bosutinib are also indicated for the treatment of patients with newly diagnosed CML. The activity of nilotinib or dasatinib in patients previously treated with a second generation TKI is not known. In contrast to the ATP-competitive TKIs, asciminib inhibits the enzymatic activity of BCR-ABL1 through an allosteric mechanism.

There remains an unmet need for new compounds in patients with CML who have failed at least two prior TKIs. Current practice suggests that a second generation TKI will have been used for first line therapy for about one half of patients with CML, meaning that most patients who have failed at least two prior TKIs will have failed at least one if not two second generation TKIs: dasatinib and/or nilotinib. Potentially, such patients may also have failed bosutinib and/or ponatinib (Soverini 2014). Patients having failed at least two TKIs may have limited sensitivity to the remaining available agents and, thus, there exists a need for new safe and effective therapy. In addition, mutations will have developed in 21 to 33% of patients that prevent the use of specific TKIs, increasing the need for a better and alternative compound (Soverini 2014). Omacetaxine, a chemotherapeutic agent, is available for patients who have failed at least two prior TKIs under these conditions but only in the US and Canada. This agent is not available for most patients globally, where a bigger unmet medical need is present. Thus, there remains an unmet need for active and safe drugs in patients with CML who have failed at least two prior tyrosine kinase inhibitors (TKI), even in the presence of approved drugs, as described below.

1.2 Introduction to investigational treatment

1.2.1 Overview of asciminib (ABL001)

Asciminib is an orally bioavailable specific BCR-ABL1 inhibitor with a novel mechanism of action. In contrast to inhibitors such as imatinib, nilotinib, dasatinib and bosutinib that bind within the ATP-binding site of the ABL kinase domain, asciminib inhibits ABL tyrosine kinase activity by binding to a particular allosteric site on the kinase domain, which has only been identified on ABL1, ABL2 and BCR-ABL1. Consequently, asciminib is specific for the latter three enzymes.

Asciminib potently and selectively inhibits the proliferation of cell lines that express BCR-ABL1. By virtue of asciminib not interacting with the ATP-binding site, the drug maintains activity against cells expressing clinically observed ATP-binding TKI resistance mutations.

1.2.1.1 Non-clinical experience

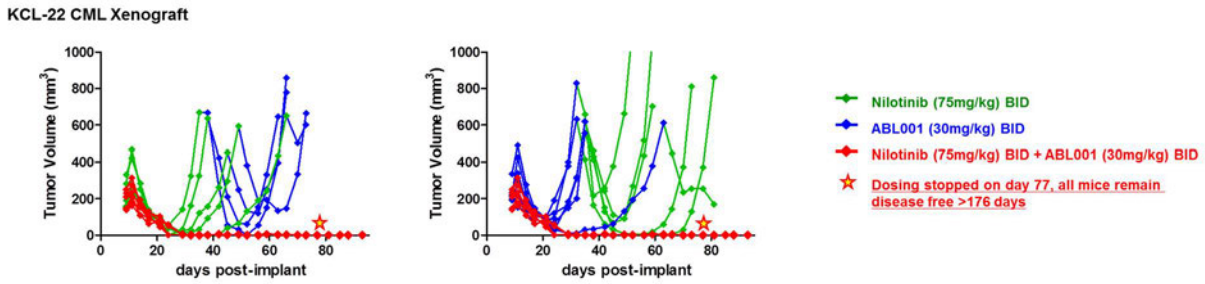
In vitro and in vivo pharmacology data

Asciminib displays potent anti-tumor activity *in vivo* with a clear pharmacokinetic (PK)/pharmacodynamic (PD)/Efficacy relationship [RD-2013-50145]. In a KCL-22 CML blast crisis (CML-BC) cell line mouse subcutaneous xenograft model, tumor regression was observed at doses of 7.5 mg/kg BID and above when asciminib was administered alone. Efficacy in the KCL-22 xenograft model correlated with stable inhibition of the downstream PD marker phospho-STAT5, consistent with finding that ABL1 inhibits STAT5 phosphorylation in KCL22 cells with an IC_{90} value of approximately 20 nM.

[redacted]

The KCL-22 xenograft model was also used to assess the activity of asciminib and nilotinib as single agents and in combination (Figure 1-1). In these experiments, when each agent was administered as monotherapy in sequence, initial sensitivity of the tumor was observed to each agent, but relapse occurred in each case. The mutations observed were as expected based on clinical experience (T315I for nilotinib) or modeling (A337V) for asciminib. In contrast, animals treated upfront with the combination of asciminib and nilotinib achieved sustained tumor regression with no evidence of disease relapse during the 70 days of treatment or for 80 days following discontinuation of treatment. Note that in this KCL-22 model, the cells (derived from a blast crisis CML patient) were grown as a solid tumor rather than as disseminated disease. Also, this model is much more aggressive than chronic phase CML in patients.

Figure 1-1 KCL-22 CML Xenograft



These data are consistent with asciminib being active against nilotinib-resistant mutations and nilotinib being active against asciminib-resistant mutations. Consequently, the findings support development of asciminib both as single agent as well as in combination with TKIs as initial therapy of CML as well as therapy after progression on nilotinib.

In addition, due to asciminib specifically targeting the ABL kinase family (ABL1, ABL2, BCR-ABL1), asciminib offers the potential for improved safety and tolerability when administered as monotherapy when compared to TKIs binding to the ATP site of BCR-ABL1, which are less specific towards ABL. Thus, there is the potential for an improved safety profile of asciminib in comparison to other TKIs.

Safety pharmacology and toxicology

An extensive toxicology safety evaluation program (subchronic, chronic, reproductive toxicology, phototoxicity and genotoxicity studies) was conducted.

Safety pharmacology studies indicate that asciminib is not expected to cause effects on the vital functions of the CNS, and the respiratory systems. The IC50 for asciminib in the hERG patch clamp is 11.4 µM (4498 ng/mL). No cardiovascular effects were observed in a single dose jacketed telemetry study in dogs at doses up to 600 mg/kg or the invasive telemetry cardiovascular safety study up to 60 mg/kg. Furthermore, no changes in cardiovascular parameters related to QTc prolongation were observed using standard electrocardiography in the 4-week dog toxicity study and in cynomolgus monkey toxicity studies (up to 39 weeks of treatment).

Asciminib does not show mutagenic, clastogenic, or aneugenic potential in the *in vitro* assays or the MNT assessment *in vivo*; therefore, no potential risk for human is perceived.

[redacted]

As determined by the results of the phototoxicity assessment (*in vitro* and *in vivo*), phototoxic potential was identified in the mouse UV-LLNA assay. Given these data, patients should be advised to avoid prolonged exposure to sunlight (sunbathing), to avoid sunbed and to use sunscreen.

Toxicity studies performed in rats, dogs and cynomolgus monkeys (up to 26, 4 and 39 weeks of treatment, respectively) identified the pancreas, liver, hematopoietic system, adrenal and gastro-intestinal tract as potential target tissues.

Fetal malformations and increased visceral and skeletal variants were observed in the rat embryo-fetal development study. There was no evidence of effects on reproductive function in the fertility study; however there was a slight effect on male sperm motility and/or sperm count in individual animals. Phototoxic potential was identified in the phototoxicity (*in vitro* and *in vivo*) assessment.

Please refer to the latest [Asciminib Investigator's Brochure] for more details.

Non-clinical pharmacokinetics and metabolism

The preclinical pharmacokinetic profile of asciminib has been investigated in three species: mouse, rat and dog. In these species, asciminib exhibited low to moderate clearance, a moderate volume of distribution and a short apparent terminal half-life. Bioavailability was found to be low in rodents and moderate to high in dog.

Asciminib displayed high plasma protein binding across all tested species (2-6% free fraction).

The metabolite profile of asciminib has been examined in vitro using rat, dog, monkey and human hepatocytes. Interspecies differences were observed in the *in vitro* metabolism of asciminib in hepatocytes, with direct glucuronidation occurred more readily in human, to a lesser extend in dog and monkey, and was noticeably absent in rat. However, no unique, major metabolites were identified in human hepatocytes. The overall metabolic turnover was low.

The metabolite profile of asciminib has also been examined *in vivo* in rats. Following intravenous and oral administration of [^{14}C-asciminib] to intact rats, asciminib was found to be the predominant component of plasma, accounting for ~86 - 91% of radioactivity from 0 - 8 h. Asciminib was excreted primarily in the feces, with ~90% of radioactivity detected in the feces from 0 - 48 h. Renal elimination represented a minor route, with ~2.4% of radioactivity detected in the urine from 0 - 72 h. In the feces, ~58% (intravenous) and ~71% (oral) of the dose was associated with unchanged asciminib, with several oxidative metabolites accounting for the remaining radioactivity. The metabolites formed *in vivo* were consistent with those observed *in vitro*. Similar observations were noted in bile-duct cannulated rats.

To assess for potential drug-drug interactions (DDI), studies have been conducted with cytochrome P450 (CYP) enzymes and several transporters *in vitro*.

In human liver microsomes, the major metabolic route of asciminib was found to be glucuronidation, followed by oxidative metabolism, consistent with findings from human hepatocytes. Several Uridin diPhospho-glucuronosyltransferase (UGT) enzymes were found to be capable of asciminib glucuronidation (UGT1A3, UGT1A4, UGT2B7, and UGT2B17). The oxidative metabolism of asciminib was also catalyzed by several CYP enzymes. CYP3A4/5 appears to contribute the most, followed by CYP2C8, CYP4F12, and potentially CYP2D6.

[redacted]

Though the DDI risk with inhibitors of these enzymes is likely to be minimal, inhibitors of CYP3A4/5 still have the potential to increase asciminib concentration. Therefore, strong inhibitors of CYP3A4/5 should be avoided and are prohibited in this study. Strong inducers of CYP3A4/5 have the potential to reduce asciminib concentrations. Therefore, the use of strong inducers of CYP3A4/5 or UGT1A/2B is prohibited in this trial.

In recombinant cellular expression systems, asciminib was identified as a substrate of Breast Cancer Resistant Protein (BCRP) (Michaelis-Menten constant (Km) ≈ 4 µM) and permeability glycoprotein (P-gp) (Km could not be estimated due to insufficient saturation of efflux activity). Late fecal metabolite analysis in the human Absorption, Distribution, Metabolism, and Excretion (ADME) study [CABL001A2102] and estimated contributions of different enzyme pathways (CYP vs. UGT) by use of in vitro enzyme phenotyping methods, do suggests that at least 24% of the parent drug in the feces is due to conversion of a glucuronide (M30.5) metabolite back to parent drug (absorption then being maximally 57%). However, this late fecal metabolite analysis could also suggest that the 24% could be active secretion by P-gp (Drug Metabolism and Pharmacokinetics [DMPK R1700912]. This is a small percentage (< 25% of the clearance by this pathway) with a weak expected impact on asciminib concentrations. Overall, inhibitors of BCRP and P-gp may increase asciminib concentration. Therefore, BCRP and P-gp inhibitors should be administered with caution.

Based on *in vitro* phenotyping studies and human ADME study outcome, the physiologically based pharmacokinetic (PBPK) model was updated and predicted minimal to no DDI for sensitive substrates of CYP3A4, CYP2C8 and CYP2C9 (Drug Metabolism and Pharmacokinetics [DMPK-DDI-R1700912]. Indeed, the effect of asciminib 40 mg BID is expected to result in increased area under the curve (AUC) of CYP3A4, CYP2C8 and CYP2C9 probe substrate by 1.21, 1.09 and 1.07. Therefore, the effect of asciminib is expected to be weak and hence substrates of CYP2C8, CYP2C9 and CYP3A4 with narrow therapeutic index (NTI) would be used with caution.

Please refer to the latest [Asciminib Investigator's Brochure] version for more details.

1.2.1.2 Clinical experience

Asciminib is undergoing evaluation in a first-in-human (FIH) phase I clinical study, study [CABL001X2101].

This study evaluates patients with 1) CML who have been treated with at least 2 prior TKIs, or 2) who have the T315I mutation and have been treated with at least 1 prior TKI, or 3) who have Acute Lymphoblastic Leukemia (ALL) and have been treated with at least 1 prior TKI. The study evaluates administration of asciminib in a BID single agent dosing schedule, as well as in a QD single agent schedule, and in combination with nilotinib, imatinib, and dasatinib. In the present document, discussion will focus on data from CML patients treated with asciminib BID single agent only.

As of 01-Sep-2017, a total of 239 CML or Ph+ ALL patients have been treated with either single agent oral asciminib or in combination cohorts. 150 CML patients have been treated with asciminib monotherapy. Based on the preliminary efficacy, safety and tolerability in patients with CML-CP or CML-AP treated with asciminib as a single agent on a BID schedule in study [CABL001X2101] and the results of a population PK/PD exposure-response model, the

[redacted]

dose of 40 mg BID has been selected as the recommended dose to be used in future studies in patients with CML-CP who do not harbor T315I mutations.

Efficacy:

Preliminary data from the ongoing Phase I FIH study [CABL001X2101] indicate that asciminib exhibits single-agent activity in patients with CML who have failed at least two prior TKIs or are intolerant to TKIs, as demonstrated by major molecular response and reduction in the BCR-ABL1 % IS. Asciminib has demonstrated anti-tumor activity at doses greater or equal to 10 mg BID as well as daily higher doses.

To date, efficacy data in 141 patients with chronic-phase CML treated with single agent asciminib therapy (10-200 mg BID and 80-200 mg QD) are available (113 patients without T315I mutation and 28 with T315I mutation).

Of the 62 patients with BCR-ABL1 no greater than 10 % IS at screening and without T315I mutation, 1-log reduction of BCRABL1 % IS was achieved in 16 of 62 (25.8%) patients by 6 months and 19 of 62 (30.6%) patients by 12 months. For asciminib 40 mg BID dose, of the 17 patients studied, 1-log reduction of BCRABL1 % IS was achieved in 5 of 17 (29.4%) patients by 6 months, and 12 months.

Please refer to the latest [Asciminib Investigator's Brochure] for more details.

Safety:

Asciminib was generally well tolerated in heavily pre-treated CML patients resistant to or intolerant of prior TKIs. All 239 patients were evaluable for safety. Seventy six study discontinuations have been reported; the most frequent reason for discontinuation was progressive disease, reported in 38 patients (15.9%). Adverse events leading to treatment discontinuation were reported in 15 patients (6.3%). Death leading to treatment discontinuation was reported in 3 patients (1.3%) (one patient in asciminib 20 mg BID due to aspiration pneumonia after bypass procedure and two patients with ALL with 80 mg and 160 mg BID due to progressive disease).

Among the 150 patients treated with asciminib monotherapy, almost all (94.7%) patients reported at least one AE, including 49.3% reported grade 3/4 AEs. The most common AEs (> 10%) among patients treated with 40 mg BID (n=35), regardless of study drug-relationship, were increased lipase, fatigue, diarrhea, thrombocytopenia, neutropenia, arthralgia, rash, headache, increased amylase, nausea, vomiting, abdominal pain, pyrexia, upper respiratory tract infection, back pain, hypertension, cough, pruritus, pain in extremity, dyspnea, bone pain, peripheral oedema, non-cardiac chest pain and insomnia. The most common reported grade 3/4 event was increased lipase (17.1%).

Forty-seven of 150 patients with CML-CP or CML-AP treated with asciminib single agent (31.3%) were reported with serious adverse events (SAE).

Electrocardiogram (ECG) data shows no reported QT prolongation (increase > 60 msec or new > 500 msec) in 40 mg BID asciminib monotherapy group. There was no reports of QT prolongation (increase > 60 msec) and two reports of new >500 msec (one each in 80 mg QD and 120 mg QD) among all asciminib monotherapy group.

[redacted]

Please refer to the latest [Asciminib Investigator's Brochure] for more details.

Pharmacokinetics:

PK data from 190 patients were available from the [CABL001X2101] study, as of 01-Sep-2017. When given as a single agent on a twice daily schedule, patients received escalating doses of asciminib ranging from 10 to 200 mg.

Based on the available PK data, asciminib, administered orally is rapidly absorbed with a median time to maximum plasma concentration (Tmax) of 2 to 3 hours, independent of dose. Systemic exposure of asciminib, following oral administration of single and multiple doses, as measured by Cmax and AUC, increased in an approximately dose proportional manner. The variability of exposure is low to moderate with inter-patient variability (geometric mean CV %) ranging from approximately 25 to 70% for both Cmax and AUClast. With the twice daily dosing regimen, median plasma asciminib accumulation ratios ranged from 1.3 to 2.5. The median accumulation half-life was estimated to be 7 to 15 hours.

The data of the hADME study [CABL001A2102] show that the relative contribution of the glucuronidation pathway to the total clearance of asciminib via metabolism is estimated to range from 30% to 61%, whereas the relative contribution of the oxidative pathway is estimated to range from 35% to 63%. CYP3A4 was the main contributor for the clearance of asciminib via the oxidative pathway while UGT2B7 and UGT2B17 were responsible for the clearance of asciminib via the glucuronidation pathway. There was no metabolite detected with mean contribution to plasma radioactivity AUC0-24hours ≥ 10%. Asciminib was the predominant drug-related component in plasma at all time points analyzed, ranging from 91.9 to 94.2% of the total radioactivity AUC0-24 hours AUC, with an average value of 92.7%.

Please refer to the latest [Asciminib Investigator's Brochure] for more details.

Exposure-response relationship:

Exposure-efficacy

A preliminary population PKPD model has been developed using data from the [CABL001X2101] study (cut-off 02-May-2016). The time course of molecular response (change in BCR-ABL1 ratio % IS levels from baseline) was described using a semi-physiological model accounting for cell maturation, disease progression and existing resistance.

Simulations performed using an asciminib population PK model revealed that a dose of 40 mg BID maintains Ctroughs above the clinical (0.07 to 61 ng/mL) threshold in ≥95% of chronic phase CML patients without T315I mutation having failed ≥ 2 TKI or intolerant to TKIs. The estimates from this clinical study were found to be similar to the threshold trough concentration required for 90% inhibition of pSTAT5 derived from a preclinical PK-PD KCL-22 mouse xenograft model (free IC90: 30 to 121 ng/mL, after correction for protein binding) and *in vitro* gIC50 assessed in the KCL-22 cell line (1 ng/mL = 2.1 nM after correction for protein binding).

Simulations performed using asciminib population PKPD model revealed that chronic phase CML patients having failed ≥ 2 TKI or intolerant to TKIs are likely to exhibit a 1 log10 reduction of (%) BCR-ABL1 mRNA transcript levels from baseline of ~33% (CI95%: 24-42%) at 6 months, and ~42% (CI95%: 32-52%) at 12 months at a dose of 20 mg BID and ~41%

[redacted]

(CI95%: 31-51%) at 6 months, and ~53% (CI95%: 43-63%) at 12 months at a dose of 40 mg BID.

Additional preliminary exposure response analyses (i.e. exploring the relationship between PK and both safety and efficacy) support the selected dose.

Food effect

The effect of food on asciminib PK was characterized in a Phase I study [CABL001A2101] in healthy volunteers. Food was found to influence the pharmacokinetics of asciminib. When administered with a low-fat meal, the exposure (AUC) decreased by approximately 30%. The overall exposure decreased by approximately 65% when administered with a high-fat meal. Therefore, asciminib will be administered in a fasted state.

1.2.2 Overview of bosutinib

Bosutinib (Bosulif®) is indicated for the treatment of adult patients with newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) and for the treatment of patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy (500 mg QD) [Bosulif® USPI] as well as for newly-diagnosed CML-CP (400 mg QD), and in Europe for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options [EU Summary of Product Characteristics (SmPC)]. Bosutinib has been evaluated in patients treated with one or more prior TKIs.

For patients treated with bosutinib after prior imatinib only, the MMR rate is approximately 15% at 24 weeks overall, and approximately 10% in imatinib-resistant patients and 20% in imatinib-intolerant patients (Gambacorti-Passerini 2014). The cytogenetic, molecular, and hematological response rates did not appear to differ greatly between patients who were imatinib-resistant or imatinib-intolerant (Gambacorti-Passerini 2014).

Twenty seven percent of patients treated with bosutinib after at least 2 previous TKIs achieved MCyR rate by Week 24 [Bosulif® USPI]. For patients previously treated with imatinib and either dasatinib or nilotinib, after a median of 28.5 months follow-up, the cumulative rate of Major Molecular Response (MMR) is 15% (Khoury 2012). The cytogenetic, molecular, and hematological response rates appeared to be lower in patients who were resistant to dasatinib after imatinib treatment as compared to patients who were intolerant to dasatinib after imatinib treatment (Khoury 2012). In a small (30 patient) compassionate use trial of patients previously treated with imatinib, dasatinib and nilotinib, after a median duration of treatment of 9.3 months, the cumulative MMR rate was 14% (García-Gutiérrez 2015). Based on these data, the MMR rate at 6 month with bosutinib treatment in patients treated with at least 2 prior TKIs is estimated to be approximately 10-15%.

Bosutinib has no activity against the T315I and V299L mutant form of BCR-ABL1. Accordingly, the pivotal trial leading to the registration in the 3rd line setting excluded patients with a known history of the T315I or V299L mutation [Bosulif® USPI].

[redacted]

2 Rationale

2.1 Study rationale and purpose

Asciminib is an agent intended to be evaluated for the treatment of patients with CML. In the ongoing study [CABL001X2101] study, asciminib was found to produce clinically meaningful and durable responses in patients who have had treatment failure after a minimum of 2 prior ATP-binding site TKIs, with an acceptable safety and tolerability profile.

The purpose of this pivotal study is to compare the efficacy of asciminib with that of bosutinib in the treatment of patients with CML-CP having previously been treated with a minimum of two prior ATP-binding site TKIs. Patients with intolerance to most recent TKI therapy must have BCR-ABL1 ratio > 0.1% IS at screening and patients experiencing failure to most recent therapy must meet the definition of treatment failure as per the 2013 ELN guidelines (Baccarani et al 2013).

Imatinib, nilotinib and dasatinib are indicated for the treatment of patients with newly diagnosed CML. Multiple agents, including nilotinib, dasatinib, ponatinib, bosutinib, radotinib (Korea) and omacetaxine (USA, Canada) are approved for patients with CML-CP previously treated with prior therapy. Imatinib is a first generation TKI; nilotinib, dasatinib, bosutinib, ponatinib and radotinib are considered second generation TKIs and have activity in patients previously treated with imatinib. The activity of nilotinib or dasatinib in patients previously treated with a second generation TKI is not known. All the currently approved BCR-ABL1 TKIs are enzymatic site inhibitors, in distinction to asciminib which is an allosteric TKI. Omacetaxine is a cytotoxic chemotherapeutic agent.

2.2 Rationale for the study design

Asciminib is an orally bioavailable specific BCR-ABL1 inhibitor with a novel mechanism of action. In contrast to other TKIs that bind within the ATP-binding site of the ABL kinase domain, asciminib inhibits ABL tyrosine kinase activity by binding to a particular allosteric site on the kinase domain that is utilized by a myristate group to auto-regulate the native ABL1 kinase. With allosteric inhibition of BCR-ABL1 being a novel mechanism of action, asciminib produces clinically meaningful and durable responses in patients who have had treatment failure after a minimum of 2 prior ATP-binding site TKIs, with an acceptable safety and tolerability profile as demonstrated in study [CABL001X2101].

The development of asciminib, presents an opportunity to evaluate the beneficial effects of inhibition of BCR-ABL1 in the treatment of patients with CML. The proposed study design is expected to adequately allow an assessment of the efficacy, safety and tolerability of asciminib in a population of patients with continuing medical need i.e., patients who have been treated with at least two prior TKIs and are in the need for further therapeutic intervention.

Bosutinib is one of the TKIs with proven clinical benefit in CP-CML patients previously treated with one or more tyrosine kinase inhibitor(s) and is currently approved for this indication in many countries, including the European Union. The proposed study will evaluate asciminib in comparison to bosutinib at the approved doses in the targeted population.

[redacted]

This study is not being conducted as a blinded study; the conditions for drug administration being distinct for the two treatments arms makes blinding complex and increases the likelihood of dosing errors. Bosutinib needs to be taken with food, whereas asciminib needs to be taken fasted. The difference in administration of the two treatments, requiring double dummy treatments, makes blinding difficult to put in place in practice and carries inherent risks of dosing errors and reduces patient compliance. Additionally, the characteristic adverse event profile of bosutinib (frequent gastrointestinal AEs of diarrhea and vomiting in 78.5% and 37.1% patients, respectively) further preclude effective blinding. Randomization and use of objective efficacy endpoints mitigate the risks of an open label study design.

The study design incorporates a 2:1 randomization, allocating more patients to the asciminib arm in order to learn more about the safety profile of the experimental therapy, whereas the safety of bosutinib therapy is well documented.

Patients randomized to the bosutinib arm who have documented treatment failure as defined by the 2013 ELN Guidelines at any time point will have the option to receive asciminib at the investigator's discretion and if it is in the patient's best interest. The purpose of the option to switch to asciminib is to provide this investigational treatment option to eligible patients who will have limited available therapeutic options outside of the study.

Treatment duration for each patient in the present study is up to 96 weeks after the last patient received the first dose in the study (which should be an adequate timeframe to address both the primary objective of the study, i.e. determination of the MMR rate at 24 weeks, as well as the secondary efficacy and safety objectives) or up to 48 weeks after the last bosutinib failure patient has switched to asciminib during the treatment period, whichever is longer unless the patient discontinues treatment earlier. Blood samples will be taken in this study from all patients randomized to asciminib in order to describe the pharmacokinetics and possibly identify the sources of variabilities. Exploratory analysis may be performed to establish the relationship between exposure and efficacy or safety.

2.2.1 Rationale for Biomarker Assessment

The primary goal of the biomarker assessments for this study is to evaluate potential mechanisms of resistance to asciminib.

Exploratory endpoints involving biomarker assessments for patients treated with asciminib, in comparison to those treated with bosutinib, will focus on 1) the PK/PD relationship; 2) BCR-ABL1 gene mutations that could influence the outcome of treatment regimens; and 3) the underlying biology of CML.

In order to evaluate tumor kinetics on a molecular level and to explore the role of mutations with respect to response to treatment, exploratory endpoints include assessment of mutations in the BCR-ABL1 gene at Week 1 Day 1, upon confirmed loss of molecular response and/or at end of treatment. Mutational status will be characterized in peripheral blood.

[redacted]

[redacted]

2.3 Rationale for dose and regimen selection

The dose and regimen of asciminib selected for this study is 40 mg BID. This dose is supported by pharmacokinetic, efficacy and safety data available from the ongoing [CABL001X2101] study.

During escalating doses of asciminib 10 mg to 200 mg on a continuous BID schedule in study [CABL001X2101], the 40 mg BID dose was shown to be active and well tolerated in CML-CP patients.

With respect to efficacy, no clear evidence of dose-response relationship was observed across dose levels when considering Complete Cytogenetic Response (CCyR) or MMR. However, as described below, PK-PD population modeling using change from baseline of BCR-ABL1 mRNA levels as a PD endpoint suggest a higher probability of achieving ≥1 log reduction at 6 and 12 months with 40 mg BID versus 20 mg BID.

With respect to safety, although no MTD (maximum tolerated dose) has been formally characterized, there is an increased toxicity observed at doses ≥ 80 mg BID (pancreatitis occurred at the dose of 80 mg in two patients who had an intra-patient escalation to 80 mg from 40 mg, and in one patient at the dose of 150 mg BID). Generally there is a trend for higher rates of discontinuation due to AE, DLT (dose limiting toxicity) and grade 3/4 AE with increasing doses.

With respect to overall exposure, the dose of 40 mg BID is expected to result in concentrations consistently above IC90 *in vitro* concentrations. The estimates from study [CABL001X2101] were found to be above the threshold trough concentration required for 90% inhibition of pSTAT5 derived from a preclinical PK-PD KCL-22 mouse xenograft model (free IC90: 30 to 121 ng/mL, after correction for protein binding) and *in vitro* gIC50 assessed in the KCL-22 cell line (1 ng/mL = 2.1 nM after correction for protein binding).

A preliminary population PK-PD model has been developed using data from the [CABL001X2101] study (cut-off 2 May 2016). The time course of molecular response (change in BCR-ABL1 ratio % IS levels from baseline) was described using a semi-physiological model accounting for cell maturation, disease progression and existing resistance. Simulations performed (with 100 patients) using asciminib population PK-PD model revealed that at a dose of 40 mg BID, ~41% (CI95%: 31-51%) of chronic phase CML patients having failed ≥ 2 TKI or intolerant to TKIs are likely to exhibit a 1 log10 reduction of (%) BCR-ABL1 mRNA transcript levels from baseline at 6 months, and 53% (CI95%: 43-63%) at 12 months, and predicting higher probability of achieving BCR-ABL1 mRNA ≥ 1 log reduction at 6 and 12 months with 40 mg BID versus 20 mg BID.

[redacted]

Additional preliminary PK-efficacy and PK-safety analyses to assess the exposure-response relationship for asciminib were conducted (Section 1.2.1.2). The efficacy measure used was Molecular Response (MR) which is defined as a decline in BCR-ABL1 transcript levels in clinical blood samples of patients with Chronic Myeloid Leukemia (CML). MR was evaluated as both a continuous variable (BCR-ABL1 transcript levels) and categorical variable (whether or not adequate decline in BCR-ABL1 was achieved). The safety measures used were occurrence of Common Toxicity Criteria (CTC) grade 2, 3 or 4 laboratory values for lipase and amylase.

Reviewing the totality of the efficacy, safety, and pharmacokinetic data derived from the [CABL001X2101] study, the recommended dose for asciminib in this phase 3 study is 40 mg BID. Of note, the dose of asciminib single agent BID is further being evaluated in patients with the T315I mutation. At present the recommended dose of 40 mg BID is for patients without the T315I mutation. For this reason, patients with the T315I mutation are excluded from this study.

2.4 Rationale for choice of combination drugs

Not Applicable.

2.5 Rationale for choice of comparators drug bosutinib

The guidance provided by the NCCN and the ELN (Baccarani et al 2013), recommends bosutinib as a treatment in CML-CP patients who fail first-line or second-line treatment with imatinib or nilotinib or dasatinib. Consistent with these recommendations and clinical practice, bosutinib was selected to be an appropriate comparator in a study of 3rd line CML-CP patients after failure of at least 2 prior TKIs, and is the comparator that will be used in the present study.

It is to be noted that bosutinib has no activity against the T315I and V299L mutant form of BCR-ABL1. Patients who have the T315I or V299L mutations documented in their medical record will already be excluded from this study. Bosutinib is known to be active against E255K/V, F317L/V/I/C, F359V/C/I, T315A, and Y253H and therefore, these mutations are not considered in the exclusion criteria for the current study.

Ponatinib is not selected as the comparator in the present clinical trial, because the comparator in this study needs to be an approved agent administered at the approved dose. Currently, the ponatinib dose is being evaluated in a randomized trial as a post-approval commitment due to the occurrence of vascular risks at the current approved dose of ponatinib. The dose of ponatinib that will be approved and will be used in practice at the completion of the present study may not be the approved dose at the time of initiation of the present study.

2.6 Risks and benefits

Appropriate eligibility criteria, as well as specific dose modification and stopping rules in the event of expected toxicities, are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events are provided in Section 6.3. Patients who have failed 2 prior TKIs are at increased risk of progression to more advanced phases of CML such as CML-AP and CML-BC. Currently available therapeutic agents in this setting are non-curative and patients remain at risk of progressing after short duration of remissions (Khoury 2012).

[redacted]

An important potential risk for patients enrolling on the experimental arm of the study with asciminib will be that this agent may be ineffective. However, the evidence to date at the doses to be administered in a similar population of patients in the study [CABL001X2101] suggests that asciminib is an active agent. Further, the adverse event profile of asciminib is similar qualitatively to that observed with other TKIs targeting BCR-ABL1 (Section 1.2.1.2). The risk of asciminib not being effective has been mitigated in that patients will be observed closely for evidence of efficacy, based on assessment of hematologic, cytogenetic and molecular response data, which will permit rapid decision making as to discontinuation of therapy if necessary.

Other risks to subjects in this trial will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, and adherence to dose modification and interruption guidance provided in the protocol.

The currently available information suggests that there is equivalence between the two arms with respect to benefit / risk to enable inclusion of patients in this study.

There may be unforeseen risks with asciminib which could be serious. Refer to the latest [Asciminib Investigator's Brochure] for additional details.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To compare the MMR rate at 24 weeks of asciminib versus bosutinib	Major Molecular Response (MMR) rate at 24 weeks	Refer to Section 10.4
Key secondary		
To compare additional parameters of the efficacy of asciminib versus bosutinib	MMR rate at 96 weeks	Refer to Section 10.5.1
Other secondary		
To compare additional parameters of the efficacy of asciminib versus bosutinib	● Cytogenetic response rate (Complete, Partial, Major, Minor, Minimal, no response) at and by all scheduled data collection time points including 24, 48 and 96 weeks ● MMR rate at all scheduled data collection time points (except 24 and 96 weeks which are already covered by primary and key secondary endpoints) ● MMR rate by all scheduled data collection time points including 24, 48 and 96 weeks ● Time to MMR ● Duration of MMR ● Time to CCyR ● Duration of CCyR ● Time to treatment failure ● Progression free survival ● Overall survival	Refer to Section 10.5.2
To compare the safety and tolerability profile of asciminib versus bosutinib	Type, frequency and severity of adverse events, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG and other safety data (vital signs, physical examination)	
To characterize the PK of asciminib in the CML-CP population	Trough plasma concentrations, PK parameters in full PK group: Cmax, Tmax, AUC0-12h, CL/F	
To assess the safety of asciminib when administered as treatment after bosutinib failure according to the 2013 ELN Guidelines	Type, frequency and severity of adverse events, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG and other safety data (vital signs, physical examination)	Refer to Section 10.6

[redacted]

Objective	Endpoint	Analysis
Exploratory		
To evaluate the influence of factors such as cytogenetic response at baseline, failure/intolerance to prior TKIs, line of therapy, gender, race and age on the effect of asciminib with respect to the primary efficacy endpoint	Major Molecular Response (MMR) rate at 24 weeks	Refer to Section 10.6
To explore the exposure-response relationships of asciminib; evaluate the effect of population covariates	Exposure-safety and exposure-PD analyses	
To characterize mutations in the BCR-ABL1 gene at Week 1 Day 1, upon confirmed loss of molecular response and/or at end of treatment and examine their association with molecular and cytogenetic response for asciminib vs. bosutinib	BCR-ABL1 gene mutations at Week 1 Day 1, upon confirmed loss of molecular response and/or at end of treatment as determined by Sanger Sequencing	
[redacted]	[redacted]	
To assess clonal evolution during treatment with asciminib vs. bosutinib	Low level BCR-ABL1 mutation profiles assessed by mass spectrometry at Week 1 Day 1, upon confirmed loss of MMR and/or at EOT. Clonal evolution of several genes implicated in CML assessed by Next Generation Sequencing (NGS) methods	
[redacted]	[redacted].	
To compare the impact of treatment on patient reported outcomes (PRO) including CML-specific symptoms, patient quality of life, and impact on work productivity and activity impairment from baseline and EOT between treatment arms in all patients	Change in symptom burden and interference from baseline over time according to the MDASI-CML PRO instrument Change in patient's impression of CML symptoms according to Patient Global Impression of Change (PGIC) Change in health utility from baseline over time according to EQ-5D-5L Change in work productivity and activity impairment over time according to WPAI	
To compare the impact of treatment on health care resource utilization between treatment arms in all patients	Health care resource burden over time	
To assess the efficacy of asciminib when administered as treatment after bosutinib failure according to the 2013 ELN Guidelines	• Cytogenetic response rate (Complete, Partial, Major, Minor, Minimal, no response) at and by all scheduled data collection time points • MMR rate at and by all scheduled data collection time points	Refer to Section 10.6

[redacted]

Objective	Endpoint	Analysis
	• Time to MMR • Duration of MMR • Time to CCyR • Duration of CCyR • Time to treatment failure	

[redacted]

4 Study design

4.1 Description of study design

The study is a phase 3, multi-center, open-label randomized study of oral asciminib versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors.

The trial is designed to compare the efficacy and safety of asciminib with that of bosutinib in the treatment of patients with CML-CP having previously been treated with a minimum of two prior ATP-binding site TKIs. Patients intolerant to the most recent TKI therapy must have BCR-ABL1 ratio > 0.1% IS at screening and patients failing their most recent TKI therapy must meet the definition of treatment failure as per the 2013 ELN guidelines (Baccarani et al 2013). No more than 66 patients (approximately 30% of the overall trial population) that are intolerant to their most recent TKI therapy with BCR-ABL1 < 1% will be recruited in order to ensure that the CML third line patient population is adequately represented.

The study will also investigate secondary endpoints for efficacy, safety and PK of single-agent asciminib compared to bosutinib. Tolerability, PK, PRO and exploratory biomarker activities will also be assessed. Safety and efficacy data for patients switching to asciminib will be collected and analyzed separately.

Patients meeting all of the inclusion and none of the exclusion criteria will be randomized into one of the 2 treatment arms, based on a 2:1 randomization between the asciminib arm and the bosutinib arm.

The randomization will be stratified to ensure the study population is balanced between the arms with respect to cytogenetic response status (See Section 7.2.1.2) at screening as follows:

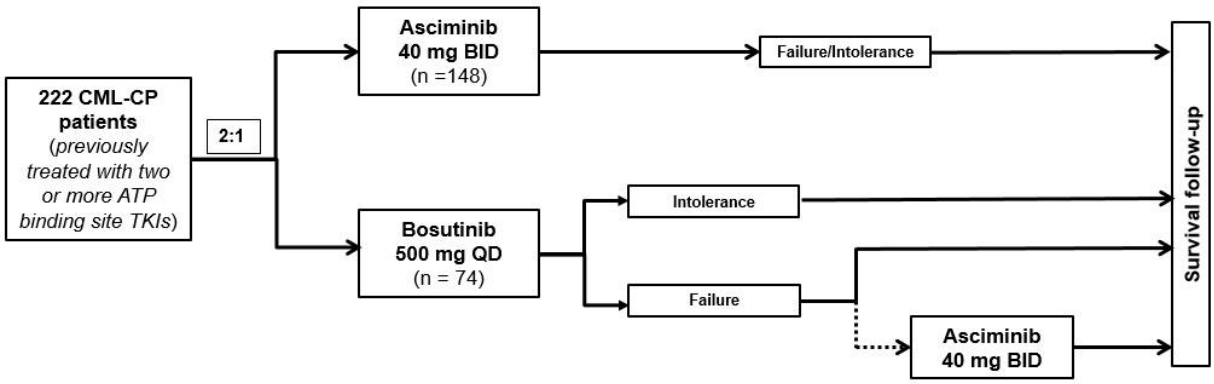
- Major cytogenetic response (complete or partial)
- No major cytogenetic response (minor, minimal or none)

Patients will continue to receive the assigned study treatments (asciminib or bosutinib) until the end of study treatment period as defined in Section 4.3. Patients who discontinue their study treatment at any time during the study will be followed up for survival and for progression to AP/BC for up to 5 years from the date the last randomized patient receives the first dose (irrespective of treatment switch for patients failing bosutinib).

Serial PK samples over 12 hours will be collected on Week 2 Day 1 from at least 20 CML-CP patients (full PK group) on the asciminib arm, in addition to trough PK samples. These patients will be identified sequentially at selected sites that are capable of serial PK sampling over 12 hours. In the remaining patients in the asciminib arm and in patients that have switched to asciminib, sparse post-dose PK samples on Week 1 Day 1 and trough PK samples will be collected (sparse PK group).

[redacted]

Figure 4-1 Schematic of Study Design



4.1.1 Study treatment switch from bosutinib to asciminib

Patients with documented treatment failure (as per the 2013 ELN guidelines; Baccarani et al 2013) while on bosutinib treatment will have the option to switch to asciminib treatment within 96 weeks after the last patient has been randomized on study. The patients who switch to asciminib will be able to receive asciminib up to end of study treatment period. At the end of the treatment period for patients who, in the opinion of the investigator still derive clinical benefit, asciminib treatment will be made available through alternative options including, but not limited to, an expanded access/compassionate use/managed access program or access to commercial supplies in applicable countries. Discontinuation of asciminib for patients who have switched over from bosutinib must follow the guidelines provided in Section 7.1.6. Eligibility criteria for patients switching to asciminib are described in Section 7.1.

4.2 Timing of interim analyses and design adaptations

Not applicable. There are no formal interim analyses or design adaptations planned for this study. See Section 8.6 for documentation of safety DMC.

4.3 Definition of end of study

The patients are treated in the study up to end of study treatment period defined as up to 96 weeks after the last patient receives the first dose or up to 48 weeks after the last patient has switched to asciminib treatment whichever is longer unless patients have discontinued treatment earlier. The end of the study, concluding the survival follow-up, will occur 5 years from the date when the last patient enrolled into the study receives the first dose of the randomized treatment.

The primary analysis (cut-off date) is defined as the date when all randomized patients have been on study treatment for 24 weeks (Section 10.4) or discontinued earlier. Subsequent to this

analysis, the primary clinical study report (CSR) will be developed. Following the cut-off date for the primary CSR, the study will remain open. Patients who are ongoing at the time of the primary analysis will continue to receive the assigned study treatments (asciminib or bosutinib) during the study treatment period as defined above. The end of study treatment analysis will be conducted with a cut-off date 30 days after the end of study treatment period to ensure all available treatment data from all patients in the study is analyzed and summarized in a CSR.

After the end of the study treatment period the assigned study treatment will be made available to patients who in the opinion of the Investigators are still deriving clinical benefit. This may be outside of this study through alternative options including, but not limited to, an expanded access/compassionate use /managed access program or access to commercial supplies in applicable countries.

Patients will be followed for survival and progression for up to 5 years from the date the last randomized patient receives the first study dose (irrespective of treatment switch for patients failing bosutinib). Information on subsequent treatments will also be collected. An updated analysis of OS and PFS will be performed at the end of the follow-up period in the final study CSR.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be contacted as soon as possible and instructed to stop taking study medication. The end of treatment visit should be scheduled and the same assessments should be performed as described in Section 7 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

Two-hundred and twenty-two (222) patients with CML-CP who had prior treatment with two or more ATP binding site TKIs will be randomized in a 2:1 fashion to receive either asciminib or bosutinib. No patients with a medical history of the T315I or V299L mutation at study entry will be included in the trial. Previous medical records should be used to confirm the patient's mutational status/history.

The definition of CML-CP will be according to the European Leukemia Network (ELN) criteria (Baccarani et al 2013), and is outlined below in the inclusion criteria.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Male or female patients with a diagnosis of CML-CP ≥ 18 years of age

[redacted]

2. Patients must meet all of the following laboratory values at the screening visit:
   - < 15% blasts in peripheral blood and bone marrow
   - < 30% blasts plus promyelocytes in peripheral blood and bone marrow
   - < 20% basophils in the peripheral blood
   - ≥ 50 x 10^9/L (≥ 50,000/mm^3) platelets
   - Transient prior therapy related thrombocytopenia (< 50,000/mm^3 for ≤ 30 days prior to screening) is acceptable
   - No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly

3a. BCR-ABL1 ratio > 0.1% IS according to central laboratory at the screening examination, for patients intolerant to the most recent TKI therapy

4. Prior treatment with a minimum of 2 prior ATP-binding site TKIs (i.e. imatinib, nilotinib, dasatinib, radotinib or ponatinib)
5. Failure (adapted from the 2013 ELN Guidelines; Baccarani et al 2013) or intolerance to the most recent TKI therapy at the time of screening
   - Failure is defined for CML-CP patients (CP at the time of initiation of last therapy) as follows. Patients must meet at least 1 of the following criteria.
     - Three months after the initiation of therapy: No CHR or > 95% Ph+ metaphases
     - Six months after the initiation of therapy: BCR-ABL1 ratio > 10% IS and/or > 65% Ph+ metaphases
     - Twelve months after initiation of therapy: BCR-ABL1 ratio > 10% IS and/or > 35% Ph+ metaphases
     - At any time after the initiation of therapy, loss of CHR, CCyR or PCyR
     - At any time after the initiation of therapy, the development of new BCR-ABL1 mutations which potentially cause resistance to current treatment
     - At any time after the initiation of therapy, confirmed loss of MMR in 2 consecutive tests, of which one must have a BCR-ABL1 ratio ≥ 1% IS
     - At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cells: CCA/Ph+
   - Intolerance is defined as:
     - Non-hematologic intolerance: Patients with grade 3 or 4 toxicity while on therapy, or with persistent grade 2 toxicity, unresponsive to optimal management, including dose adjustments (unless dose reduction is not considered in the best interest of the patient if response is already suboptimal)
     - Hematologic intolerance: Patients with grade 3 or 4 toxicity (absolute neutrophil count [ANC] or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by manufacturer
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2
7. Adequate end organ function as defined by (as per central laboratory tests):
   - Total bilirubin ≤ 1.5 x ULN except for patients with Gilbert's syndrome who may only be included if total bilirubin ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN

[redacted]

- Aspartate transaminase (AST) ≤ 3.0 x ULN
- Alanine transaminase (ALT) ≤ 3.0 x ULN
- Serum lipase ≤ 1.5 x ULN. For serum lipase > ULN - ≤ 1.5 x ULN, value must be considered not clinically significant and not associated with risk factors for acute pancreatitis
- Alkaline phosphatase ≤ 2.5 x ULN
- Creatinine clearance ≥ 50 mL/min as calculated using Cockcroft-Gault formula

8. Patients must avoid consumption of grapefruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.
9. Written informed consent obtained prior to any screening procedures.

10a. Patients must have the following electrolyte values (as per central laboratory tests) within normal limits or corrected to be within normal limits with supplements prior to first dose of study medication:

- Potassium (potassium increase of up to 6.0 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits)
- Total calcium (corrected for serum albumin); (calcium increase of up to 12.5 mg/dl or 3.1 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits)
- Magnesium, with the exception of magnesium increase > ULN – 3.0 mg/dL; > ULN - 1.23 mmol/L associated with creatinine clearance (calculated using Cockcroft-Gault formula) within normal limits.

11. Evidence of typical BCR-ABL1 transcript [e14a2 and/or e13a2] at the time of screening which are amenable to standardized RQ-PCR quantification.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Known presence of the T315I or V299L mutation at any time prior to study entry
2. Known second chronic phase of CML after previous progression to AP/BC
3. Previous treatment with a hematopoietic stem-cell transplantation
4. Patient planning to undergo allogeneic hematopoietic stem cell transplantation
5. Cardiac or cardiac repolarization abnormality, including any of the following:
   - History within 6 months prior to starting study treatment of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG)
   - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)
   - QTcF at screening ≥450 msec (male patients), ≥460 msec (female patients)
   - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:

[redacted]

- Risk factors for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
- Concomitant medication(s) with a "Known risk of Torsades de Pointes" per wwwcrediblemeds.org/ that cannot be discontinued or replaced 7 days prior to starting study drug by safe alternative medication.
- Inability to determine the QTcF interval

6. Severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol (e.g. uncontrolled diabetes, active or uncontrolled infection, pulmonary hypertension)
7. History of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis
9. History of acute or chronic liver disease
10. Known presence of significant congenital or acquired bleeding disorder unrelated to cancer
11. History of other active malignancy within 3 years prior to study entry with the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively
12. Known history of Human Immunodeficiency Virus (HIV), chronic Hepatitis B (HBV), or chronic Hepatitis C (HCV) infection. Testing for Hepatitis B surface antigen (HBs Ag) and Hepatitis B core antibody (HBcAb / anti HBc) will be performed at screening
13. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or gastric bypass surgery)

14a. Treatment with medications that meet one of the following criteria and that cannot be discontinued at least one week prior to the start of treatment with study treatment

- Moderate or strong inducers of CYP3A
- Moderate or strong inhibitors of CYP3A

15. Previous treatment with or known/ suspected hypersensitivity to asciminib or any of its excipients.
16. Previous treatment with or known/ suspected hypersensitivity to bosutinib or any of its excipients.
17. Participation in a prior investigational study within 30 days prior to randomization or within 5 half-lives of the investigational product, whichever is longer
18. Pregnant or nursing (lactating) women

19a. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 days after last dose of asciminib and one month after last dose of bosutinib. Highly effective contraception methods include:

[redacted]

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy) total hysterectomy or bilateral tubal ligation at least six weeks before taking study treatment). In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking study medication. In the case of oophorectomy alone, women are considered post-menopausal and not of child bearing potential only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

6 Treatment

6.1 Study treatment

The investigational treatments for this study are asciminib (40 mg BID) and bosutinib (500 mg QD). Novartis will supply asciminib to the investigational site as 20 mg and 40 mg tablets. Bosutinib will be supplied to the investigational site as 100 mg and 500 mg tablets.

6.1.1 Dosing regimen

Asciminib

Asciminib 20 or 40 mg strength tablets will be administered orally twice-daily (BID), without food. Asciminib tablets should be ingested as follows:

- Asciminib should be administered in the fasted state: avoid food for at least 2 hours before the dose is taken and for at least 1 hour after the dose is taken. Water is permitted during this period.
- Asciminib should be taken with approximately 8 ounces (240 mL) of water.
- Asciminib should be swallowed whole and not chewed or crushed.
- If vomiting occurs within the first hour after taking the drug, re-dosing is allowed before the next scheduled dose

[redacted]

- If the patient does not take asciminib within 6 hours after the approximate time of the usual dosing time, that dose should be skipped and treatment should continue with the next daily dose at the prescribed level

Bosutinib

Bosutinib 500 mg or 100 mg tablets will be administered orally once daily (QD) with food. If a dose is missed beyond 12 hours, the patient should skip the dose and take the usual dose on the following day.

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen	Fasting Condition
Asciminib	Tablet for oral use	20 mg[a]	Twice-daily	Fasting
Asciminib	Tablet for oral use	40 mg	Twice-daily	Fasting
Bosutinib	Tablet for oral use	100 mg[b]	Once-daily	Non-fasting
Bosutinib	Tablet for oral use	500 mg	Once-daily	Non-fasting

[a] 20 mg tablets will be dispensed to patients in the instance of dose reduction.
[b] 100 mg tablets will be dispensed to patients in the instance of dose modifications.

On days when serial blood samples are collected for asciminib PK analysis, patients will be instructed to bring their drug supply to the site, and take the dose in the clinic, under supervision of the site personnel. The exact time for dose administration and meal intake must be recorded in the electronic Case Report Form (eCRF).

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.1.2 Ancillary treatments

Not applicable.

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

Not applicable. See Section 6.3.

6.1.5 Treatment duration

There is no fixed duration of treatment planned per patient. The patients are treated in the study up to end of study treatment period defined as up to 96 weeks after the last patient receives the first dose or up to 48 weeks after the last patient has switched to asciminib treatment whichever is longer unless patients have discontinued treatment earlier. Patients may be discontinued from treatment with the study drug at any time due to unacceptable toxicity, disease progression and/or at the discretion of the investigator or the patient.

[redacted]

6.2 Dose escalation guidelines

Dose escalation beyond the standard doses of 40 mg BID for asciminib is not permitted.

Dose escalation above 500 mg QD for bosutinib is permitted in this study. Bosutinib escalation guidelines are as follows:

Consider dose escalation to 600 mg once daily in patients who are currently taking 500 mg daily, did not have Grade 3 or higher adverse events and who:

- Did not reach complete hematological response (CHR) by week 8
- Did not reach complete cytogenetic response (CCyR) by week 12

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to allow the patient to continue the study treatment.

These dose modifications are summarized in Table 6-2. The dose reduction indicated as "recommendations" are provided to assist investigators in the event the patient experiences toxicity. However, deviations from "mandatory" dose interruptions and/or reductions are not allowed and mandatory interruptions or reductions must be strictly followed. Re-escalation to asciminib 40 mg BID is permitted if a change in the patient's individual benefit/risk assessment at the lower dose level is seen. Re-escalation will be allowed only once for any given patient on the asciminib arm per protocol. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-2. Any dose changes must be recorded on the Dosage Administration Record eCRF.

A patient must discontinue treatment with either asciminib or bosutinib if, after treatment is resumed at a lower dose level, the toxicity recurs with the same or worse severity, except for recurrence of cytopenias (Table 6-2). If a patient requires a dose interruption of > 28 days for each non-hematologic toxicity, then the patient must be discontinued from the study treatment. If a hematologic toxicity (cytopenia Grade 3 or 4) lasts for more than 42 days without recovery to at least a Grade 2, despite TKI interruption and adequate management (including hematopoietic growth factors), then the patient must be discontinued from the study treatment.

[redacted]

Table 6-2 Criteria for dose reduction/interruption and re-initiation of asciminib and bosutinib treatment for adverse drug reactions

Dose modifications for both asciminib and bosutinib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**		
Worst toxicity **CTCAE Grade 4.03**	**Asciminib**	**Bosutinib**
Investigations (Hematologic) If a hematologic toxicity (cytopenia Grade 3 or 4) lasts for more than 42 days without recovery to at least a Grade 2, despite TKI interruption and adequate management (including hematopoietic growth factors), then the patient must be discontinued from the study treatment.		
Neutropenia (ANC)		
Grade 1 (ANC < LLN – 1.5 x 10^9/L)	**Recommendation**: Maintain dose level	**Recommendation**: Maintain dose level
Grade 2 (ANC < 1.5 – 1.0 x 10^9/L)	**Recommendation**: Maintain dose level	**Recommendation**: Maintain dose level
Grade 3 (ANC < 1.0 – 0.5 x 10^9/L)	**Mandatory**: Hold dose until resolved to ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, then reduce dose ↓ 1 dose level	**Mandatory**: Hold dose until resolved to ≤ Grade 2 and platelets ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, reduce dose ↓ 1 dose level
Grade 4 (ANC < 0.5 x 10^9/L)	**Mandatory**: Hold dose until resolved to ≤ Grade 2, (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved to ≤ Grade 2 and platelets ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level
Febrile neutropenia (ANC < 1.0 x 109/L, fever ≥ 38.5°C)	**Mandatory:** Hold dose until resolved, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved, then reduce dose ↓ 1 dose level
Thrombocytopenia		
Grade 1 (PLT < LLN – 75 X 10^9/L)	**Recommendation**: Maintain dose level	**Recommendation:** Maintain dose level
Grade 2 (PLT < 75 - 50 x 10^9/L)	**Recommendation**: Maintain dose level	**Recommendation:** Maintain dose level

[redacted]

Dose modifications for both asciminib and bosutinib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**		
Worst toxicity **CTCAE Grade 4.03**	**Asciminib**	**Bosutinib**
Grade 3 (PLT < 50 - 25 x 10^9/L)	**Mandatory:** Hold dose until resolved to ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved to ≤ Grade 2 and neutrophils ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	**Mandatory:** Hold dose until resolved to ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved to ≤ Grade 2 and neutrophils ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level
Recurrence of all cytopenias	**Recommendation:** Hold dose until resolved to ≤ Grade 2, then maintain current dose level.	**Recommendation:** Hold dose until resolved to ≤ Grade 2, then reduce dose ↓ 1 additional level
Non-hematologic adverse reactions except where further specified in individual sections		
Grade 1	**Recommendation**: Maintain dose level	**Recommendation:** Maintain dose level
Grade 2	**Recommendation:** Hold dose until resolved to ≤ Grade 1, then maintain dose level	**Recommendation:** Maintain dose level
Grade 3	**Mandatory:** Hold dose until resolved to ≤ Grade 1, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved to ≤ Grade 1, then reduce dose ↓ 1 dose level, If clinically appropriate, re-escalation of the dose back to baseline dose level (500 mg) should be considered
Grade 4	**Mandatory**: Permanently discontinue patient from study drug treatment.	**Mandatory:** Hold dose until resolved to ≤ Grade 1, then reduce dose ↓ 1 dose level; If clinically appropriate, re-escalation of the dose back to baseline dose level (500 mg) should be considered
Investigations (Renal)		
Serum creatinine		
Grade 1 (> ULN - 1.5 x ULN)	**Recommendation:** Maintain dose level	**Recommendation:** Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN)	**Recommendation:** Hold dose until resolved to ≤ Grade 1 or baseline, then maintain dose level	**Recommendation:** Hold dose until resolved to ≤ Grade 1 or baseline, then maintain dose level
Grade 3 (> 3.0 - 6.0 x ULN)	**Mandatory:** Permanently discontinue patient from study drug treatment.	**Mandatory:** Permanently discontinue patient from study drug treatment.
Grade 4 (> 6.0 x ULN)	**Mandatory:** Permanently discontinue patient from study drug treatment.	**Mandatory:** Permanently discontinue patient from study drug treatment.

[redacted]

Dose modifications for both asciminib and bosutinib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**		
Worst toxicity **CTCAE Grade 4.03**	**Asciminib**	**Bosutinib**
Investigations (Hepatic)		
Isolated total Bilirubin elevation		
> ULN – 1.5 x ULN	**Recommendation:** Maintain dose level	**Recommendation:** Maintain dose level
> 1.5 - 3.0 x ULN	**Recommendation:** Hold dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level	**Recommendation:** Hold dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level
> 3.0 - 10.0 x ULN*	**Mandatory:** Hold dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: if resolved in ≤ 14 days, then reduce dose ↓ 1 dose level if resolved in > 14 days, then discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.	**Mandatory:** Hold dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: if resolved in ≤ 14 days, then reduce dose ↓ 1 dose level if resolved in > 14 days, then discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
> 10.0 x ULN*	**Mandatory:** Permanently discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.	**Mandatory:** Permanently discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
Isolated AST or ALT elevation		
> ULN - 3.0 x ULN	**Recommendation:** Maintain dose level	**Recommendation:** Maintain dose level
> 3.0 - 5.0 x ULN	**Recommendation:** Maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN	**Recommendation:** Maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN

[redacted]

Dose modifications for both asciminib and bosutinib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**		
Worst toxicity **CTCAE Grade 4.03**	**Asciminib**	**Bosutinib**
> 5.0 - 10.0 x ULN	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN: Then If resolved in ≤ 14 days, maintain dose level If resolved in > 14 days, reduce dose ↓ 1 dose level	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 2.5 x ULN: Then **Recommendation:** If resolved in ≤ 28 days, reduce dose ↓ 1 dose level **Recommendation**: If resolved in > 28 days, Discontinue patient from study drug treatment
> 10.0 - 20.0 x ULN	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ baseline. Then reduce dose ↓ 1 dose level.	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 2.5 x ULN. Then **Recommendation:** If resolved in ≤ 28 days, reduce dose ↓ 1 dose level maintain dose level **Recommendation:** If resolved in > 28 days, Discontinue patient from study drug treatment.
> 20.0 x ULN	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3 x ULN (or ≤ 5 x ULN for patients with baseline value > 3.0 -5.0 x ULN), then resume treatment at reduce dose ↓ 1 dose level. Only 1 dose reduction is allowed; if reoccurs at > 5 x ULN, discontinue patient from study drug treatment.	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 2.5 x ULN (then **Recommendation:** If resolved in ≤ 28 days, reduce dose ↓ 1 dose level maintain dose level **Recommendation:** If resolved in > 28 days, Discontinue patient from study drug treatment

[redacted]

Dose modifications for both asciminib and bosutinib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**		
Worst toxicity **CTCAE Grade 4.03**	**Asciminib**	**Bosutinib**
Combined [c] elevations of AST or ALT and total bilirubin		
For patients with normal baseline ALT and AST and total bilirubin value: AST or ALT >3.0 x ULN combined with total bilirubin >2.0 x ULN without evidence of cholestasis[d] For patients with elevated baseline AST or ALT or total bilirubin value [AST or ALT>2 x baseline AND > 3.0 x ULN]	**Mandatory:** Permanently discontinue patient from study drug treatment. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b]), or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Refer to Section 6.3.3.1 for additional follow-up evaluations as applicable.	**Mandatory:** Permanently discontinue patient from study drug treatment. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTsb), or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Refer to Section 6.3.3.1 for additional follow-up evaluations as applicable.
Investigation (metabolic)		
Asymptomatic amylase and/or lipase elevation		
Grade 1 (> ULN - 1.5 x ULN)	**Recommendation:** Maintain dose level, measure 2x week	**Recommendation:** Maintain dose level, measure 2x week
Grade 2 (> 1.5 - 2.0 x ULN)	**Recommendation:** Maintain dose level, measure 2x week	**Recommendation:** Maintain dose level, measure 2x week
Grade 3 (> 2.0 - 5.0 x ULN)	**Mandatory:** Hold dose until resolved to Grade ≤ 1 or baseline, then: If resolved in ≤ 7 days, then reduce dose ↓ 1 dose level If resolved in > 7 days, then discontinue treatment and obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).	**Mandatory:** Hold dose until resolved to Grade ≤ 1 or baseline, then: If resolved in ≤ 7 days, then reduce dose ↓ 1 dose level If resolved in > 7 days, then discontinue treatment and obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).
Grade 4 (> 5.0 x ULN)	**Mandatory:** Permanently discontinue patient from study drug treatment. Obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).	**Mandatory:** Permanently discontinue patient from study drug treatment. Obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).

[redacted]

Dose modifications for both asciminib and bosutinib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**		
Worst toxicity **CTCAE Grade 4.03**	**Asciminib**	**Bosutinib**
Vascular disorders		
Hypertension		
CTCAE Grade 3	**Mandatory:** Hold dose until resolved ≤ Grade 1, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved ≤ Grade 1, then reduce dose ↓ 1 dose level
CTCAE Grade 4	**Mandatory:** Permanently discontinue patient from study drug treatment.	**Mandatory:** Permanently discontinue patient from study drug treatment.
Gastro intestinal		
Pancreatitis		
Grade 2 (radiologic findings for pancreatitis as per CTCAE v4.03, for increased enzymes please see table for asymptomatic amylase and/or lipase elevation)	**Mandatory:** If asymptomatic radiologic pancreatitis, hold treatment until recovery of the radiologic findings. If treatment delay is ≤ 21 days, then reduce dose ↓ 1 dose level. If treatment delay > 21 days, discontinue treatment and keep monitoring with appropriate imaging (i.e., MRI, CT scan or ultrasound).	**Mandatory**: If asymptomatic radiologic pancreatitis, hold treatment until recovery of the radiologic findings. If treatment delay is ≤ 21 days, then reduce dose ↓ 1 dose level. If treatment delay > 21 days, discontinue treatment and keep monitoring with appropriate imaging (i.e., MRI, CT scan or ultrasound).
Grade ≥ 3	**Mandatory:** Permanently discontinue patient from study drug treatment. Obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).	**Mandatory:** Permanently discontinue patient from study drug treatment. Obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).
Diarrhea***		
Grade 1	**Recommendation:** Maintain dose level but, initiate anti-diarrhea treatment	**Recommendation:** Maintain dose level but, initiate anti-diarrhea treatment
Grade 2	**Recommendation:** Hold dose until resolved to ≤ grade 1, then maintain dose level. If diarrhea returns as ≥ grade 2, then hold dose until resolved to ≤ grade 1, then reduce dose ↓ 1 dose level	**Recommendation:** Hold dose until resolved to ≤ grade 1, then maintain dose level. If diarrhea returns as ≥ grade 2, then hold dose until resolved to ≤ grade 1, then reduce dose ↓ 1 dose level
Grade 3	**Recommendation:** Hold dose and discontinue patient from study drug treatment	**Mandatory:** Hold dose until recovery to ≤ grade 1. **Recommendation:** Bosutinib may then be resumed at ↓ 1 dose level
Grade 4	**Mandatory:** Permanently discontinue patient from study drug treatment	**Mandatory**: Hold dose until recovery to ≤ grade 1. **Recommendation:** Bosutinib may then be resumed at ↓ 1 dose level

[redacted]

Dose modifications for both asciminib and bosutinib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**		
Worst toxicity **CTCAE Grade 4.03**	**Asciminib**	**Bosutinib**
Skin and subcutaneous tissue disorders		
Rash/photosensitivity		
Grade 1	**Recommendation:** Maintain dose level. Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)	**Recommendation:** Maintain dose level. Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
Grade 2	**Recommendation**: Maintain dose level, but initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)	**Recommendation:** Maintain dose level, but initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
Grade 3, despite skin toxicity therapy	**Recommendation:** Hold dose until resolved to Grade ≤ 1, then: If resolved in ≤ 7 days, then reduce dose ↓ 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then discontinue patient from study drug treatment	**Recommendation:** Hold dose until resolved to Grade ≤ 1, then: If resolved in ≤ 7 days, then reduce dose ↓ 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then discontinue patient from study drug treatment
Grade 4, despite skin toxicity therapy	**Mandatory:** Permanently discontinue patient from study drug treatment.	**Mandatory:** Permanently discontinue patient from study drug treatment.
General disorders and administration site conditions		
Fatigue/ Asthenia		
Grade 1 or 2	**Recommendation:** Maintain dose level	**Recommendation:** Maintain dose level
Grade 3	**Recommendation:** Hold dose until resolved to ≤ grade 1, then : If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then reduce dose ↓ 1 dose level	**Recommendation:** Hold dose until resolved to ≤ grade 1, then : If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then reduce dose ↓ 1 dose level
All dose modifications should be based on the worst preceding toxicity. [a] Common Toxicity Criteria for Adverse Events (CTCAE Version 4.03) [b] Core LFTs consist of ALT, AST, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.) [c] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold		

[redacted]

Dose modifications for both asciminib and bosutinib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**		
Worst toxicity **CTCAE Grade 4.03**	**Asciminib**	**Bosutinib**
If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when hold dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction [d] "Cholestasis" defined as ALP elevation (>2.0 x ULN and R value <2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury * Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator. ** Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study treatment. *** Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea		

[redacted]

Table 6-3 Dose reduction steps for asciminib and bosutinib

Dose reduction*			
	Starting dose level – 0	Dose level – 1	
Asciminib BID	40 mg tablet BID (total daily dose 80 mg)	20 mg tablet BID (total daily dose 40 mg)	
*Dose reduction should be based on the worst toxicity demonstrated at the last dose.			
Asciminib dose reduction below total daily 40 mg is not allowed. 20 mg tablets will be dispensed to patients in the instance of dose reduction.			
Dose reduction*			
	Starting dose level – 0	Dose level – 1	Dose level – 2
Bosutinib QD	500 mg (1-500 mg tablet QD)	400 mg (4-100 mg tablets QD)	300 mg (3-100 mg tablets QD)
* Dose reduction should be based on the worst toxicity demonstrated at the last dose.			
Bosutinib dose reduction below total daily 300 mg is not allowed. 100 mg tablets will be dispensed to patients in the instance of dose reduction.			

6.3.2 Dose adjustments for QTcF prolongation

If QTcF >500 msec or QTcF prolongation >60 msec from baseline is observed at any point during study treatment, and confirmed, the below guidance must be followed:

1. Assess the quality of the ECG recording and the QT value and repeat if needed
2. Interrupt study treatment until confirmed resolution of QTcF and as per dose reduction guidelines for non-hematological AEs.
3. Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment.
4. Review concomitant medication associated with QT prolongation, including drugs with a "Known", "Possible", or "Conditional risk of Torsades de Pointes" (refer to wwwcrediblemeds.org/), and drugs with the potential to increase the risk of study drug exposure related QT prolongation.
5. Check study drug dosing schedule and treatment compliance.

After confirming ECG reading at site, if QTcF > 500 msec

- Interrupt study treatment
- Repeat ECG and confirm ECG diagnosis by a cardiologist or central ECG lab
- If QTcF confirmed > 500 msec:
  - Correct electrolytes, eliminate culprit concomitant treatments, and identify and address clinical conditions that could potentially prolong the QT as per the ECG and QTc Clinical Safety Standards Guidelines Section 3.3.1.
  - Consult with a cardiologist (or qualified specialist)
  - Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 msec.
- After resolution to ≤ 480 msec, consider re-introducing treatment at reduced dose, and increase ECG monitoring for the next treatment(s), (e.g. pre-dose and 2 hours post dose after one week and two weeks of treatment re-introduction):

[redacted]

- If QTcF remains ≤ 500 msec after dose reduction, continue planned ECG monitoring during subsequent treatment
- If QTcF > 500 msec recurs after dose reduction, discontinue patient from trial.

6.3.3 Follow-up for toxicities

Patients whose treatment is permanently discontinued due to a study drug related adverse event or clinically significant laboratory value, must be followed up at least once a week for 4 weeks, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary. All patients must be followed up for adverse events and serious adverse events for 30 days following the last dose of study treatment.

6.3.3.1 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatinine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2 . A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.

[redacted]

4. Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.3.4 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e., hyperglycemia, skin toxicity and diarrhea are provided in Table 6-2. Refer to preclinical toxicity and or clinical data found in the [Asciminib Investigator's Brochure] or bosutinib label.

6.4 Concomitant medications for patients on asciminib

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug and including over-the-counter treatment and nutritional or vitamin supplements) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the "Concomitant Medications/Significant non-drug therapies" section of the eCRF.

Chronic medication should be maintained at the same dose and schedule throughout the study period, as medically feasible.

All prior antineoplastic surgery, chemotherapy, biologic, immunologic and radiation therapy must be recorded in the "Prior antineoplastic therapy" section of the eCRF.

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records and on the appropriate case report form, including the medication's duration (start and end dates or if continuing at final exam). These include blood and platelet transfusions for patients with anemia and with thrombocytopenia.

6.4.1 Permitted concomitant therapy

Drugs that affect gastric pH

Asciminib does not have a pH-dependent solubility. Drugs that elevate gastric pH will not affect asciminib absorption. All acid reducing agents are allowed.

[redacted]

6.4.2 Permitted concomitant therapy requiring caution and/or action

The *in vivo* potential of asciminib to interact with sensitive CYP3A4/5, CYP2C8 and CYP2C9 substrates has been evaluated and would indicate a minimal or negligible risk (Section 1.2.1.1). Therefore CYP3A4/5, CYP2C8 and CYP2C9 substrates with narrow therapeutic index (NTI) should be used with caution.

In recombinant cellular expression systems, asciminib was identified as a substrate of BCRP (Km ≈ 4 μM) and P-gP (Km could not be estimated due to insufficient saturation of efflux activity). Inhibitors of BCRP and P-gP may increase asciminib concentration. Based on human ADME study, P-gp may represent maximally 24% of the total clearance resulting in modest increase in AUC. Therefore, both BCRP and P-gp inhibitors should be administered with caution. If a medication listed in Section 14 appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.

6.4.3 Prohibited concomitant therapy

Other anticancer agents

The administration of any other anticancer agents including chemotherapy and biologic agents is not permitted except for anti-cancer treatments of newly diagnosed solid cancers (e.g. prostate cancer) that would not impact the level of minimal residual disease of patients. These patients may remain in the current study after consultation with Novartis. The administration of other tyrosine kinase inhibitors indicated for treatment of CML is **not** allowed.

Strong CYP3A4/5 inhibitors

Every effort should be made NOT to concomitantly administer strong CYP3A4/5 inhibitors. CYP3A4/5 inhibitors may decrease the metabolism of asciminib and resulting in increased serum concentrations and increased exposure. If administration of a strong CYP3A4/5 inhibitor cannot be avoided during the study and cannot be switched to an alternative therapy that does not strongly inhibit CYP3A4/5, asciminib must be interrupted.

A list of cytochrome P450 isoenzymes and CYP3A4/5inhibitors may be found at medicine.iupui.edu/CLINPHARM/ddis/clinical-table.

A classification of CYP3A4/5 SmPC can be found in Section 14-Appendices.

Further information can also be found in the following reference (Venkatakrishnan et al 2001).

Strong CYP3A4/5, and UGT1A/2B inducers

Every effort should be made NOT to concomitantly administer strong CYP3A4 inducers during the study.

Additionally, the use of strong inducers of UGT1A/2B is prohibited during the study.

If administration of a strong CYP3A4/5 inducer or UGT1A/2B inducer cannot be avoided during the study and cannot be switched to an alternative therapy, temporary interruption of study treatment is NOT needed.

[redacted]

QT prolonging agents

As far as possible avoid co-administering drugs with a "Known", "Possible" or "Conditional" risk of Torsades de Pointes (per wwwcrediblemeds.org/) during the course of the study:

- If concomitant administration of drugs with a "Known risk of Torsades de Pointes" is required and cannot be avoided, study drug must be interrupted. If, based on the investigator assessment and clinical need, study treatment is resumed, close ECG monitoring is advised.
- If during the course of the study, concomitant administration of a drug with "Possible risk" or "Conditional risk of Torsades de Pointes" is required, based on the investigator assessment and clinical need, study treatment may be continued under close ECG monitoring to ensure patient safety.

A list of drugs associated with QT prolongation and/or Torsades de Pointes is available online at wwwcrediblemeds.org/.

Herbal medications

Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

6.4.4 Other concomitant medications

Anti-emetics

Use of anti-emetics is allowed. Prophylactic anti-emetics should be started only once the patient experiences nausea or vomiting, at the discretion of the investigator. It is recommended that patients use drugs that do not cause QT prolongation. Please note that some anti-emetics have a known risk for Torsade de Pointes and are prohibited (refer to Section 6.4.2 and Section 14.1 Appendix 1).

Bisphosphonates

The use of bisphosphonates regardless of indication is allowed.

Contraceptives

Hormonal contraceptives are allowed as contraception methods. Highly effective contraception should be maintained throughout the study and for 3 days after study treatment discontinuation.

Anticoagulation agents

All anticoagulants or anti-aggregation agents may be administered under the discretion of the investigator.

Therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants should be used with caution and fully avoided whenever possible because of its known interaction with many commonly used medications and certain foods. As warfarin has a narrow therapeutic range, and asciminib is possibly an inhibitor of CYP2C9, the major

[redacted]

metabolizing enzyme of S-warfarin (R-warfarin is metabolized by multiple CYP enzymes), warfarin should be carefully monitored whenever used.

Caution is also advised when asciminib is co-administered with anti-platelet pro-drugs such as clopidogrel, ticlopidine and prasugrel, which require metabolic activation by CYP3A4 and CYP2C9. While the weak reversible *in vitro* inhibition potential of asciminib is unlikely to translate into clinical significance as the steady-state plasma concentrations at the maximum therapeutic doses are significantly lower than the experimentally determined inhibition constants, patients using anti-platelet pro-drugs should still be carefully monitored.

Direct Thrombin inhibitors (DTIs) and Factor Xa inhibitors are allowed as anticoagulants. Individual medications from each of the classes should be checked if they are not prohibited due to other drug-drug-interactions with asciminib. Alternatively, therapeutic anticoagulation may be accomplished using low-molecular weight heparin.

6.5 Concomitant medications for patients on bosutinib

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug and including over-the-counter treatment and nutritional or vitamin supplements) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the "Concomitant Medications/Significant non-drug therapies" section of the eCRF.

Chronic medication should be maintained at the same dose and schedule throughout the study period, as medically feasible.

All prior antineoplastic surgery, chemotherapy, biologic, immunologic and radiation therapy must be recorded in the "Prior antineoplastic therapy" section of the eCRF.

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records and on the appropriate case report form, including the medication's duration (start and end dates or if continuing at final exam). These include blood and platelet transfusions for patients with anemia and with thrombocytopenia

6.5.1 Permitted concomitant therapy requiring caution

Bosutinib should be used with caution in patients who have or may develop prolongation of QT, including those patients who are taking medicinal products that are known to prolong the QTc (e.g., anti-arrhythmic medicinal products such as amiodarone, disopyramide, procainamide, quinidine and sotalol and other substances that may prolong QTc) (in accordance with EU SmPC dated 05/2018).

If a medication listed in Section 14-Appendices appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.

[redacted]

6.5.2 Prohibited concomitant therapy

Other anticancer agents

The administration of any other anticancer agents including chemotherapy and biologic agents is not permitted except for anti-cancer treatments of newly diagnosed solid cancers (e.g. prostate cancer) that would not impact the level of minimal residual disease of patients. These patients may remain in the current study after consultation with Novartis. The administration of other tyrosine kinase inhibitors indicated for treatment of CML is **not** allowed.

Concomitant use with CYP3A inhibitors

Avoid the concomitant use of strong or moderate CYP3A inhibitors as an increase in bosutinib plasma concentration is expected. Strong CYP3A inhibitors include boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole.

Moderate CYP3A inhibitors include amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit products, imatinib and verapamil) [Bosulif® USPI]. If administration of a strong or moderate CYP3A4/5 inhibitor cannot be avoided during the study and cannot be switched to an alternative therapy, bosutinib must be interrupted.

Concomitant use with CYP3A inducers

Avoid the concomitant use of strong or moderate CYP3A inducers as a large reduction in exposure is expected (strong CYP3A inducers include carbamazepine, phenytoin, rifampin and St. John's Wort. Moderate CYP3A inducers include bosentan, efavirenz, etravirine, modafinil and nafcillin) [Bosulif® USPI]. However, if administration of a strong or moderate CYP3A4/5 inducer cannot be avoided during the study and cannot be switched to an alternative therapy, temporary interruption of bosutinib is NOT required.

pH Altering Medications

Bosutinib displays pH-dependent aqueous solubility, in vitro. In a cross-over trial in 23 healthy volunteers, a single oral dose of 400 mg of bosutinib was either administered alone or in combination with multiple-oral doses of 60 mg of lansoprazole (PPI) under fasting conditions. Lansoprazole decreased bosutinib Cmax and AUC by 46% and 26%, respectively.

Concomitant administration with PPIs is not allowed.

Consider using short-acting antacids or H2 blockers instead of PPIs to avoid a reduction in bosutinib exposure. Separate antacid or H2 blocker dosing by more than 2 hours [Bosulif® USPI].

6.6 Patient numbering, treatment assignment or randomization

6.6.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient

[redacted]

throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Screening Disposition page. IRT must be notified within 2 days that the patient was not randomized.

6.6.2 Treatment assignment or randomization

Patients will be assigned to one of the 2 treatment arms (Section 4.1 and Section 6.1) in a ratio of 2:1. Randomization will be stratified by cytogenetic response status at screening.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

6.6.3 Treatment blinding

Not applicable.

6.7 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

[redacted]

6.7.1 Study treatment packaging and labeling

Study treatment, asciminib and bosutinib tablets, will be provided as global clinical open-label supply and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

Study treatment labels will comply with the legal requirements of each country and will include storage conditions, a unique medication number (corresponding to study treatment and strength). Responsible site personnel will identify the study treatment package(s) to dispense by the medication number(s) assigned by IRT to the patient. Site personnel will add the patient number on the label. If the label has 2-parts (base plus tear-off label), immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document.

Table 6-4 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
asciminib (20 mg and 40 mg)	Tablets in bottle	Labeled as 'ABL001 20 mg/ABL001 40 mg'(BID)
bosutinib (100 mg or 500 mg)	Tablets in bottle or tablets in blister	Labeled as 'bosutinib 100 mg or bosutinib 500 mg'(QD)

6.7.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, asciminib and bosutinib should be stored according to the instructions specified on the drug labels.

6.7.3 Study drug compliance and accountability

6.7.3.1 Study drug compliance

Total daily dose of study treatment administered with start and end date will be collected on the Dosage Administration Record eCRF page. Name, start and end dates of any Concomitant Medications and Surgical and Medical procedures will be collected on the Prior and Concomitant medications and Surgical and Medical procedures eCRFs respectively.

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each dispensing patient visit.

6.7.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study treatment or at the time of study treatment discontinuation during the treatment period as well as during the switch treatment period with asciminib.

[redacted]

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.3.3 Handling of other study treatment

Not applicable.

6.7.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, or at the site only if permitted by local regulations and authorized by Novartis in a prior agreement.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. Patients can be consented for study participation prior to study day -21.

Table 7-2 lists all of the assessments required by patients that switch treatment from bosutinib to asciminib after documented treatment failure of bosutinib.

No eCRF will be used as a source document.

(S) is defined as "Source"

(D) is defined as "Data Based"

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section 7	Screening Phase	Treatment Phase																	
Visit name			Screening/ Baseline (Day -21 to -1)	Week 1 Day 1	Week 2 Day 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Obtain Informed Consent	D		X (Screening window - 56 days)																		
IRT																					
Eligibility checklist/registration	D		X																		
Randomization	D			X																	
Demography	D	7.1.2.4	X																		
Inclusion/exclusion criteria	D		X																		
Medical History	D	7.1.2.4	X																		
Disease History	D	7.1.2.4	X																		
Mutation status	D	7.1.2.4	X																		
Prior antineoplastic therapy	D	7.1.2.4	X																		
Prior TKI therapy	D	7.1.2.4	X																		

[redacted]

	Category	Protocol Section 7	Screening Phase	Treatment Phase																	
Visit name			Screening/ Baseline (Day -21 to -1)	Week 1 Day 1	Week 2 Day 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Prior/concomitant medications	D	7.1.2.4	X	Continuous																	
Physical examination	S	7.2.2.1	X	X		X	If needed	X	If needed	X	If needed	X	X	X	X	X	X	X	X	X	X
Extramedullary Involvement	D	7.2.2.1	X	X		X	If needed	X	If needed	X	If needed	X	X	X	X	X	X	X	X	X	X
ECOG Performance status	D	7.2.2.4	X	X		X	If needed	X	If needed	X	If needed	X	X	X	X	X	X	X	X	X	X
Height	D	7.2.2.3	X																		
Weight	D	7.2.2.3	X	X						X				X			X			X	
Vital signs	D	7.2.2.2	X	X	X	X	If needed	X	If needed	X	If needed	X	X	X	X	X	X	X	X	X	X
Laboratory assessments		7.2.2.5																			
Hematology	D	7.2.2.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	D	7.2.2.5.2	X	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X
Chemistry-Hemoglobin A1c	D	7.2.2.5.2	X	Week 12 and as clinically indicated																	
Coagulation	D	7.2.2.5.2	X	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X

[redacted]

	Category	Protocol Section 7	Screening Phase	Treatment Phase																	
Visit name			**Screening/ Baseline (Day -21 to -1)**	**Week 1 Day 1**	**Week 2 Day 1**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**
Serum Pregnancy test (if applicable)	D	7.2.2.5.3	X			X		X		X		X	X	X	X	X	X	X	X	X	X
Hepatitis markers	D	7.2.2.5.2	X																		
Liver assessments	D			as clinically indicated																	
Efficacy assessments		7.2.1																			
Blood collection for BCR-ABL1 quantification by RQ-PCR	D	7.2.1.1	X			X		X		X		X		X			X			X	
Blood collection for exploratory BCR-ABL1 mutation analysis by Sanger Sequencing	D	7.2.1.1		X																	

[redacted]

	Category	Protocol Section 7	Screening Phase	Treatment Phase																	
Visit name			Screening/ Baseline (Day -21 to -1)	Week 1 Day 1	Week 2 Day 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Exploratory BCR-ABL1 mutation analysis (Sanger Sequencing) for patients with mutations at Week 1 Day 1	D	7.2.1.1								X				X			X			X	
Bone Marrow Aspirate/Cytogenetics -scheduled	D	7.2.1.2	X (Screening window - 56 days)											X						X	
Cardiac Assessments		7.2.2.6																			
ECG	D	7.2.2.6.1	X	X	X	X				X				X							
Cardiovascular risk factor assessments (including Family History)	D	7.2.2.6.2	X																		
Echocardiogram	D	7.2.2.6.3	X										X								
Pulmonary Function Test	D	7.2.2.6.4	X										X								

[redacted]

	Category	Protocol Section 7	Screening Phase	Treatment Phase																	
Visit name			**Screening/ Baseline (Day -21 to -1)**	**Week 1 Day 1**	**Week 2 Day 1**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**
Adverse events / SAE	D		X	Continuous																	
Biomarker Assessments		7.2.4																			
[redacted]	D	7.2.4.1	X (Screening window -56 days)											X							
[redacted]	D	7.2.4.1	X (Screening window -56 days)																		
Blood collection for Low level mutation analysis	D	7.2.4.2		X	Upon visit to confirm loss of MMR																
[redacted]	D	7.2.4.2		X																X	
[redacted]	D	7.2.4.2		X																	

[redacted]

	Category	Protocol Section 7	Screening Phase	Treatment Phase																	
Visit name			Screening/ Baseline (Day -21 to -1)	Week 1 Day 1	Week 2 Day 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Patient reported Outcomes		7.2.6																			
MDASI-CML	D	7.2.6	X			X		X		X		X		X			X			X	
EQ 5D 5L	D	7.2.6	X			X		X		X		X		X			X			X	
PGIC	D	7.2.6				X		X		X		X		X			X			X	
WPAI	D	7.2.6	X			X				X				X						X	
Resource Utilization Assessments	D	7.2.5	X	Continuous																	
Asciminib Drug administration	D			Continuous																	
Bosutinib Drug administration	D			Continuous																	
PK sampling (asciminib arm only)		7.2.3																			
Sparse PK blood collection	D	7.2.3		X	X	X				X				X							
Full PK blood collection (at least 20 patients)	D	7.2.3		X	X	X				X				X							
Meal record	D			X	X	X				X				X							

[redacted]

	Category	Protocol Section 7	Treatment Phase											EOT/Early Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	**Week 76**	**Week 80**	**Week 84**	**Week 88**	**Week 92**	**Week 96**	**Every 12 weeks up to end of study treatment**			
Prior/concomitant medications	D		Continuous														
Physical examination	S	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X		
Extramedullary	D	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance status	D	7.2.2.4	X	X	X	X	X	X	X	X	X	X	X	X	X		
Weight	D	7.2.2.3		X			X			X			X	X	X		
Vital signs	D	7.2.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory assessments		7.2.2.5															
Hematology	D	7.2.2.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry	D	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry-Hemoglobin A1c	D	7.2.2.5.2	as clinically indicated														
Coagulation	D	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum Pregnancy test (if applicable)	D	7.2.2.5.3	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urine Pregnancy test (if applicable	D	7.2.2.5.3											Monthly between visits				
Liver assessments	D		as clinically indicated														

[redacted]

	Category	Protocol Section 7	Treatment Phase											EOT/Early Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	**Week 76**	**Week 80**	**Week 84**	**Week 88**	**Week 92**	**Week 96**	**Every 12 weeks up to end of study treatment**			
Efficacy assessments		7.2.1															
Blood collection for BCR-ABL1 quantification by RQ-PCR	D	7.2.1.1		X			X			X			X	X	X		
Exploratory BCR-ABL1 Mutation analysis by Sanger sequencing	D	7.2.1.1													X		
Exploratory BCR-ABL1 Mutation analysis by Sanger sequencing for patients with mutations at Week 1 Day 1	D	7.2.1.1		X			X			X			X	X			
Bone Marrow Aspirate/Cytogenetics - scheduled	D	7.2.1.2					X						X		X		
Cardiac Assessments		7.2.2.6															
ECG	D	7.2.2.6.1											X				
Cardiovascular risk factor assessments (including Family History)	D	7.2.2.6.2													X		
Echocardiogram	D	7.2.2.6.3													X		
Pulmonary Function Test	D	7.2.2.6.4													X		

[redacted]

	Category	Protocol Section 7	Treatment Phase											EOT/Early Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	**Week 76**	**Week 80**	**Week 84**	**Week 88**	**Week 92**	**Week 96**	**Every 12 weeks up to end of study treatment**			
Adverse events / SAE	D		Continuous													
Biomarker Assessments		7.2.4														
Blood collection for Low level mutation analysis	D	7.2.4.2	Upon visit to confirm loss of MMR											X		
[redacted]	D	7.2.4.2												X		
[redacted]	D	7.2.4.1												X		
[redacted]	D	7.2.4.1												X		
Patient reported Outcomes		7.2.6														
MDASI-CML	D	7.2.6											X			
EQ 5D 5L	D	7.2.6											X			
PGIC	D	7.2.6											X			
WPAI	D	7.2.6											X			
Resource Utilization Assessments	D	7.2.5	Continuous													
Asciminib Drug administration	D		Continuous													
Bosutinib Drug administration	D		Continuous													

[redacted]

	Category	Protocol Section 7	Treatment Phase											EOT/Early Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96	Every 12 weeks up to end of study treatment			
PK sampling (asciminib arm only)		7.2.3															
Sparse PK blood collection	D	7.2.3											X				
Full PK blood collection (at least 20 patients)	D	7.2.3											X				
Survival follow-up	D																X
Antineoplastic therapies since discontinuation of study treatment	D															X	X
Stem Cell Transplant status	D																X
Progression status	D																X
Meal Record	D												X				

[redacted]

Table 7-2 Visit evaluation schedule (study treatment switch phase)

	Category	Protocol Section 7	Switch Screening Phase	Treatment Switch Phase																	
Visit name			EOT (Bosutinib) / S-Screening/ S-Baseline	S-Week 1 Day 1	S-Week 2 Day 1	S-Week 4	S-Week 6	S-Week 8	S-Week 10	S-Week 12	S-Week 14	S-Week 16	S-Week 20	S-Week 24	S-Week 28	S-Week 32	S-Week 36	S-Week 40	S-Week 44	S-Week 48	S-Week 52
IRT																					
Treatment Switch Eligibility checklist	D		X																		
Treatment switch criteria	D		X																		
Mutation status	D	7.1.2.4	X																		
Prior/concomitant medications	D	7.1.2.4	X	Continuous																	
Physical examination	S	7.2.2.1	X	X		X	If needed	X	If needed	X	If needed	X	X	X	X	X	X	X	X	X	X
Extramedullary Involvement	D	7.2.2.1	X	X		X	If needed	X	If needed	X	If needed	X	X	X	X	X	X	X	X	X	X
ECOG Performance status	D	7.2.2.4	X	X		X	If needed	X	If needed	X	If needed	X	X	X	X	X	X	X	X	X	X
Weight	D	7.2.2.3	X	X						X				X			X			X	
Vital signs	D	7.2.2.2	X	X	X	X	If needed	X	If needed	X	If needed	X	X	X	X	X	X	X	X	X	X
Laboratory assessments		7.2.2.5																			

[redacted]

	Category	Protocol Section 7	Switch Screening Phase	Treatment Switch Phase																	
Visit name			**EOT (Bosutinib) / S-Screening/ S-Baseline**	**S-Week 1 Day 1**	**S-Week 2 Day 1**	**S-Week 4**	**S-Week 6**	**S-Week 8**	**S-Week 10**	**S-Week 12**	**S-Week 14**	**S-Week 16**	**S-Week 20**	**S-Week 24**	**S-Week 28**	**S-Week 32**	**S-Week 36**	**S-Week 40**	**S-Week 44**	**S-Week 48**	**S-Week 52**
Hematology	D	7.2.2.5.1	X (if not done at EOT)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	D	7.2.2.5.2	X (if not done at EOT)	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X
Chemistry-Hemoglobin A1c	D	7.2.2.5.2	X (if not done at EOT)	Week 12 and as clinically indicated																	
Coagulation	D	7.2.2.5.2	X (if not done at EOT)	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X
Serum Pregnancy test (if applicable)	D	7.2.2.5.3	X (if not done at EOT)			X		X		X		X	X	X	X	X	X	X	X	X	X
Liver assessments	D			as clinically indicated																	

[redacted]

	Category	Protocol Section 7	Switch Screening Phase	Treatment Switch Phase																	
Visit name			**EOT (Bosutinib) / S-Screening/ S-Baseline**	**S-Week 1 Day 1**	**S-Week 2 Day 1**	**S-Week 4**	**S-Week 6**	**S-Week 8**	**S-Week 10**	**S-Week 12**	**S-Week 14**	**S-Week 16**	**S-Week 20**	**S-Week 24**	**S-Week 28**	**S-Week 32**	**S-Week 36**	**S-Week 40**	**S-Week 44**	**S-Week 48**	**S-Week 52**
Efficacy assessments		7.2.1																			
Blood collection for BCR-ABL1 quantification by RQ-PCR	D	7.2.1.1	X			X		X		X		X		X			X			X	
Exploratory BCR-ABL1 Mutation analysis by Sanger sequencing	D	7.2.1.1		X (if not done at EOT)																	
Exploratory BCR-ABL1 Mutation analysis by Sanger sequencing for patients with mutations at Week 1 Day 1	D	7.2.1.1								X				X			X			X	
Bone Marrow Aspirate/Cytogenetics -scheduled	D	7.2.1.2												X						X	

[redacted]

	Category	Protocol Section 7	Switch Screening Phase	Treatment Switch Phase																	
Visit name			EOT (Bosutinib) / S-Screening/ S-Baseline	S-Week 1 Day 1	S-Week 2 Day 1	S-Week 4	S-Week 6	S-Week 8	S-Week 10	S-Week 12	S-Week 14	S-Week 16	S-Week 20	S-Week 24	S-Week 28	S-Week 32	S-Week 36	S-Week 40	S-Week 44	S-Week 48	S-Week 52
Cardiac Assessments		7.2.2.6																			
ECG	D	7.2.2.6.1	X	X	X	X				X				X							
Cardiovascular risk factor assessments (including Family History)	D	7.2.2.6.2	X																		
Adverse events / SAE	D		X	Continuous																	
Biomarker Assessments		7.2.4																			
[redacted]	D	7.2.4.1	X (if not done at EOT)																		
[redacted]	D	7.2.4.1	X (if not done at EOT)																		
Blood collection for Low level mutation analysis	D	7.2.4.2		X (if not done at EOT)	Upon visit to confirm loss of MMR																

[redacted]

	Category	Protocol Section 7	Switch Screening Phase	Treatment Switch Phase																	
Visit name			**EOT (Bosutinib) / S-Screening/ S-Baseline**	**S-Week 1 Day 1**	**S-Week 2 Day 1**	**S-Week 4**	**S-Week 6**	**S-Week 8**	**S-Week 10**	**S-Week 12**	**S-Week 14**	**S-Week 16**	**S-Week 20**	**S-Week 24**	**S-Week 28**	**S-Week 32**	**S-Week 36**	**S-Week 40**	**S-Week 44**	**S-Week 48**	**S-Week 52**
[redacted]	D	7.2.4.2		X (if not done at EOT)																	
[redacted]	D	7.2.4.2		X (if not done at W1D 1)																	
Asciminib Drug administration	D			Continuous																	
PK sampling		7.2.3																			
Sparse PK blood collection	D	7.2.3		X	X	X				X				X							
Meal record	D			X	X	X				X				X							

[redacted]

	Category	Protocol Section 7	Treatment Switch Phase											S-EOT/Early S-Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			S-Week 56	S-Week 60	S-Week 64	S-Week 68	S-Week 72	S-Week 76	S-Week 80	S-Week 84	S-Week 88	S-Week 92	S-Week 96	Every 12 weeks up to end of study treatment			
Prior/concomitant medications	D		Continuous														
Physical examination	S	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X		
Extramedullary	D	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance status	D	7.2.2.4	X	X	X	X	X	X	X	X	X	X	X	X	X		
Weight	D	7.2.2.3		X			X			X			X	X	X		
Vital signs	D	7.2.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory assessments		7.2.2.5															
Hematology	D	7.2.2.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry	D	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry-Hemoglobin A1c	D	7.2.2.5.2	as clinically indicated														
Coagulation	D	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum Pregnancy test (if applicable)	D	7.2.2.5.3	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urine Pregnancy test (if applicable	D	7.2.2.5.3											Monthly between visits				
Liver assessments	D		as clinically indicated														

[redacted]

	Category	Protocol Section 7	Treatment Switch Phase											S-EOT/Early S-Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			S-Week 56	S-Week 60	S-Week 64	S-Week 68	S-Week 72	S-Week 76	S-Week 80	S-Week 84	S-Week 88	S-Week 92	S-Week 96	Every 12 weeks up to end of study treatment			
Efficacy assessments		7.2.1															
Blood collection for BCR-ABL1 quantification by RQ-PCR	D	7.2.1.1		X			X			X			X	X	X		
Exploratory BCR-ABL1 Mutation analysis by Sanger sequencing	D	7.2.1.1													X		
Exploratory BCR-ABL1 Mutation analysis by Sanger sequencing for patients with mutations at Week 1 Day 1	D	7.2.1.1		X			X			X			X	X			
Bone Marrow Aspirate/Cytogenetics – scheduled	D	7.2.1.2					X						X		X		
Cardiac Assessments		7.2.2.6															
ECG	D	7.2.2.6.1											X				
Cardiovascular risk factor assessments (including Family History)	D	7.2.2.6.2													X		
Adverse events / SAE	D		Continuous														
Asciminib Drug administration	D		Continuous														

[redacted]

	Category	Protocol Section 7	Treatment Switch Phase											S-EOT/Early S-Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			S-Week 56	S-Week 60	S-Week 64	S-Week 68	S-Week 72	S-Week 76	S-Week 80	S-Week 84	S-Week 88	S-Week 92	S-Week 96	Every 12 weeks up to end of study treatment			
PK sampling		7.2.3															
Sparse PK blood collection	D	7.2.3											X				
Survival follow-up	D																X
Antineoplastic therapies since discontinuation of study treatment	D															X	X
Stem Cell Transplant status	D																X
Progression status	D																X
Meal Record	D												X				

[redacted]

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 Screening

Written informed consent must be obtained before any study specific medical procedures are performed. All screening/baseline assessments (with the exception of Bone Marrow Aspirates) should occur within 21 days before Week 1 Day 1.

The screening visit window for bone marrow assessments is 56 days prior to Week 1 Day 1. Should bone marrow assessments have been performed before the main informed consent is signed but within 56 days of Week 1 Day 1, no further bone marrow sampling will be required at screening. At end of treatment, a bone marrow exploratory aspirate and/or biopsy must be collected even if the screening/baseline bone marrow exploratory aspirate and/or biopsy samples were not collected. During the screening visit, inclusion and exclusion criteria will be assessed. Screening assessments to confirm eligibility must be performed prior to randomization. The results of the real time quantitative polymerase chain reaction (RQ-PCR) and the bone marrow aspirate must be available prior to randomization and first dose of study treatment.

For details of assessments required during screening please refer to Table 7-1.

Laboratory baseline assessments (including hematology, chemistry, coagulation and serum pregnancy test), physical examination including extramedullary involvement, performance status, ECG, height, weight and vital signs, evaluation of all relevant medical history including cardiovascular risk factors, CML disease history, including prior TKI therapy and antineoplastic medication and prior and concomitant medication must be performed prior to the first dose of study treatment. Patients with potassium, and/or magnesium and/or total calcium levels that are < LLN at screening, must have their potassium, and/or magnesium, and/or calcium replenished through supplementation and the levels must be within normal limits prior to the first dose of study drug.

A patient who has a laboratory test (peripheral blood test) results that do not satisfy the entrance criteria may have the tests repeated. These tests may be repeated as soon as the investigator believes the re-test results are likely to be within the acceptable range to satisfy the entrance criteria, but should be completed within approximately 2 weeks of the original screening visit date. In this case, the subject will not be required to sign another Informed Consent Form (ICF), and the original patient ID number assigned by the investigator will be used. In the event that the laboratory tests cannot be performed within the screening visit window, or the re-tests do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the patient is considered a screen failure, and must be discontinued from the study.

A new ICF will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed, however, the patient ID number will remain the same. All required screening activities must be performed when the patient is re-screened for participation in the study. No further bone marrow sampling will be done at re-screening if a previous assessment was done within 56 days of Week 1 Day 1. After 56 days, new bone marrow biopsy and aspirates samples for cytogenetic assessment and exploratory biomarker purpose should be re-

[redacted]

collected at the time of the bone marrow assessment. An individual patient may be re-screened up to three times for the study. Once the number of patients screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the patients who screen failed will not be permitted to re-screen.

7.1.2.1 Eligibility screening

Following registering in the IRT for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be managed via IRT system. Please refer and comply with detailed guidelines in the IRT manual.

7.1.2.2 Conditions to be fulfilled for asciminib switch

The eligibility assessments of patients who are candidates for asciminib switch will start with the bosutinib EOT visit. Assessments conducted during the EOT visit will be used to evaluate if all conditions for asciminib switch are fulfilled and there are no conditions preventing patients from receiving asciminib treatment. Therefore all efforts **MUST** be made to ensure that all EOT assessments are completed per Table 7-1. In the event that all EOT assessments cannot be completed during the EOT visit, they must be completed within 42 days (6 weeks) after the bosutinib EOT visit. For details of assessments required for patients that switch treatment from bosutinib to asciminib, please refer to Table 7-2. The maximum allowed time frame for patients failing bosutinib to start treatment with asciminib is 42 days after bosutinib EOT.

In case a patient presents with a grade 3 or 4 adverse event at the time of the EOT visit or develops it after the EOT visit, the adverse event must be resolved to grade 2 or lower before starting asciminib treatment and within 28 days of the date of occurrence of the adverse event as outlined in the criteria listed below.

However, a patient who has laboratory test (peripheral blood test) results or ECG results that do not satisfy the treatment switch conditions may have the tests repeated multiple times during the treatment switch screening period. The last test performed before start of asciminib dosing must meet the conditions for treatment switch as listed below.

If a patient does not meet the conditions for treatment switch, they should enter the survival follow-up phase.

The conditions for treatment switch will be checked via the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

Conditions to fulfill to allow the switch to asciminib:

1. Failure to bosutinib treatment up to 96 weeks after the last patient received the first dose (adapted from the 2013 ELN Guidelines; Baccarani et al 2013). Patients must meet at least 1 of the following criteria. Failure is defined as follows:
   - Three months after the initiation of therapy or thereafter: No CHR or > 95% Ph+ metaphases.
   - Six months after the initiation of therapy or thereafter: BCR-ABL1 ratio > 10% IS and/or > 65% Ph+ metaphases.
   - Twelve months after initiation of therapy or thereafter: BCR-ABL1 ratio > 10% IS and/or > 35% Ph+ metaphases.

[redacted]

- At any time after the initiation of therapy, loss of CHR, CCyR or PCyR.
- At any time after the initiation of therapy, detection of new BCR-ABL1 mutations which potentially cause resistance to study treatment (asciminib or bosutinib).
- At any time after the initiation of therapy, confirmed loss of MMR in 2 consecutive tests.
- At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cells: CCA/Ph+.

Conditions preventing patients to switch to asciminib

- Any Grade 3 or 4 toxicity which has not resolved to Grade 2 or lower within 28 days and before starting asciminib treatment.
- Asymptomatic (Grade 2) pancreatitis if not resolved within 28 days
- Disease progression while on bosutinib treatment. The following events are considered disease progression:
  - Accelerated phase (AP) as defined by any of the following:
    - ≥ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate.
    - ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate.
    - ≥ 20% basophils in the peripheral blood.
    - Thrombocytopenia (< 100 x 10^9/L) that is unrelated to therapy.
  - Blast crisis (BC) as defined by any of the following:
    - ≥ 30% blasts in peripheral blood or bone marrow aspirate
    - Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e. chloroma).
- QTcF at time of switch > 480msec or inability to determine QTc interval

7.1.2.3 Information to be collected on screening failures

Patients who sign an informed consent but fail to be randomized for any reason will be considered a screen failure. The reason for not being randomized will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details). If the patient fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

7.1.2.4 Patient demographics and other baseline characteristics

Patient demographics and baseline characteristics collected will include the following: date of birth, gender (and child bearing potential for female), race and ethnicity, height, weight, all relevant medical history including cardiovascular disease history, CML disease history,

[redacted]

including mutation status, and prior and concomitant medication including prior TKI therapy and antineoplastic medication.

Physical examination including extramedullary involvement, performance status, vital signs, ECGs, and laboratory assessments will be performed at screening.

Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the subject's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the patient's eCRF.

The central reading of the screening ECGs as well as the results of the RQ-PCR and the bone marrow aspirate must be available prior to randomization and first dose of study treatment to evaluate eligibility and to stratify the patient.

7.1.2.5 Local recruitment procedures-Japan

Given the limited safety data available in Japanese patients, specific recruitment and data monitoring procedures will be put in place for Japanese patients randomized to asciminib. Randomization of these patients will be staggered to avoid enrollment of more than one patient on the same day. Safety parameters from a minimum of 2 patients treated on the asciminib arm will be reviewed for determining the appropriateness of continuing patient enrollment in Japan.

7.1.3 Run-in period

Not applicable.

7.1.4 Treatment period

There is no fixed duration of treatment planned per patient. All patients will be given the opportunity to receive study treatment until the end of study treatment period as defined in (Section 4.3).

During the treatment phase, the patients will receive either asciminib treatment 40 mg BID or bosutinib 500 mg QD according to randomization. The dose can be modified, if required from the perspective of tolerance, following the guidance in Section 6.2 and Section 6.3. Treatment will be administered until patient experiences treatment failure, unacceptable toxicity, disease progression, death, lost to follow-up and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent.

The patients are advised to adhere to the food restrictions during the treatment (fasting status regarding study treatment administration, avoidance of prohibited concomitant medication).

7.1.5 Visit windows

Study visits from Week 1 Day 1 to Week 2 Day 1 / S-Week 1 Day 1 to S-Week 2 Day 1 should be completed on the designated date [with an allowed "visit window" of +/- 1 day for Week 2 Day 1 / S-Week 2 Day 1]

Study visits from Week 4 to Week 16 / S-Week 4 to S-Week 16 should be completed every 2 weeks on the designated date [with an allowed "visit window" of +/- 1 day]

[redacted]

Study visits from Week 20 to Week 96 / S-Week 20 to S-Week 96 should be completed every 4 weeks on the designated date [with an allowed "visit window" of +/- 2 days]

Study visits from Week 108 to EOT / S-Week 108 to S-EOT should be completed every 12 weeks on the designated date [with an allowed "visit window" of +/- 7 days]

A delayed visit will have no impact on the next planned visit. The next visit should be completed as scheduled in order to avoid accumulation of additional weeks.

7.1.6 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate eCRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if, he/she believes that continuation would be detrimental to the patient's well-being. Patients who discontinue study treatment should undergo an end of treatment visit.

For patients who discontinue treatment in treatment period or switch treatment period for reasons other than death, lost to follow-up, or withdrawal of consent, the patient should enter the survival follow-up phase. Survival visit assessments (survival, antineoplastic therapies, stem cell transplant and progression) should be performed every 12 weeks until documented death, lost to follow-up, withdrawal of consent or until the end of the study. This visit can be conducted by telephone.

Patients who discontinue the study treatment for an adverse event suspected to be related to study drug or an abnormal laboratory value suspected to be related to study drug must be followed as described in Section 8

Patients may also be discontinued from the study treatment if any of the following occurs:

- discovery of patient ineligibility
- errors in treatment compliance [study treatment, other prescribed or non-prescribed medications]
- missed/unscheduled/off schedule/incomplete/incorrect assessments
- major protocol deviation
- use of prohibited treatment refer to Section 14-Appendices
- any other protocol deviation that results in a significant risk to the patient's safety

In addition to the general discontinuation criteria, the following study specific criteria will also require discontinuation of study treatment:

- In the event of detection of T315I or V299L mutations at any time the patient **must** be discontinued from the study treatment.
- In the event of a pregnancy during study, if a patient wants to pursue the pregnancy then patient **must** be discontinued from the study treatment. However, in the event of a

[redacted]

spontaneous miscarriage or in the event of elective abortion, the patient is permitted to continue study treatment.

- In the event of treatment failure the patient must be discontinued from the study treatment. Patients randomized to bosutinib treatment experiencing treatment failure may switch to asciminib treatment. The following events will constitute 'treatment failure', and are based on the ELN criteria (Baccarani et al 2013) defining failure of a second line treatment:
  - No CHR or > 95% Ph+ metaphases at three months after initiation of therapy or thereafter
  - BCR-ABL1 ratio > 10% IS and/or > 65% Ph+ metaphases at six months after initiation of therapy or thereafter
  - BCR-ABL1 ratio > 10% IS and/or > 35% Ph+ metaphases at 12 months after initiation of therapy or thereafter
  - Loss of CHR, CCyR or PCyR at any time after initiation of therapy
  - Detection of new BCR-ABL1 mutations which potentially cause resistance to study treatment (asciminib or bosutinib) at any time after initiation of therapy
  - Confirmed loss of MMR in 2 consecutive tests (Section 7.2.1.1)
  - New clonal chromosome abnormalities in Ph+ cells: CCA/Ph+: at any time after initiation of therapy
- In the event of disease progression the patient must be discontinued from the study treatment. The following events are considered disease progression.

1. CML-related death (any death during treatment or follow-up if the principal cause of death is marked as "study indication" in the eCRF by the investigator, or if the death occurred subsequent to documented progression to AP/BC and the cause of death is reported as "unknown" or not reported by the investigator)
2. Accelerated phase (AP) as defined by any of the following:
   - ≥ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate
   - ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate
   - ≥ 20% basophils in the peripheral blood
   - Thrombocytopenia (<100 x 109/L) that is unrelated to therapy
3. Blast crisis (BC) as defined by any of the following:
   - ≥ 30% blasts in peripheral blood or bone marrow aspirate
   - Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma).

7.1.7 Withdrawal of consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

[redacted]

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and Rest of World: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 Molecular response

Molecular response (MR) will be assessed in all patients randomized to each treatment arm as well as in patients that switch study treatment from bosutinib to asciminib.

Levels of BCR-ABL1 transcripts will be determined by real-time quantitative PCR (RQ-PCR) testing of peripheral blood and analyzed at a central testing laboratory. Log reduction in BCR-ABL1 transcripts levels from the standardized baseline value, or the percent ratio of BCR-ABL1 transcripts versus control gene (ABL) transcripts converted to a reference standard, international scale (Hughes and Branford 2006), will be calculated for each sample.

Major molecular response and related variables are defined as the following:

- Rate of Major Molecular Response (MMR) where MMR is defined as a $\geq$ 3.0 log reduction in BCR-ABL1 transcripts compared to the standardized baseline equivalent to $\leq$ 0.1 % BCR-ABL1/ABL % by international scale as measured by RQ-PCR, confirmed by duplicate analysis of the same sample
- Time to MMR defined as the time from the date of randomization to the date of the first documented MMR,
- Duration of MMR defined as the time from the date of first documented MMR to the earliest date of loss of MMR, progression to AP or BC, or CML-related death.

[redacted]

Loss of MMR is defined as increase of BCR-ABL1/ABL to > 0.1% by international scale (IS) in association with a ≥ 5-fold rise in BCR-ABL1 from the lowest value achieved on study treatment and replicated by a second analysis of the same sample. Loss of MMR must be confirmed by subsequent sample analysis within 4 to 6 weeks showing loss of MMR associated with a ≥ 5-fold rise in BCR-ABL1 from the lowest value achieved on study treatment, unless it is associated with confirmed loss of CHR or loss of CCyR or progression to AP/BC or CML-related death. Mutational analysis will be performed at a Novartis designated laboratory by Sanger sequencing at Week 1 Day 1, upon confirmed loss of MMR and/or at end of treatment. If the result at Week 1 Day 1 is positive for a mutation, analysis will be performed every 12 weeks.

The blood samples will be taken as described in Table 7-1, Table 7-2 and Table 7-3.

Table 7-3 Blood samples (efficacy primary endpoint)

Sample Type	Volume	Visit	Time point
Blood for BCR-ABL1 quantification by RQ-PCR	20 mL	Screening/Baseline / S-Screening/S-Baseline*	Pre-dose
	20 mL	Week 4 / S-Week 4	Pre-dose
	20 mL	Week 8 / S-Week 8	Pre-dose
	20 mL	Week 12 / S-Week 12	Pre-dose
	20 mL	Week 16 / S-Week 16	Pre-dose
	20 mL	Week 24 / S-Week 24	Pre-dose
	20 mL	Week 36 / S-Week 36	Pre-dose
	20 mL	Week 48 / S-Week 48	Pre-dose
	20 mL	Week 60 / S-Week 60	Pre-dose
	20 mL	Week 72 / S-Week 72	Pre-dose
	20 mL	Week 84 / S-Week 84	Pre-dose
	20 mL	Week 96 / S-Week 96	Pre-dose
	20 mL	Every 12 weeks thereafter up to end of study treatment	Pre-dose
	20 mL	End of Treatment / S-End of Treatment	Anytime
Blood for BCR-ABL1 Mutation analysis by Sanger Sequencing	5 mL	Week 1 Day 1 /S-Week 1 Day 1*	Pre-dose
	No sample collected - testing is performed on the "Blood for BCR-ABL1 quantification by RQ-PCR" sample	Upon confirmed loss of MMR and/or End of Treatment/ S-End of Treatment	Anytime
Blood for BCR-ABL1 Mutation analysis **only** for patients with mutations at Week 1 Day 1	No sample collected - testing is performed on the "Blood for BCR-ABL1 quantification by RQ-PCR" sample	Week 12 and every 12 weeks thereafter up to end of study treatment	Anytime
*Assessment does not need to be completed during the visit for patients in the treatment switch if already collected during the EOT or the treatment switch screening visit.			

[redacted]

During the study, peripheral blood samples will be collected into PAXgene™ Blood RNA tubes for all RQ-PCR assessments. Detailed instructions for the collection, handling, and shipment of RQ-PCR and mutation samples are outlined in the [CABL001A2301 Laboratory Manual].

7.2.1.2 Bone marrow analysis and cytogenetics

Cytogenetic response will be assessed locally as the percentage of Ph+ metaphases in the bone marrow and is defined as the following (a review of a minimum of 20 metaphases is required):

- Complete (CCyR) - 0% Ph+ metaphases
- Partial (PCyR) - >0 to 35% Ph+ metaphases
- Major (MCyR) - 0 to 35% Ph+ metaphases
- Minor (mCyR) - >35 to 65% Ph+ metaphases
- Minimal - >65 to 95% Ph+ metaphases
- None - >95 to 100% Ph+ metaphases.

Bone marrow aspirate for cytogenetic analyses will be performed at screening/baseline (performed up to 56 days prior to Week 1 Day 1), at Week 24/S-Week 24, 48/S-48, 72/S-72, 96/S-96 as long as patient has not achieved MMR and at end of treatment (S-end of treatment as specified in Table 7-1 and Table 7-2. For patients on the bosutinib arm an unscheduled bone marrow assessment at week 12 may be performed to evaluate cytogenetic response in consideration for potential dose escalation.

Quantification of the percentage of Ph+ chromosome metaphases, number of metaphases, number positive for Ph chromosome, additional chromosomal abnormalities as well as data from cytologic evaluation (microscopic analysis) of percentage of blasts and promyelocytes will be recorded on the Bone Marrow eCRF. These exams will be performed and analyzed locally. Fluorescent In-situ hybridization (FISH) analysis will not be accepted.

7.2.1.3 Hematologic response

A complete hematologic response (CHR) is defined as all of the following present for ≥ 4 weeks:

- WBC count <10 x 10^9/L
- Platelet count <450 x 10^9/L
- Basophils <5%
- No blasts and promyelocytes in peripheral blood
- Myelocytes + metamyelocytes < 5% in peripheral blood
- No evidence of extramedullary disease, including spleen and liver

7.2.2 Safety and tolerability assessments

Safety will be monitored by the assessments described below as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8. Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the patient's eCRF.

[redacted]

7.2.2.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. Information about the physical examination must be present in the source documentation at the study center and will be collected on the following visits as specified in Table 7-1 and Table 7-2:

- Screening /S-Screening
- Week 1 Day 1 / S-Week 1 Day 1
- Every 2 weeks from Week 4 to Week 16 / S-Week 4 to S-Week 16. Week 6, 10 and 14 / S-Week 6, 10 and 14 assessments must be performed in case of previous or newly occurring adverse events.
- Every 4 weeks from Week 16 to Week 96 / S-Week 16 to S-Week 96
- Every 12 weeks from Week 96 to EOT / S-Week 96 to S-EOT
- End of treatment / S-End of treatment visit or early discontinuation / S-early discontinuation visit in case of premature discontinuation.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF. Presence of extramedullary leukemic involvement will be checked with each physical examination as outlined above. Findings on physical examination consistent with extra-medullary leukemic involvement will be recorded (e.g. liver and spleen size, any other organ involvement).

7.2.2.2 Vital signs

Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature and must be performed at the following visits as specified in Table 7-1 and Table 7-2:

- Screening / S-Screening
- Week 1 Day 1 / S-Week 1 Day 1
- Week 2 Day 1 / S-Week 2 Day 1
- Every 2 weeks from Week 4 to Week 16 / S-Week 4 to S-Week 16
- Every 4 weeks from Week 16 to Week 96 / S-Week 16 to S-Week 96
- Every 12 weeks from Week 96 to EOT/ S-Week 96 to S-EOT
- End of treatment / S-End of treatment visit or early discontinuation / S-early discontinuation visit in case of premature discontinuation.

7.2.2.3 Height and weight

Height in centimeters (cm) will be measured at screening only.

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1 and Table 7-2:

- Screening / S-Screening

[redacted]

- Week 1 Day 1 / S-Week 1 Day 1
- Every 12 weeks from Week 12 to EOT / S-Week 12 to S-EOT
- End of treatment visit / S-End of treatment or early discontinuation / S-early discontinuation visit in case of premature discontinuation.

7.2.2.4 Performance status

ECOG Performance status scale (Table 7-4) will be used as described in the Table 7-1, Table 7-2 and Table 7-4:

- Screening / S-Screening
- Week 1 Day 1 / S-Week 1 Day 1
- Every 2 weeks from Week 4 to Week 16 / S-Week 4 to S-Week 16
- Every 4 weeks from Week 16 to Week 96 / S-Week 16 to S-Week 96
- Every 12 weeks from Week 96 to EOT / S-Week 96 to S-EOT
- End of treatment / S-End of treatment visit or early discontinuation / S-early discontinuation visit in case of premature discontinuation.

More frequent examinations may be performed at the investigator's discretion, if medically indicated.

Table 7-4 ECOG Performance status scale

Description	Grade
Fully active, able to carry on all pre-disease activities without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light housework, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead.	5

7.2.2.5 Laboratory evaluations

Central laboratory will be used for analysis of hematology, biochemistry, coagulation, serum pregnancy and hepatitis marker specimens collected (safety monitoring) as specified in Table 7-1, Table 7-2 and Table 7-5. Details on the collections, shipment of the samples and reporting of results by the central laboratory are provided to investigators in the [CABL001A2301 Laboratory Manual]. The time windows granted for laboratory evaluations are identical with the corresponding visit time windows for each visit (see Section 7.1.5).

Local laboratory analysis are allowed if there is a clinical suspicion of abnormal laboratory values which is supported by a reported adverse event and for hematology assessments at Week 6, 10 and 14.

[redacted]

Table 7-5 Central clinical laboratory parameters collection plan

Test Category	Test Name	Frequency
Hematology	Hemoglobin, platelets, red blood cells, white blood cells, WBC morphology with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils, promyelocytes, myelocytes, metamyelocytes, blast and other)	Screening/baseline, Week 1 Day 1, Week 2 Day 1, every 2 weeks from week 4 up to week 16, every 4 weeks up to week 96, and every 12 weeks thereafter, EOT and as clinically indicated / S-Screening/S-baseline*, S-Week 1 Day 1, S-Week 2 Day 1, every 2 weeks from S-week 4 up to S-week 16, every 4 weeks up to S-week 96, and every 12 weeks thereafter, S-EOT and as clinically indicated
Chemistry	Hemoglobin A1c	Screening/baseline, Week 12 and as clinically indicated / S-Screening/S-baseline*, S-Week 12 and as clinically indicated
Chemistry	Creatinine clearance	Screening/baseline / S-Screening/S-baseline*
Chemistry	Albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), total calcium, total calcium (corrected for albumin), creatinine, creatine kinase, potassium, magnesium, sodium, phosphate (inorganic phosphorus), direct bilirubin, indirect bilirubin, total bilirubin, total cholesterol, LDL cholesterol, HDL cholesterol, total protein, triglycerides, blood urea or Blood Urea Nitrogen (BUN), uric acid, amylase, lipase, glucose (fasting)	Screening/baseline, Week 1 Day 1, Week 2 Day 1, every 4 weeks from week 4 up to week 96, and every 12 weeks thereafter, EOT, and as clinically indicated / S-Screening/S-baseline*, S-Week 1 Day 1, S-Week 2 Day 1, every 4 weeks from S-week 4 up to S-week 96, and every 12 weeks thereafter, S-EOT, and as clinically indicated
Coagulation	International Normalized Ratio (INR)	
Hepatitis markers	HbsAg, HbcAb /anti-Hbc	Screening/baseline**
Serum Pregnancy test (if applicable)	Serum ß-HCG testing	Screening/baseline, every 4 weeks up to week 96, and every 12 weeks thereafter, EOT, unscheduled / S-Screening/S-baseline*, every 4 weeks up to S-week 96, and every 12 weeks thereafter, S-EOT, unscheduled
*Assessment does not need to be completed during the screening visit for patients in the treatment switch if already collected during the EOT. **Not applicable for patients being assessed for treatment switch as part of the treatment switch screening/baseline visit.		

7.2.2.5.1 Hematology

Hematology labs are to be analyzed at each scheduled visit by a central laboratory (Week 6, 10 and 14 assessments can be performed at site or at any peripheral local laboratory) as specified in Table 7-1 and Table 7-2. Hematology includes assessment of hemoglobin, platelets count, red blood cells, total white blood cell count (WBC) and a full manual differential count including basophils, eosinophils, lymphocytes, monocytes, neutrophils, promyelocytes, myelocytes, metamyelocytes, blast and other cells (Table 7-5).

[redacted]

7.2.2.5.2 Clinical chemistry

Blood chemistry labs are to be analyzed at each scheduled visits by a central laboratory as specified in Table 7-1 and Table 7-2. Chemistry includes albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), total calcium, total calcium (corrected for albumin), creatinine, creatinine clearance, creatine kinase, potassium, magnesium, sodium, phosphate (inorganic phosphorus), direct bilirubin, indirect bilirubin, total bilirubin, total cholesterol, LDL cholesterol, HDL cholesterol, total protein, triglycerides, blood urea, Blood Urea Nitrogen (BUN), uric acid, amylase, lipase and fasting glucose. In addition the coagulation parameter INR is analyzed at each scheduled visit.

HbA1c is analyzed at screening/baseline, week 12 and as clinically indicated.

The hepatitis markers HbsAg, HbcAb/anti-Hbc are analyzed at screening/baseline (Table 7-5).

7.2.2.5.3 Pregnancy and assessments of fertility

All women of childbearing potential have to complete a serum pregnancy test at the screening visit, at every monthly visit until end of treatment visit. Pregnancy testing is not required for patients who are determined to be post-menopausal. The time windows granted for pregnancy testing are identical with the corresponding visit time windows for each visit. Refer to Table 7-1 and Table 7-2 of the Visit evaluation schedules. Serum pregnancy test will be performed by a central laboratory.

After Week 96 / S-Week 96, monthly urine pregnancy test must be performed by all women of child-bearing potential between the three monthly visits (beginning at Week 100 / S-Week 100). Urine pregnancy tests may be performed at the investigational site or at home. Test results performed at home should be recorded onto a patient diary and brought to each scheduled visit for the site to review. If a test result indicates a pregnancy, the patient must contact the investigator immediately.

Pregnancies diagnosed in female patients participating in the study should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the Oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) Department.

During the whole study, women of childbearing potential should employ the use of highly effective contraception. Highly effective contraception methods are defined in Section 5.3

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

After the subject has rested approximately 10 minutes in a semi-supine position, standard 12-lead ECGs must be obtained in triplicate with a recommended minimal interval of 5 minutes between each ECG at the time points specified in Table 7-1, Table 7-2, Table 7-6 and Table 7-7. ECGs should be taken before blood samples for PK if both assessments are scheduled at the same time point. In this case recording of ECGs should be planned according to the true time of blood sample for PK rather than to the scheduled time point.

[redacted]

Table 7-6 Central ECG collection (all patients)

Week (or Day)	Number of ECGs (per visit)	Time of ECG
Screening/Baseline Day -21 to -1 / S-Screening/S-Baseline Day -42 to -1 (all patients)	3	3 serial ECGs at the screening visit
Week 1 Day 1 / S-Week 1 Day 1 (all patients)	3	3 serial ECGs at 2 h post dose
Week 2 Day 1 / S-Week 2 Day 1 (asciminib/asciminib switch patients)	12	3 serial ECGs pre-dose and at 2, 3, 4 h post-dose
Week 2 Day 1 / S-Week 2 Day 1 (bosutinib)	3	3 serial ECGs pre-dose
Week 4 / S-Week 4 (all patients)	3	3 serial ECGs pre-dose
Week 12 / S-Week 12 (all patients)	3	3 serial ECGs pre-dose
Week 24 / S-Week 24 (all patients)	3	3 serial ECGs pre-dose
Week 96 / S-Week 96 (all patients)	3	3 serial ECGs 30 min* post-dose
Unscheduled (all patients)	3	3 serial ECGs
* 30 min +/- 5min allowed		

Table 7-7 Central ECG collection plan for patients in full PK asciminib group

Week (or Day)	Number of ECGs (per visit)	Time of ECG
Day -21 to -1	3	3 serial ECGs at the screening visit
Week 1 Day 1	3	3 serial ECGs at 2 h post dose
Week 2 Day 1	24	3 serial ECGs pre-dose and at 1, 2, 3, 4, 6, 8, 12 h post-dose
Week 4	3	3 serial ECGs pre-dose
Week 12	3	3 serial ECGs pre-dose
Week 24	3	3 serial ECGs pre-dose
Week 96	3	3 serial ECGs 30 min* post-dose
Unscheduled	3	3 serial ECGs
* 30 min +/- 5min allowed		

All ECGs performed will be independently reviewed. Instructions for the collection and transmission of these ECGs to the independent central reader (ERT (Electronic Research Technology, Inc.)) will be provided in the [CABL001A2301 ECG Manual].

Three serial ECGs (triplicate) should be performed ½ hour prior to dosing for pre-dose assessment. The serial ECGs should be taken approximately 5 minutes apart. All 3 ECGs for each time point should be sent to ERT. Readings for QTc prolongation will be based on the average seen in the scans for each time point. The enrollment of patients has to be based on centrally assessed QTcF time. If one of the 3 serial ECGs prior to dosing on day 1 shows a QTcF ≥ 450 msec (male) or ≥ 460 msec (female) by automated reading, an immediate manual

[redacted]

central reading must be requested by calling ERT. The patient may not be dosed if the average of the manually read ECGs confirms a QTcF ≥ 450 msec (male) or ≥ 460 msec (female).

Dose adjustments in case of QT prolongation should be performed per Section 6.3.2.

Additional unscheduled ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator.

All ECGs, including unscheduled triplicate safety ECGs with clinically relevant findings, collected during the study should be transmitted to the central core ECG laboratory for review.

The results of the centrally assessed ECGs are automatically transferred into the clinical database.

Clinically significant ECG abnormalities present at screening should be reported on the Medical History eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

7.2.2.6.2 Cardiovascular risk factor assessment

Cardiovascular events (CVE) including ischemic heart disease, peripheral arterial occlusive disease and ischemic cerebrovascular events have been reported in CML patients receiving TKI therapies as specified in Table 7-1 and Table 7-2. As both study treatments in the trial are TKIs (asciminib and bosutinib), the cardiovascular risk factors (hypertension, tobacco use, raised blood glucose (diabetes), physical inactivity, unhealthy diet, cholesterol/lipids, overweight and obesity) of each patient will be collected prior to randomization and end of treatment. This will also include the patient's Family History.

7.2.2.6.3 Echocardiogram

Echocardiograms will be performed to monitor cardiac safety. Assessments are scheduled at screening/baseline, Week 20 and end of treatment visits. The echocardiogram will be performed and evaluated locally to assess the left ventricular ejection fraction. Any clinically significant findings will be collected and reported in the database (i.e. reported as adverse events). For patients that switch from bosutinib to asciminib treatment, an echocardiogram will no longer be required.

7.2.2.6.4 Pulmonary function test

Pulmonary function test will be performed to monitor cardio-pulmonary safety. Assessments are scheduled at screening/baseline, Week 20 and end of treatment visits. The pulmonary function test with the plethysmograph includes the assessment of the lung volumes FEV1, FVC, FEV1/FVC, TLC and VC. In addition the DLCO to evaluate the gas exchange will be assessed at the same time points. Any clinically significant findings will be collected and reported in the database (i.e. reported as adverse events). For patients that switch from bosutinib to asciminib treatment, the pulmonary function testing will no longer be required.

[redacted]

7.2.3 Pharmacokinetics

Blood samples for asciminib pharmacokinetics will be collected on all study subjects allocated to the asciminib treatment arm. Blood samples for full PK profiles will be collected from at least 20 patients. These patients will be identified sequentially at selected sites that are capable of serial PK sampling over 12 hours. Asciminib should be taken for at least 3 consecutive days without interruption or dose modification prior to full PK day.

Blood samples for asciminib pharmacokinetics will also be collected on patients switching from bosutinib to asciminib (see Table 7-8).

For the assessment of asciminib pharmacokinetics in plasma, serial blood samples will be collected following asciminib administration at several time-points (see Table 7-1, Table 7-2, Table 7-8 and Table 7-9 below for further details). Remaining plasma samples may be used for identification and/or measurement of metabolites of asciminib.

Refer to the [CABL001A2301 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

Table 7-8 Pharmacokinetic blood collection log (Sparse PK-group-asciminib arm/ asciminib treatment switch patients)

Week / S-Week	Day	Scheduled Time Point	Dose Reference ID	PK Sample No	Blood Volume (mL)
1	1	2 h (± 10 min)	101	101	2
2	1	0 h (Pre-dose)[a]	102/2001[b]	102	2
	1	2 h (± 10 min)	102	103	2
	1	3 h (± 15 min)	102	104	2
	1	4 h (± 15 min)	102	105	2
4	Any	0 h (Pre-dose)[a]	103/3001[b]	106	2
12	Any	0 h (Pre-dose)[a]	104/4001[b]	107	2
24	Any	0 h (Pre-dose)[a]	105/5001[b]	108	2
96	Any	0 h (Pre-dose)[a]	106/6001 [b]	109	2
		Unscheduled		1001+	

[a] Pre-dose PK sample should be taken immediately prior to the next administration of asciminib. PK samples on Week 2 Day 1 should be taken before and after the morning dose (i.e. 1st dose of the day). PK samples on other weeks may be taken immediately prior to the morning dose (i.e. 1st dose of the day) or the evening dose (i.e. 2nd dose of the day).
[b] The first dose reference ID refers to the first dose administered after PK sampling and the second dose reference ID refers to the last dose administered prior to the PK sampling.

[redacted]

Table 7-9 Pharmacokinetic blood collection log (Full PK group-asciminib arm)

Week	Day	Scheduled Time Point	Dose Reference ID	PK Sample No	Blood Volume (mL)
1	1	2 h (± 10 min)	1	1	2
2	1	0 h (Pre-dose)[a]	2/201[b]	2	2
	1	0.5 h (± 10 min)	2	3	2
	1	1 h (± 10 min)	2	4	2
	1	2 h (± 10 min)	2	5	2
	1	3 h (± 15 min)	2	6	2
	1	4 h (± 15 min)	2	7	2
	1	6 h (± 30 min)	2	8	2
	1	8 h (± 60 min)	2	9	2
	1	12 h (± 60 min) (Pre-dose)[a]	3/2[b]	10	2
4	Any	0 h (Pre-dose)[a]	4/401[b]	11	2
12	Any	0 h (Pre-dose)[a]	5/501[b]	12	2
24	Any	0 h (Pre-dose)[a]	6/601[b]	13	2
96	Any	0 h (Pre-dose)[a]	7/701[b]	14	2
		Unscheduled		2001+	

[a] Pre-dose PK sample should be taken immediately prior to the next administration of asciminib. PK samples on Week 2 Day 1 should be taken before and after the morning dose (i.e. 1st dose of the day). PK samples on other weeks may be taken immediately prior to the morning dose (i.e. 1st dose of the day) or the evening dose (i.e. 2nd dose of the day).
[b] The first dose reference ID refers to the first dose administered after PK sampling and the second dose reference ID refers to the last dose administered prior to the PK sampling.

7.2.3.1 Analytical method

Plasma asciminib concentrations will be measured at the designated laboratory using a validated high-performance liquid chromatography/tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) was 1.00 ng/mL.

7.2.4 Biomarkers

[redacted]

7.2.4.2 Biomarker assessments in blood samples

Blood samples will be requested from all patients participating in the study.

Characterization of low level mutations in BCR-ABL1 gene

A 10 mL blood sample to be collected at Week1 Day 1 pre-dose, to confirm loss of MMR and/or end of treatment to assess whether there are low level mutations undetected by Sanger Sequencing in BCR-ABL1 gene at Week 1 Day 1 or new mutations appearing during treatment and at time of disease progression which potentially cause resistance to asciminib or bosutinib treatment as specified in Table 7-1, Table 7-2 and Table 7-10.

[redacted]

Table 7-10 Biomarker sample collection plan

Sample Type	Volume	Visit	Time point
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
Blood samples (exploratory)			
Blood for low level mutation analysis	10mL	Week 1 Day 1/ S-Week 1 Day 1*	Pre-dose
	10mL	Upon visit to confirm loss of MMR and/or End of Treatment	Anytime
[redacted]			
[redacted]			
[redacted]			
[redacted]			

*Assessment does not need to be completed during the S-Week 1 Day 1 visit for patients in the treatment switch if already collected during the EOT.

**Assessment does not need to be completed during the S-Week 1 Day 1 visit for patients in the treatment switch if already collected during the Week 1 Day 1 visit.

[redacted]

7.2.5 Resource utilization

The measures of healthcare Resource Utilization (RU) to be collected include: hospitalization (H), emergency room (ER) visit, general practitioner (GP) visits, specialist (Sp) visit and urgent care (UC) visit. These measures will be used to derive the economic impact of asciminib and bosutinib.

Hospitalization visits will also record the number of days in ward and the type of ward (hospital unit) and the discharge status. At each RU collection, the reason for the visit (i.e. related to CML, AE related to CML therapy or other reason) will be collected in order to quantify the impact of asciminib and bosutinib on healthcare resources.

The RU assessment will be completed at each scheduled clinical trial visit as specified in Table 7-1; the RU will be completed by the investigator however information with respect to the number of GP, UC, Sp or ER visits will be ascertained from the patient.

All attempts to collect as much information from the patient as possible should be made in order to minimize selection bias.

7.2.6 Patient reported outcomes

The MDASI CML, PGIC, WPAI along with EQ-5D-5L (EuroQol Group (1990), Brooks (1996), Herdman et al (2011)) will be used to compare data on the patient's disease-related symptoms and health-related quality of life from baseline to EOT between the treatment arms. The WPAI will be used to assess work productivity and activity impairment related to the patient's CML. All measures will assess differences between the treatment arms. All tools require patient's direct completion and will be administered utilizing an electronic device for data collection.

Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses. Missing data items in a scale will be handled according to the manual for each instrument. No imputation will be applied if the total or subscale scores are missing at a visit.

The patient should be given the questionnaire(s) to be completed at the scheduled visit before any clinical assessments are conducted as specified in Table 7-1. Completion of all questionnaires is mandatory; they cannot be skipped. In the event a patient refuses to complete the questionnaire(s), the patient's refusal should be documented in the study data capture system and should not be captured as a protocol deviation. Patient questionnaires should be completed in the language most familiar to the patient.

The patient should be given sufficient space and time to complete the questionnaires and the administered questionnaire should be reviewed for completeness. If missing responses are noted, patients should be encouraged to complete any missing responses.

Completed questionnaire(s) and any unsolicited comments written by the patient should be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the patient to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 8 (e.g. reference "Adverse Events" Section) of the study protocol.

[redacted]

MDASI-CML

The M.D. Anderson Symptom Inventory – Chronic Myeloid Leukemia (MDASI-CML) is a 26 item self-administered questionnaire for adult CML patients. Twenty of the items measure the severity of disease-related symptoms and are scored from 0 (Not present) to 10 (As Bad as you can imagine) and 6 items that measure symptom interference with daily life scored from 0 (Did not interfere) to 10 (Interfered completely). Descriptive statistics will be provided for the MDASI-CML symptom score and interference score, and the change in the MDASI-CML symptom score and interference score from baseline to all available time points to the end of study. Additional analysis may be performed and details will be described in the analysis plan.

EQ-5D-5L

EQ-5D-5L is a two-part standardized instrument for measuring health outcomes in a wide range of health conditions and treatments. It consists of a descriptive system and a visual analogue scale (EQ VAS). The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems (or unable to perform the activity). The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'worst imaginable health state'. The health states derived from the descriptive system can be summarized into a single index score that provides a simple measure of health for clinical and economic appraisal. Descriptive statistics will be provided for EQ-5D-5L health index score and for the EQ VAS, at each scheduled assessment time point. There should be only ONE response for each dimension. Missing values can be coded as '9'. Ambiguous values (e.g. 2 boxes are ticked for a single dimension) should be treated as missing values. Additional analysis may be performed and details will be described in a separate analysis plan.

WPAI

The Work Productivity and Activity Impairment Questionnaire (WPAI) is a four-item questionnaire which is intended to measure work and activity impairment associated with CML for those who self-identify as currently employed for pay. This questionnaire measures self-reported productivity loss associated with CML during the past seven days. It consists of questions about absence from work due to CML, hours spent at work, the reduction in productivity at work attributed to CML, and the reduction in productivity while performing regular activities. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, Scoring will be done according to WPAI instrument guidance resulting in four scores including: Percent work time missed due to problem; percent impairment while working due to problem; Percent overall work impairment due to problem; and, percent activity impairment due to problem. Change from baseline in WPAI at each visit, where measured, will be done for each of the four derived scores.

PGIC

The Patient Global Impression of Change is comprised of a single question intended to measure a patient's perspective of improvement or deterioration over time relative to treatment. The

[redacted]

PGIC uses a seven-point scale where one (1) equals very much improved and seven (7) equals very much worse. A summary of Patient Global Impression of Change (PGIC) at each visit, where measured will be provided.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)

[redacted]

5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)

If the event worsens the event should be reported a second time in the eCRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the eCRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Natural progression or deterioration of the malignancy under treatment (including loss of response, progression to accelerated phase or blast crisis and death due to disease progression), will be recorded as part of the efficacy evaluation and should NOT be reported as an AE/SAE.

Signs and symptoms clearly associated with the disease under study should NOT be reported as AEs unless they are newly emergent (i.e. not previously observed in the patient), judged by the Investigator to be unusually severe or accelerated, or if the Investigator considers deterioration of disease-related signs and symptoms to be caused directly by the study drug. If there is any uncertainty about an AE being due solely to the disease under study, it should be reported as an AE or SAE as appropriate.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by

[redacted]

the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the [Asciminib Investigator's Brochure].

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time

[redacted]

interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

[redacted]

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided asciminib Investigator's Brochure or bosutinib label. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

This study will institute a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will be constituted prior to the randomization of the first patient. The DMC will be responsible to review safety data at approximately 6 months after the first randomized patient has started study treatment. Subsequent reviews will be conducted approximately every 6 months on an as and when needed basis thereafter (i.e. if significant safety findings are noted). This includes but does not limit the role of the DMC to evaluate these data and to provide recommendations to the sponsor to continue, modify or stop the study early. The DMC will be in place at least until the conduct of the primary analysis.

It is expected that the DMC will consist at a minimum of two physicians with appropriate disease area qualifications and one statistician. There will be a meeting with the DMC describing their roles and responsibilities and discussing potential data format and process issues prior to the finalization of DMC charter.

It is envisioned that the DMC may make certain types of recommendations, namely:

- No safety concerns, ethical to continue the study as planned
- Serious safety concerns precluding further study treatment, regardless of efficacy
- Recommendation to continue the study but proposing an amendment to the protocol (e.g., incorporate an additional safety assessments)

8.7 Steering Committee

In order to monitor study conduct, a Steering Committee (SC) will be established comprising investigators participating in the trial. Additionally two sponsor representatives (a physician and a statistician) will be active members of this committee.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. Novartis will make final decisions on trial conduct based on SC recommendations. Together with the clinical trial team, the SC will review protocol amendments as appropriate, and also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

[redacted]

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

[redacted]

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Data collected by third parties (biochemistry, PCR assessments, biomarkers, PK) will be sent electronically to Novartis.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using the Novartis Interactive Response Technology.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

The data will be analyzed by Novartis and/or designated CRO. It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis.

[redacted]

Study data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant PK and PD measurements.

The cut-off date for the primary analysis is defined as the date when all patients have been on study treatment for 24 weeks or discontinued earlier. The cut-off date for the end of study treatment analysis is defined as 30 days after the end of study treatment period (see Section 4.3) to ensure that all available treatment phase data from all patients up to the last dose of study drug taken in this study, will be analyzed and summarized in the end of study treatment phase CSR. Patients will be further followed for survival and progression for up to 5 years from the date the last randomized patient receives the first study dose. An update analysis of OS and PFS will be performed at the end of the follow-up period in the final study CSR.

10.1 Analysis sets

10.1.1 Full Analysis Set

The **Full Analysis Set (FAS)** comprises all patients to whom study treatment has been assigned by randomization. According to the intention to treat principle, patients will be analyzed according to the treatment and stratum they have been assigned to during the randomization procedure.

10.1.2 Safety set

The **Safety Set** includes all patients who received at least one dose of study treatment. Patients will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

10.1.3 Per-Protocol set

The **Per-Protocol Set (PPS)** consists of a subset of the patients in the FAS who are compliant with requirements of the CSP. The PPS will be used for sensitivity analyses on the primary endpoint only.

Oncology standards for protocol deviations potentially leading to exclusion from the PPS are:

- Type of indication different from those required by the CSP
- If prior therapy does not match with CSP requirements in terms of number and types of previous therapy regimens
- Another anti-neoplastic therapy administered after start of study treatment and prior to first efficacy assessment
- Study treatment received different from treatment assigned by randomization

10.1.4 Dose-determining analysis set

Not applicable.

[redacted]

10.1.5 Pharmacokinetic analysis set

The **Pharmacokinetic analysis set (PAS)** includes all patients who provide at least one evaluable PK concentration. For a concentration to be evaluable, patients are required to:

- Take a dose of asciminib prior to sampling,
- Take the same dose of asciminib for at least 3 consecutive days without dose interruption or dose modification prior to sampling,
- For post-dose samples, do not vomit within 4 hours after the dosing of asciminib (this is the current dose); for pre-dose samples do not vomit within 4 hours after the dosing of asciminib prior to sampling (this is the previous dose),
- Have the pre-dose sample collected before the next dose administration.

10.1.6 Other analysis set

For duration of MMR and time to MMR, the MMR Responder Set that will be used is a subset of FAS and includes patients who achieve MMR at any time.

For CCyR rates at and by scheduled time points, the CCyR Analysis Set that will be used is a subset of FAS and includes patients who are not in CCyR at baseline.

For duration of CCyR and time to CCyR, the Cytogenetic Responder Set that will be used is a subset of FAS and includes patients who do not have CCyR at baseline and achieve CCyR at any time on study treatment.

Patients who will receive at least one dose of asciminib after bosutinib failure will form the Switch Analysis Set which will be used for safety and exploratory efficacy endpoints defined on these patients.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the FAS or the Safety Set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, by treatment group.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The Safety set will be used for the analyses below.

Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in days to asciminib and bosutinib, as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and

[redacted]

the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics.

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized by treatment group and all dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

10.4 Primary objective

The primary objective of the study is to evaluate the efficacy of asciminib at the recommended dose in CML patients in chronic phase, previously treated with 2 or more tyrosine kinase inhibitors and to compare this efficacy profile in this population with that achieved by patients receiving bosutinib.

10.4.1 Variable

The primary efficacy variable of the study is the Major Molecular Response (MMR) rate at 24 weeks. A patient will be counted as having achieved MMR at 24 weeks if he meets the MMR criteria (BCR-ABL1 ratio $\leq$ 0.1%) at 24 weeks.

10.4.2 Statistical hypothesis, model, and method of analysis

The MMR rate at 24 weeks will be calculated based on the FAS and according to the Intention-ToTreat (ITT) principle. MMR rate and its 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. The confidence interval for the difference in MMR rate between treatment groups will be provided using the Wald method.

The null hypothesis is that there is no difference between the treatment groups with respect to MMR rate at 24 weeks. The Cochrane-Mantel-Haenszel chi-square test, stratified by the randomization stratification factor, i.e. major cytogenetic response status (PCyR or CCyR vs. others) at screening, will be used to compare MMR rate between the two treatment groups, at the two-sided 5% level of significance. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

10.4.3 Handling of missing values/censoring/discontinuations

Only patients with MMR at 24 week visit are considered responders. In other words, any patient who achieves MMR before 24 weeks, but is no longer in MMR at 24 weeks, will be considered as a non-responder in this primary analysis. Patients discontinuing the randomized treatment (having performed an EOT visit) prior to 24 weeks due to any reason will be considered as non-responders. One exception to the rule above is if the 24-week PCR evaluation is missing, but both a PCR evaluation at 16 weeks and a PCR evaluation at 36 weeks indicate MMR, the 24-week assessment is imputed as a ‘Response’. If PCR evaluations are performed at unscheduled visits closer to the Week 24 visit (before or after), these will be taken into account for the imputation.

[redacted]

10.4.4 Supportive and Sensitivity analyses

The analysis of the primary endpoint will also be repeated on the PPS if the PPS is different from the FAS.

Subgroup analyses and a logistic regression analysis will be employed. Refer to the exploratory objectives Section 10.6.1 for further details.

10.5 Secondary objectives

The secondary objectives in this study are as follows:

- To compare additional parameters of the efficacy of asciminib versus bosutinib, defined as:

Key secondary endpoints

- MMR rate at 96 weeks

Other efficacy endpoints

- Cytogenetic response (Complete, Partial, Major, Minor, Minimal, no response) rate at all scheduled data collection time points including, 24, 48 and 96 weeks.
- Cytogenetic response (Complete, Partial, Major, Minor, Minimal, no response) rate by all scheduled data collection time points including, 24, 48 and 96 weeks.
- MMR rate at all scheduled data collection time points (except 24 and 96 weeks which are already covered by primary and key secondary endpoints)
- MMR rate by all scheduled data collection time points including 24, 48 and 96 weeks.
- Time to MMR
- Duration of MMR
- Time to CCyR
- Duration of CCyR
- Time to treatment failure
- Progression free survival
- Overall survival
- To compare the safety and tolerability profile of asciminib versus bosutinib
- To characterize the PK of asciminib in the CML-CP population

10.5.1 Key secondary objective(s)

The key secondary endpoint to be evaluated is MMR rate at 96 weeks, which is defined as the proportion of patients with MMR at 96 weeks and derived in a similar fashion to MMR rate at 24 weeks.

[redacted]

10.5.1.1 Analysis for key secondary objectives

The null hypothesis is that there is no difference between the treatment groups with respect to MMR rate at 96 weeks. Formal statistical testing of the key secondary endpoint will be performed with $\alpha = 0.05$ (two-sided) only if the primary endpoint (i.e. MMR rate at 24 weeks) is significant by means of a gatekeeping procedure to control the overall alpha level. Otherwise, no statistical testing will be performed, and any analysis will be considered exploratory.

MMR rate at 96 weeks will be evaluated in a similar fashion to the primary analysis of MMR rate at 24 weeks. The rate and the associated 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. Confidence interval for the difference between treatment groups will be provided using the Wald method.

Statistical testing will be performed via CMH chi-square test stratified by the randomization strata. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

If the PCR evaluation at 96 weeks is missing, but a PCR evaluation both at 84 weeks and 108 weeks indicate MMR, the 96 week assessment is imputed as a "response", assuming that MMR is maintained between 84 and 108 weeks. If PCR evaluations are performed at unscheduled visits closer to the Week 96 visit (before or after), these will be taken into account for the imputation.

10.5.2 Other secondary efficacy objectives

Unless otherwise stated the FAS will be used for the analysis of all other secondary efficacy endpoints. The exceptions are using the Molecular Responder Set for duration of MMR and time to MMR, the CCyR Analysis Set for CCyR rates, and the Cytogenetic Responder Set for duration of CCyR and time to CCyR.

No statistical testing of non-key secondary efficacy endpoints will be performed, and any analysis will be considered exploratory.

Molecular Response

MMR rates at scheduled time points (except 24 and 96 weeks which have been specified as primary and key secondary endpoints) will be evaluated in a similar fashion to the primary analysis of MMR rate at 24 weeks. Patients discontinuing the randomized treatment prior to a specific time point due to any reason will be considered as non-responders for that time point.

MMR rates by scheduled time points are defined as the proportion of patients who achieve MMR at or before the specified visit, i.e. if a patient achieves an MMR but then loses it before or at the visit, he/she will still be classed as achieving MMR by that time point.

For each endpoint the rate and the associated 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. Confidence intervals for the differences in any response rates between treatment groups will be provided using the Wald method.

Statistical testing will be performed via CMH chi-square tests stratified by the randomization strata. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

[redacted]

Duration of MMR is defined in Section 7.2.1.1 as the time between the date of the first documented MMR and the earliest date of loss of MMR, progression to AP/BC, or CML-related death for patients in the Molecular Responder Set. The time will be censored at the last molecular assessment (PCR) date while on treatment for patients who have not experienced any of the above events.

Duration of MMR will be analyzed by K-M method and presented by K-M plots. The estimated rates of patients who are still responding at various time points will also be provided using K-M method.

The cumulative incidence of MMR will be graphically displayed by an increasing step function. This curve will increase each time (after randomization) at which a new responder is observed and thus will increase up to the best observed response rate (e.g. up to 50% if half of the patients in the analysis population are able to achieve response).

Time to MMR is defined in Section 7.2.1.1 and calculated as: date of first MMR - date of randomization +1, for patients in the Molecular Responder Set. Descriptive statistics (minimum, maximum, median, quartiles, mean, sd) of time to MMR will be provided for the two treatment groups separately.

Cytogenetic Response

Patients in FAS will be categorized with counts and percentages provided for cytogenetic response (Complete, Partial, Major, Minor, Minimal, No Response) at and by (i.e. best response up to a specified time point) scheduled time points. Shift tables will also be employed to examine the changes in cytogenetic response category from baseline.

Since there are expected to be only limited numbers who are actually in CCyR at baseline the analysis of CCyR rate at and by scheduled time points will only include patients who are not in CCyR at baseline, i.e. the CCyR Analysis Set.

CCyR rates at and by scheduled time points etc. and the associated 95% confidence intervals based on the Pearson-Clopper method will be presented by treatment group with the analysis of these endpoints only including patients who are not in CCyR at baseline.

Confidence intervals for the differences in any response rates between treatment groups will be provided using the Wald method.

Statistical testing will be performed via CMH chi-square tests stratified by the randomization strata. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

Time to CCyR is defined for patients in the Cytogenetic Responder Set as: date of first CCyR - date of randomization +1. Descriptive statistics (minimum, maximum, median, quartiles, mean, sd) of time to CCyR will be provided for the two treatment groups separately.

The cumulative incidence of CCyR will also be graphically displayed by an increasing step function. This curve will increase each time (after randomization) at which a new responder is observed and thus will increase up to the best observed response rate.

Duration of CCyR is defined as the time between date of first documented CCyR and the earliest date of loss of CCyR, progression to AP/BC, or CML-related death for patients in the

[redacted]

Cytogenetic Responder Set. The time will be censored at the last cytogenetic assessment date on treatment for patients for whom none of the above events is reported or last PCR evaluation on treatment indicating MMR.

Duration of CCyR response will be analyzed by K-M method and presented by K-M plots. The estimated rates of patients who are still responding at various time points will also be provided using K-M method.

Treatment failure, disease progression and survival

Time to treatment failure (TTF) is defined as the time from date of randomization to an event of treatment failure. The following events will constitute 'treatment failure', and are based on the ELN criteria (Baccarani et al 2013) defining failure of a second line treatment adapted to include discontinuation of randomized treatment as an event:

- No CHR or > 95% Ph+ metaphases at three months after randomization or thereafter
- BCR-ABL1 ratio > 10% IS and/or > 65% Ph+ metaphases at six months after randomization or thereafter
- BCR-ABL1 ratio > 10% IS and/or > 35% Ph+ metaphases at 12 months after randomization or thereafter
- Loss of CHR, CCyR or PCyR at any time after randomization
- Detection of new BCR-ABL1 mutations which potentially cause resistance to study treatment at any time after randomization
- Confirmed loss of MMR
- New clonal chromosome abnormalities in Ph+ cells: CCA/Ph+: at any time after randomization
- Discontinuation from randomized treatment for any reason

For patients who have not reached treatment failure, their TTFs will be censored at the time of last study assessment (PCR, cytogenetic, hematologic or extramedullary) before the cut-off date.

Progression-Free-Survival (PFS) is defined as the time from the date of randomization to the earliest occurrence of documented disease progression to AP/BC or the date of death from any cause (including progressions and deaths observed during the survival follow-up period) before the cut-off date.

The time will be censored at the date of last study assessment (PCR, cytogenetic, hematologic or extramedullary) or last post-treatment follow-up for patients without event.

Overall survival (OS) is defined as the time from the date of randomization to the date of death (including the survival follow-up period). Patients who are alive at the time of the analysis data cutoff date will be censored at the date of last contact before the cut-off date.

TTF, PFS and OS will be estimated and graphically displayed using the K-M approach on FAS. The estimated rates by K-M method at various time points will be provided and the endpoints will be compared between the two treatment groups using stratified log-rank test stratified by the randomization strata. The hazard ratio and 95% confidence intervals will be computed from a stratified Cox model.

[redacted]

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

The overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of subject's first informed consent to the day before first administration of study treatment
2. on-treatment period: from day of first administration of study treatment to 30 days after last actual administration of the same study treatment (including start and stop date)
3. post-treatment period: starting at day 31 after last administration of any study treatment

Summary tables for safety data will be presented for the on-treatment period. Comparative analysis will be performed only for the on-treatment period. Listings of safety data will include pre-treatment, on-treatment, and post-treatment periods, with a flag to indicate data collected before or after the on-treatment period.

The same analysis will be done for patients that switch to asciminib after treatment failure on bosutinib. However, safety events that initiated on or after start of asciminib during the switch treatment phase will be included.

10.5.3.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and serious adverse events (including those from the pre-treatment, on-treatment and post-treatment periods) will be listed and those collected before or after the on-treatment period will be flagged.

10.5.3.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

[redacted]

For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following listings and summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v4.03

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline in the on-treatment period.
- Shift tables using CTCAE grades to compare respective baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v4.03,

- Shift tables using the low/normal/high/ (low and high) classification to compare respective baseline to the worst on-treatment value.

10.5.3.4 Other safety data

ECG

ECGs (12-lead) including PR, QRS, QT, QTcF, and HR intervals will be obtained for each subject during the study. ECG data will be read and interpreted centrally.

Categorical analysis of QT/QTc interval data based on the number of patients meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these patients will be produced by treatment group.

Vital signs

Data on vital signs will be tabulated and listed, notable values will be flagged.

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

10.5.3.6 Tolerability

Tolerability of each study treatment will be assessed by summarizing the number of subjects with dose interruptions and dose reductions. Reasons for dose interruptions and dose reductions will be listed by subject and summarized.

10.5.4 Secondary PK objectives

The PK objective is to characterize the PK of asciminib in CML population.

Using PAS, summary statistics (n, mean, SD, coefficient of variation (CV) for mean, geometric mean, CV for geometric mean, median, minimum and maximum) will be presented for plasma concentration at each scheduled time point. The geometric mean with mean (SD) and individual plasma concentration versus time profiles of asciminib will be displayed graphically.

[redacted]

Using Safety set, concentration data will be listed. Concentration values below the limit of quantification (BLQ) will be set to zero by the Bioanalyst and displayed in listings as zero with a flag. BLQ values will be handled as zero in any calculations of summary statistics, but handled as missing for the calculation of the geometric means and CVs.

Pharmacokinetic parameters will be determined by non-compartmental method(s) using the pharmacokinetic profile of asciminib in patients with full PK sampling. PK parameters listed in Table 10-1 will be derived and reported, when feasible.

Population PK modeling may be performed and the results may be reported in a separate population PK report. Data from this study may be combined with data from other studies for this analysis.

Table 10-1 Non compartmental pharmacokinetic parameters in full PK group

AUC0-12h	The area under the plasma concentration-time curve from time zero to 12 h (mass x time x volume-1)[a]
Cmax	The maximum (peak) observed plasma drug concentration after dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma drug concentration after dose administration (time)
CL/F	The total body clearance of drug from the plasma after oral administration (volume x time-1)

10.6 Exploratory objectives

10.6.1 Exploratory efficacy objectives

- To evaluate the influence of factors such as major cytogenetic status at baseline, failure/intolerance to prior TKIs, line of therapy, gender, race and age on the effect of asciminib with respect to the primary efficacy endpoint.
- To characterize mutations in the BCR-ABL1 gene at Week 1 Day 1, upon confirmed loss of molecular response and/or at end of treatment and examine their association with molecular and cytogenetic response for asciminib vs. bosutinib.
- To assess the efficacy of asciminib when administered as treatment after bosutinib failure according to the 2013 ELN Guidelines.

10.6.1.1 Data analysis of exploratory efficacy objectives

Subgroup analyses will be performed to evaluate the influence of factors such as baseline major cytogenetic response status, baseline/Week 1 Day 1 BCR-ABL1 ATP-binding site mutation status (from local historical record and from Sanger Sequencing), failure/intolerance to prior TKIs, line of therapy, gender, race and age on the primary efficacy endpoint. In addition, a logistic regression analysis will incorporate the key baseline variables into the model to further evaluate the impact of these variables on the primary endpoint and to provide a treatment effect estimate which is adjusted for imbalances in the treatment groups. An adjusted odds ratio for the treatment effect with associated 95% confidence intervals will be presented. Mantel-Haenszel estimates of the common odds ratio and the corresponding 95% confidence interval will also be provided. The effect of asciminib when administered as treatment after bosutinib failure will be assessed using the Switch Analysis Set to estimate response rates (cytogenetic and molecular response) at all scheduled time points after switch, as well as time-to and duration

[redacted]

of response. The analysis of time-to-event endpoints will be conducted only if at least 5 events are observed.

10.6.2 Exploratory PK objectives

The potential relationship between asciminib exposure (e.g. trough concentration) and efficacy or safety endpoints may be assessed by graphic exploration and/or statistical modeling as appropriate. The details will be further specified in the SAP. Additional exposure-response analyses for ECG may be conducted and reported separately.

10.6.3 Exploratory biomarker objectives

The study is not powered to assess specific biomarker-related hypotheses, thus the statistical analyses of these data should be considered exploratory in nature. Analytical results from such analyses may be used to generate additional hypotheses that must then be verified with data derived from subsequent clinical trials. Furthermore, additional post hoc exploratory assessments may be performed.

While the goal of the biomarker analyses is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a sample collection, or not perform/ discontinue the analysis of blood and bone marrow (e.g. issues related to the quality and or quantity of samples, or issues related to the assay that preclude the analysis of samples). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed.

Unless otherwise specified, all statistical analyses of biomarker data will be performed on subjects with valid biomarker samples.

The exploratory biomarker objectives are:

- To characterize mutations in the BCR-ABL1 gene at Week 1 Day 1, upon confirmed loss of molecular response and/or at end of treatment and examine their association with molecular and cytogenetic response for asciminib vs. bosutinib
- [redacted]
- To assess clonal evolution of pre-existing mutations versus mutations acquired during treatment with asciminib vs. bosutinib

10.6.3.1 Data analysis of exploratory biomarker objectives

[redacted]

- [redacted]
- Explore the relationship between BCR-ABL1 mutations at baseline/Week 1 Day 1 and efficacy outcomes for the primary endpoint and key secondary endpoints. The association between loss of response and BCR-ABL1 mutations will also be explored descriptively.
- [redacted]

Additional exploratory biomarker analyses may be performed depending on the data. All patients with evaluable biomarker measurements in the FAS will be included in the analysis and will be reported in a separate biomarker report.

10.6.4 Exploratory Patient Reported Outcomes objectives

The exploratory patient reported outcomes objectives are:

- To compare the impact of treatment on health care resource utilization between treatment arms in all patients
- To compare the impact of treatment on patient reported outcomes (PRO) including CML-specific symptoms, patient quality of life, and impact on work productivity and activity impairment from baseline through end of treatment between treatment arms in all patients

10.6.4.1 Resource Utilization

Data relating to Resource Utilization from the FAS will be used for the purpose of economic evaluation. Descriptive statistics of the levels of resource utilization over time will be done for each treatment arm. The measures of healthcare Resource Utilization (RU) include: hospitalization (H), Emergency Room (ER) visit, general practitioner (GP) visits, specialist (Sp) visit and urgent care (UC) visit. Medical resource utilization (MRU) will be assessed as follows: frequency and duration of hospitalization from Baseline up to End of Treatment; frequency of emergency room visits from Baseline up to End of Treatment; frequency of additional outpatient office visits general practitioner, specialist, and urgent care visits from Baseline up to End of Treatment. Hospitalization visits will also record the number of days on ward and the type of ward (hospital unit) and the discharge status. At each RU collected, the reason for the visit, i.e. related to CML, AE related to CML therapy or other reason, will be collected, in order to quantify the impact of treatment on healthcare resources.

[redacted]

10.6.4.2 Patient Reported Outcomes

The MDASI CML, PGIC along with EQ-5D-5L will be used to compare data on the patient's disease-related symptoms and health-related quality of life from baseline to EOT between the treatment arms. The WPAI will be used to assess work productivity and activity impairment related to the patient's CML. All measures will assess differences between the treatment arms.

Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses. Missing data items in a scale will be handled according to the manual for each instrument. No imputation will be applied if the total or subscale scores are missing at a visit.

10.7 Interim analysis

No formal interim analysis is planned for this trial. As described in Section 10, three or four formal analyses are planned: the primary at week 24, another at the 96-week end of study treatment and a PFS/OS update at year 5.

- 24-week primary analysis: Formal testing of the primary endpoint with full alpha will be performed. Analyses of other efficacy endpoints at and by 24 weeks will also be performed.
- 96-week analysis: Formal statistical testing of the key secondary endpoint will be performed with $\alpha = 0.05$ (two-sided) only if the primary endpoint (i.e. MMR rate at 24 weeks) is significant. Otherwise, no statistical testing will be performed, and any analysis will be considered exploratory. Analyses of other efficacy endpoints (including MMR rate at 48 weeks) will also be performed.
- End of study treatment analysis (if required) similar to the 96-week analysis without formal statistical testing.
- 5-year PFS/OS update analysis: PFS and OS

In addition DMC safety analyses will be conducted as described in Section 8.6.

10.8 Sample size calculation

To test the null hypothesis that the response rate is equal in the two groups, based on two-sided 5% level of significance and with 90% power, 222 patients will be needed in total (i.e. 148 patients in the asciminib arm and 74 patients in the bosutinib arm based on 2:1 randomization allocation). This assumes that asciminib leads to a 20% improvement in the MMR rate at 24 weeks over bosutinib from 15% to 35% which corresponds to an odds ratio of 3.05.

The assumed bosutinib MMR rate of 15% at 24 weeks is based on previous trials evaluating bosutinib therapy (Khoury 2012, Gambacorti-Passerini 2014, García-Gutiérrez 2015).

No more than 66 patients (approximately 30% of the overall trial population) that are intolerant to their most recent TKI therapy with BCR-ABL1 < 1% will be recruited in order to ensure that the CML third line patient population is adequately represented.

[redacted]

10.9 Power for analysis of key secondary variables

If the primary analysis of MMR rate at 24 weeks is statistically significant, then the key secondary endpoint MMR rate at 96 weeks will be tested, with the overall alpha controlled at the 5% two-sided level. The testing will use a gatekeeping strategy. Full details of the testing strategy are provided in Section 10.5.1.

Table 10-2 below summarizes the treatment effects of the key secondary endpoint which can be detected with 80% and 90% power, based on the specified assumptions regarding the bosutinib effect. The calculations were made using the software package PASS (2008).

Table 10-2 Detectable effect sizes for key secondary endpoint

Endpoint	Anticipated effect with bosutinib	2-sided alpha	Power	Detectable effect size§
MMR rate at 96 weeks	30%*	0.05	90% 80%	≥ 23% ≥ 20%

*: Gambacorti-Passerini et al. 2014, Figure 1D.
§: Absolute difference from the anticipated effect with bosutinib.

For MMR rate at 96 weeks, if the anticipated effect with bosutinib is 30%, then the given sample size with 2-sided alpha=0.05 would allow to detect an absolute difference of at least 23% (i.e. MMR rate at 96 weeks with asciminib is at least 53%) for 90% power and of at least 20% (i.e. MMR rate at 96 weeks with asciminib is at least 50%) for 80% power.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

[redacted]

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Additional consent form

Not applicable.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.3.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

[redacted]

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study electronic case report form (eCRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

[redacted]

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[redacted]

14 Appendices

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited in Section 6.4 for patients on asciminib and Section 6.5 for patients on bosutinib.

The following lists are based on the internal [Pharmacokinetic Sciences memorandum on Drug-Drug Interaction] (release date: January 2018), which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (2017), and the University of Washington's Drug Interaction Database (2017). These lists are not comprehensive and are only meant to be used as a guide. Please contact the medical monitor with any questions. **If a medication appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.**

14.1 Appendix 1 List of concomitant medications for patients on asciminib

Table 14-1 Prohibited concomitant medications for asciminib arm

Category	Drug Names
Strong inhibitors of CYP3A	atazanavir/ritonavir[1], danoprevir/ritonavir[1], darunavir/ritonavir[1], elvitegravir/ritonavir[1], indinavir/ritonavir[1], lopinavir/ritonavir[1], saquinavir/ritonavir[1], tipranavir/ritonavir[1], ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[1], boceprevir, clarithromycin, cobicistat, conivaptan, grapefruit juice[2], idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, telaprevir, telithromycin, troleandomycin, voriconazole,
Strong inducers of CYP3A	carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort (*Hypericum perforatum*)[1]
UGT1A1/2B7 inducers	UGT1A1: carbamazepine, cigarette smoke, rifampicin, testosterone propiate, UGT2B7: Barbiturates
Torsade de pointe (TdP) TdP/QT risk : Known	amiodarone, anagrelide, arsenic trioxide, astemizole (off us mkt), azithromycin, bepridil (off us mkt), chloroquine, chlorpromazine, cilostazol, cisapride (off us mkt), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on us mkt), donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, grepafloxacin (off market worldwide), halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (off mkt worldwide), mesoridazine (off mkt worldwide), methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl, pentamidine, pimozide, probucol (off mkt worldwide), procainamide (oral off us mkt), propofol, quinidine, sevoflurane, sotalol, sparfloxacin (off us mkt), sulpiride (not on us mkt), terfenadine (off us mkt), thioridazine, vandetanib
TdP/QT risk: Possible	alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine, asenapine, bedaquiline, bortezomib, buprenorphine, capecitabine, ceritinib, clomipramine, clozapine, crizotinib, cyamemazine (cyamepromazine) (Only on Non US Market), dabrafenib, dasatinib, degarilix, delamanid (off US mkt), desipramine, dexmedetomidine, dolasetron, eribulin, ezogabine, famotidine, felbamate, fingolimod, foscarnet, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, lapatinib, lenvatinib, leuprolide, lithium, mifepristone, mirabegron, mirtazapine, moexipril/hctz, nicardipine, nilotinib, norfloxacin, nortriptyline, ofloxacin, olanzapine, osimertinib, oxytocin, paliperidone, panabinostat, pasireotide, pazopanib, perflutren lipid microspheres, pipamperone (not on us mkt), promethazine, quetiapine, ranolazine, rilpivirine, risperidone, roxithromycin (on non us mkt), saquinavir, sertindole (on non us mkt), sorafenib, sunitinib, tacrolimus, tamoxifen, telavancin, telithromycin, tetrabenazine

[redacted]

Category	Drug Names
	(orphan drug in us), tizanidine, tolterodine, toremifene, trimipramine, vardenafil, vemurafenib, venlafaxine, vorinostat, zotepine
TdP/QT risk: Conditional	amantadine, amisulpride, amitriptyline, atazanavir, chloral hydrate, diphenhydramine, doxepin, fluoxetine, furosemide (frusemide), galantamine, hydrochlorothiazide, hydroxyzine, hydroxychloroquine, indapamide, itraconazole, ivabradine (on non us mkt), ketoconazole, loperamide, metoclopramide, metronidazole, nelfinavir, pantoprazole, paroxetine, posaconazole, quinine sulfate, ritonavir, sertraline, solifenacin, telaprevir, torsemide, trazodone, voriconazole, ziprasidone
[1] Combination ritonavir-boosted regimens are listed here in the DDI memo as strong CYP3A inhibitors (to avoid potential confusion), even though some are considered moderate CYP3A inhibitors in the UW DDI Database. [2] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).	

Table 14-2 Concomitant medications to be used with caution in asciminib arm

Category	Drug Names
Narrow Therapeutic index substrates of CYP2C8	Paclitaxel
Narrow Therapeutic index substrates of CYP2C9	phenytoin, warfarin (also sensitive)
Narrow Therapeutic index substrates of CYP3A	alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus, terfanadine,
BCRP Inhibitors	abacavir, amprenavir, atorvastatin, ,curcumin[3], cyclosporine[3], daclatasvir, declatasvir[3], delavirdine, efavirenz, elbasvir, eltrombopag[3], elvitegravir[3], erlotinib, fluvastatin, fostamatinib, fumitremorgin, gefitinib, grazoprevir, lapatinib[3], ledipasvir[3], lopinavir, paritepravir[3], pitavastatin, rosuvastatin, simvastatin, sulfasalazine, tipranavir[3], velpatasvir, venetoclax
P-gp inhibitors	alogliptin, amiodarone[4], azithromycin[4], canaglifozin, captopril[4], carvedilol[4], clopidrogel, cremophor RH40, curcumin, diltiazem[4], dronedarone[4], elacridar[4], eliglustat, felodipine[4], fluvoxamine[4], fostamatinib, ginko[4,5], isavuconazole, ivacaftor, lopinavir,, milk thistle (silymarin, silibinin)[4,5], nifedipine[4], nitredipine[4],ombitasvir, paritaprevir, propafenone, quercetin,[4], ritonavir[4], sequinavir[4], schisandra chinesis extract[4,5], simepravir, St. John's wort extract (HYPERICUM PERFORATUM) [4,5],survorexant, talinolol[4], telaprevir[4], telmisartan[4], ticagrelor[4], tipranavir[4], tolvaptan[4], valspodar, vandetanib, verapamil[4], voclosporin, vorapaxar.
[3] Evidence of *in vivo* DDI [4] Dual P-gp and CYP3A4 inhibitor [5] Herbal product	

[redacted]

14.2 Appendix 2 List of concomitant medications for patients on bosutinib

Table 14-3 Prohibited concomitant medications for bosutinib arm

Category	Drug Names
Strong inhibitors of CYP3A	boceprevir, clarithromycin, cobicistat, conivaptan, grapefruit juice[2], idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, telaprevir, telithromycin, troleandomycin, voriconazole, atazanavir/ritonavir[1], danoprevir/ritonavir[1], darunavir/ritonavir[1], elvitegravir/ritonavir[1], indinavir/ritonavir[1], lopinavir/ritonavir[1], ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[1] , saquinavir/ritonavir[1], tipranavir/ritonavir[1]
Moderate inhibitors of CYP3A	aprepitant, amprenavir, atazanavir, cimetidine, ciprofloxacin, crizotinib, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, faldaprevir, fluconazole, grapefruit juice[2], imatinib, isavuconazole, netupitant, nilotinib, tofisopam, *Schisandra sphenanthera* (nan wu wei zi)[3], asafoetida resin (*Ferula asafoetida*)[3], verapamil
Strong inducers of CYP3A	carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort (*Hypericum perforatum*)[3]
Moderate inducers of CYP3A	bosentan, efavirenz, etravirine, modafinil, nafcillin, ritonavir/tipranavir, thioridazine, semagacestat[4], talviraline[4], lopinavir, lersivirine,
Proton pump inhibitors	dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole.

[1] Combination ritonavir-boosted regimens are listed here in the DDI memo as strong CYP3A inhibitors (to avoid potential confusion), even though some are considered moderate CYP3A inhibitors in the UW DDI Database.

[2] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

[3] Herbal product

[4] Dual P-gp and CYP3A4 inhibitor

Table 14-4 Concomitant medications to be used with caution in bosutinib arm

Category	Drug Names
Torsade de pointe (TdP) TdP/QT risk : Known	amiodarone, anagrelide, arsenic trioxide, astemizole (off us mkt), azithromycin, bepridil (off us mkt), chloroquine, chlorpromazine, cilostazol, cisapride (off us mkt), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on us mkt), donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, grepafloxacin (off market worldwide), halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (off mkt worldwide), mesoridazine (off mkt worldwide), methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl, pentamidine, pimozide, probucol (off mkt worldwide), procainamide (oral off us mkt), propofol, quinidine, sevoflurane, sotalol, sparfloxacin (off us mkt), sulpiride (not on us mkt), terfenadine (off us mkt), thioridazine, vandetanib
TdP/QT risk: Possible	alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine, asenapine, bedaquiline, bortezomib, buprenorphine, capecitabine, ceritinib, clomipramine, clozapine, crizotinib, cyamemazine (cyamepromazine) (Only on Non US Market), dabrafenib, dasatinib, degarilix, delamanid (off US mkt), desipramine, dexmedetomidine, dolasetron, eribulin, ezogabine, famotidine, felbamate, fingolimod, foscarnet, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, lapatinib, lenvatinib, leuprolide, lithium, mifepristone, mirabegron, mirtazapine, moexipril/hctz, nicardipine, nilotinib, norfloxacin, nortriptyline, ofloxacin, olanzapine, osimertinib, oxytocin, paliperidone, panabinostat, pasireotide, pazopanib, perflutren lipid microspheres, pipamperone (not on us mkt), promethazine, quetiapine, ranolazine, rilpivirine, risperidone, roxithromycin (on non us mkt), saquinavir, sertindole (on non us mkt), sorafenib, sunitinib, tacrolimus, tamoxifen, telavancin, telithromycin, tetrabenazine

[redacted]

Category	Drug Names
	(orphan drug in us), tizanidine, tolterodine, toremifene, trimipramine, vardenafil, vemurafenib, venlafaxine, vorinostat, zotepine
TdP/QT risk: Conditional	amantadine, amisulpride, amitriptyline, atazanavir, chloral hydrate, diphenhydramine, doxepin, fluoxetine, furosemide (frusemide), galantamine, hydrochlorothiazide, hydroxyzine, hydroxychloroquine, indapamide, itraconazole, ivabradine (on non us mkt), ketoconazole, loperamide, metoclopramide, metronidazole, nelfinavir, pantoprazole, paroxetine, posaconazole, quinine sulfate, ritonavir, sertraline, solifenacin, telaprevir, torsemide, trazodone, voriconazole, ziprasidone

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Clinical Development

Asciminib/ABL001

Oncology Clinical Trial Protocol CABL001A2301

A phase 3, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors

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List of abbreviations

ABL	Abelson proto-oncogene
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute neutrophil count
AP	Accelerated phase
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATP	Adenosine triphosphate
AUC	Area under the curve
AV block	Atrioventricular block
BC	Blast crisis
BCR	Breakpoint Cluster Region gene
BCR-ABL	BCR-ABL fusion gene (also called the Philadelphia chromosome)
BCRP	Breast Cancer Resistant Protein
BID	*bis in diem*/twice a day
BMA	Bone marrow aspirate
BUN	Blood urea nitrogen
CBC	Complete Blood Count
CCA	Clonal chromosome abnormalities
CCyR	Complete Cytogenetic Response
CD8	Cluster of differentiation 8
CD34	Cluster of differentiation 34
CHR	Complete Hematological Response
CI	Confidence Interval
CMH	Cochran–Mantel–Haenszel
CML	Chronic Myelogenous Leukemia
CML-AP	Chronic Myelogenous Leukemia-Accelerated Phase
CMO&PS	Chief Medical Office and Patient Safety
CP	Chronic phase
CRO	Contract Research Organization
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP3A4	Cytochrome P450 3A4
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DLCO	Carbon monoxide diffusing capacity
DMC	Data Monitoring Committee
DNA	Desoxyribonucleic acid
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram

[redacted]

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ELN	European Leukemia Network
EOT	End of Treatment
ERT	Electronic Research Technology, Inc
EU	European Union
FAS	Full Analysis Set
FIH	First In Human
GDPR	General Data Protection Regulation
GFR	Glomerular Filtration Rate
hADME	Human ADME study (Absorption, Distribution, Metabolism and Excretion)
HDL	High density lipoprotein
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
[redacted]	[redacted]
INN	International Nonproprietary Name
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
K-M	Kaplan-Meyer
Km	Michaelis-Menten constant
LDL	Low density lipoprotein
LFT	Liver function test
LLN	Lower limit of normal
[redacted]	[redacted]
MCyR	Major Cytogenetic Response
mCyR	Minor Cytogenetic Response
MDASI-CML	MD Anderson Symptom Inventory – Chronic Myelogenous Leukemia
MMR	Major Molecular Response
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NGS	Next Generation Sequencing
NTI	Narrow Therapeutic Index
OS	Overall survival
PAS	Pharmacokinetic analysis set
PBPK	Physiologically based pharmacokinetic
PCR	Polymerase Chain Reaction
PCyR	Partial Cytogenetic Response
PD	Pharmacodynamic
[redacted]	[redacted]
[redacted]	[redacted]
PGIC	Patient Global Impression of Change
P-gp	Permeability glycoprotein

[redacted]

Ph+	Philadelphia chromosome positive
PHI	Protected Health Information
PK	Pharmacokinetics
PLT	Platelets
PPS	Per-protocol set
QD	Quaque die/once a day
QT	Q to T interval (ECG)
QTcF	QTc Fredericia
REB	Research Ethics Board
RNA	Ribonucleic acid
RQ-PCR	Real time quantitative polymerase chain reaction
RU	Resource Utilization
SAE	Serious Adverse Event
SAP	The Statistical Analysis Plan (SAP) is a regulatory document which provides evidence of preplanned analyses
SC	Steering committee
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TBIL	Total bilirubin
TdP	Torsades de Pointes
TKI	Tyrosine Kinase Inhibitor
TTF	Time to treatment failure
UGT	Uridin diPhospho-glucuronosyltransferase
ULN	Upper limit of normal
US	United States
USPI	US prescribing information
WBC	White blood cell count
WPAI	Work Productivity and Activity Impairment

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Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g. q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

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Protocol summary:

Title	A phase 3, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors
Brief title	Study of efficacy of CML-CP patients treated with asciminib versus bosutinib, previously treated with 2 or more TKIs
Sponsor and Clinical Phase	Novartis Phase 3
Investigation type	Drug
Study type	Interventional
Purpose and rationale	**Purpose:** The purpose of this pivotal study is to compare the efficacy of asciminib with that of bosutinib in the treatment of patients with CML-CP having previously been treated with a minimum of two prior ATP-binding site TKIs with BCR-ABL1 ratios ≥ 1% IS at screening. Patients intolerant to the most recent TKI therapy must have BCR-ABL1 ratio > 0.1% IS at screening and patients failing their most recent TKI therapy must meet the definition of treatment failure as per the 2013 ELN guidelines (Baccarani et al 2013). No more than 66 patients (approximately 30% of the overall trial population) that are intolerant to their most recent TKI therapy with BCR-ABL1< 1% will be recruited in order to ensure that the CML third line patient population is adequately represented. **Rationale:** There remains an unmet need for new compounds in patients with CML who have failed at least two prior TKIs. Current practice suggests that a second generation TKI will have been used for first line therapy for about one half of patients with CML, meaning that most patients who have failed at least two prior TKIs will have failed at least one if not two second generation TKIs (such as dasatinib and/or nilotinib). Potentially, such patients may also have failed bosutinib and/or ponatinib (Soverini 2014). Patients having failed at least two TKIs may have limited sensitivity to the remaining available agents and, thus, there exists a need for new safe and effective therapy. In addition, mutations will have developed in 21 to 33% of patients that prevent the use of specific TKIs, increasing the need for a better and alternative compound (Soverini 2014). Omacetaxine, a chemotherapeutic agent, is available for patients who have failed at least two prior TKIs under these conditions but only in the US and Canada. This agent is not available for most patients globally, where a bigger unmet medical need is present. Thus, there remains an unmet need for patients with CML who have failed at least two prior TKIs despite the existence of multiple agents.
Primary Objective and Key Secondary Objective	**Primary Objective:** To compare the Major Molecular Response (MMR) rate at 24 weeks of asciminib versus bosutinib **Key Secondary Objective:** To compare MMR rate at 96 weeks of asciminib versus bosutinib
Secondary Objectives	● To compare additional efficacy parameters of asciminib versus bosutinib: ● cytogenetic response rate (Complete, Partial, Major, Minor, Minimal, no response) at and by all scheduled data collection time points, including 24, 48 and 96 weeks ● MMR rate at all scheduled data collection time points (except 24 and 96 weeks which are already covered by primary and key secondary endpoints) ● MMR rate by all scheduled data collection time points, including 24, 48 and 96 weeks ● Time to MMR ● Duration of MMR ● Time to CCyR ● Duration of CCyR ● Time to treatment failure

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	● Progression free survival ● Overall survival ● To compare the safety and tolerability profile of asciminib versus bosutinib by type, frequency and severity of adverse events, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG and other safety data (vital signs, physical examination) ● To characterize the PK of asciminib in the CML-CP population (Trough plasma concentrations, PK parameters in full PK group: Cmax, Tmax, AUC0-12h, CL/F) ● To assess the safety of asciminib when administered as treatment after bosutinib failure according to the 2013 ELN Guidelines
Study design	This study is a randomized, phase 3, open-label, active-controlled multi-center study. Patients will be randomized to the novel BCR-ABL1 TKI asciminib and bosutinib in a 2:1 ratio. The randomization is to be stratified to ensure the study population is balanced between the arms with respect to the patient's cytogenetic response status at baseline (Major Cytogenetic response (complete or partial) vs. No major cytogenetic response (minor, minimal or none)). The study design incorporates a 2:1 randomization, allocating more patients to the asciminib arm in order to learn more about the safety profile of the experimental therapy, whereas the safety of bosutinib therapy is well documented. Treatment duration for each patient in the present study is for up to 96 weeks after the last randomized patient receives the first dose, or up to 48 weeks after the last patient has switched from bosutinib to asciminib whichever is longer unless patients have discontinued treatment earlier, which should be adequate to address both the primary objective of the study, i.e. determination of the MMR rate at 24 weeks, as well as secondary efficacy and safety objectives. Patients on bosutinib will be able to switch to asciminib treatment up to 96 weeks after the last patient has been randomized. If patients in the bosutinib arm have documented treatment failure according to the 2013 ELN Guidelines (Baccarani et al 2013), they will have the option to receive asciminib. Each patient who switches to asciminib after bosutinib failure can remain on asciminib treatment for up to 48 weeks after the last bosutinib failure patient has switched to asciminib during the treatment period unless patients have discontinued treatment earlier.
Population	Two-hundred and twenty-two (222) patients with CML-CP who had prior treatment with two or more ATP binding site TKIs will be randomized on a 2:1 basis to receive either asciminib or bosutinib. Patients with known history of T315I and/or V299L mutations at study entry will be excluded from the trial since bosutinib, the comparator, is not approved for these patients.
Inclusion criteria	Patients eligible for inclusion in this study have to meet **all** of the following criteria: 1. Male or female patients with a diagnosis of CML-CP ≥ 18 years of age 2. Patients must meet all of the following laboratory values at the screening visit: ● < 15% blasts in peripheral blood and bone marrow ● < 30% blasts plus promyelocytes in peripheral blood and bone marrow ● < 20% basophils in the peripheral blood ● ≥ 50 x 10^9/L (≥ 50,000/mm^3) platelets ● Transient prior therapy related thrombocytopenia (< 50,000/mm^3 for ≤30 days prior to screening) is acceptable ● No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly 3a. Patients intolerant to the most recent TKI therapy, BCR-ABL1 ratio > 0.1% IS according to central laboratory at the screening examination 4. Prior treatment with a minimum of 2 prior ATP-binding site TKIs (i.e. imatinib, nilotinib, dasatinib, radotinib or ponatinib) 5. Failure (adapted from the 2013 ELN Guidelines; Baccarani et al 2013) or intolerance to the most recent TKI therapy at the time of screening

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	● Failure is defined for CML-CP patients (CP at the time of initiation of last therapy) as follows. Patients must meet at least 1 of the following criteria. ● Three months after the initiation of therapy: No CHR or > 95% Ph+ metaphases ● Six months after the initiation of therapy: BCR-ABL1 ratio > 10% IS and/or > 65% Ph+ metaphases ● Twelve months after initiation of therapy: BCR-ABL1 ratio > 10% IS and/or > 35% Ph+ metaphases ● At any time after the initiation of therapy, loss of CHR, CCyR or PCyR ● At any time after the initiation of therapy, the development of new BCR-ABL1 mutations which potentially cause resistance to study treatment ● At any time after the initiation of therapy, confirmed loss of MMR in 2 consecutive tests, of which one must have a BCR-ABL1 ratio ≥ 1% IS ● At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cells: CCA/Ph+ ● Intolerance is defined as: ● Non-hematologic intolerance: Patients with grade 3 or 4 toxicity while on therapy, or with persistent grade 2 toxicity, unresponsive to optimal management, including dose adjustments (unless dose reduction is not considered in the best interest of the patient if response is already suboptimal) ● Hematologic intolerance: Patients with grade 3 or 4 toxicity (absolute neutrophil count [ANC] or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by manufacturer 6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2 7. Adequate end organ function as defined by (as per central laboratory tests): ● Total bilirubin ≤ 1.5 x ULN) except for patients with Gilbert's syndrome who may only be included if total bilirubin ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN ● Aspartate transaminase (AST) ≤ 3.0 x ULN ● Alanine transaminase (ALT) ≤ 3.0 x ULN ● Serum lipase ≤ 1.5 x ULN. For serum lipase > ULN - ≤ 1.5 x ULN, value must be considered not clinically significant and not associated with risk factors for acute pancreatitis ● Alkaline phosphatase ≤ 2.5 x ULN ● Creatinine clearance ≥ 50mL/min as calculated using Cockcroft-Gault formula 8. Patients must avoid consumption of grapefruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed. 9. Written informed consent obtained prior to any screening procedures. 10a. Patients must have the following electrolyte values (as per central laboratory tests) within normal limits or corrected to be within normal limits with supplements prior to first dose of study medication: • Potassium (potassium increase of up to 6.0 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits) • Total calcium (corrected for serum albumin); (calcium increase of up to 12.5 mg/dl or 3.1 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits) • Magnesium, with the exception of magnesium increase > ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L associated with creatinine clearance (calculated using Cockcroft-Gault formula) within normal limits 11. Evidence of typical BCR-ABL1 transcript [e14a2 and/or e13a2] at the time of screening which are amenable to standardized RQ-PCR quantification.
Exclusion criteria	Patients eligible for this study must not meet **any** of the following criteria: 1. Known presence of the T315I or V299L mutation at any time prior to study entry 2. Known second chronic phase of CML after previous progression to AP/BC

[redacted]

	3. Previous treatment with a hematopoietic stem-cell transplantation 4. Patient planning to undergo allogeneic hematopoietic stem cell transplantation 5. Cardiac or cardiac repolarization abnormality, including any of the following: ● History within 6 months prior to starting study treatment of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG) ● Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block) ● QTcF at screening ≥450 msec (male patients), ≥460 msec (female patients) ● Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following: ● Risk factors for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia ● Concomitant medication(s) with a "known risk of TdP" per wwwcrediblemeds.org/ that cannot be discontinued or replaced 7 days prior to starting study drug by safe alternative medication. ● Inability to determine the QTcF interval 6. Severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol (e.g. uncontrolled diabetes, active or uncontrolled infection, pulmonary hypertension) 7. History of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis 9. History of acute or chronic liver disease 10. Known presence of significant congenital or acquired bleeding disorder unrelated to cancer 11. History of other active malignancy within 3 years prior to study entry with the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively 12. Known history of Human Immunodeficiency Virus (HIV), chronic Hepatitis B (HBV), or chronic Hepatitis C (HCV) infection. Testing for Hepatitis B surface antigen (HBs Ag) and Hepatitis B core antibody (HBcAb / anti HBc) will be performed at screening 13. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or gastric bypass surgery) 14a. Treatment with medications that meet one of the following criteria and that cannot be discontinued at least one week prior to the start of treatment with study treatment ● Moderate or strong inducers of CYP3A ● Moderate or strong inhibitors of CYP3A 15. Previous treatment with or known/ suspected hypersensitivity to asciminib or any of its excipients. 16. Previous treatment with or known/ suspected hypersensitivity to bosutinib or any of its excipients. 17. Participation in a prior investigational study within 30 days prior to randomization or within 5 half-lives of the investigational product, whichever is longer 18. Pregnant or nursing (lactating) women 19a. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 days after last dose of asciminib and one month after last dose of bosutinib. Highly effective contraception methods include: ● Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

	● Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy) total hysterectomy or bilateral tubal ligation at least six weeks before taking study treatment). In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment ● Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject. ● Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. ● In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. ● Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking study medication. In the case of oophorectomy alone, women are considered post-menopausal and not of child bearing potential only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

Conditions to be fulfilled for asciminib switch	1. Failure to bosutinib treatment up to 96 weeks after the last patient received the first dose (adapted from the 2013 ELN Guidelines; Baccarani et al 2013). Patients must meet at least 1 of the following criteria. Failure is defined as follows:
	• Three months after the initiation of therapy or thereafter: No CHR or > 95% Ph+ metaphases.
	• Six months after the initiation of therapy or thereafter: BCR-ABL1 ratio > 10% IS and/or > 65% Ph+ metaphases.
	• Twelve months after initiation of therapy or thereafter: BCR-ABL1 ratio > 10% IS and/or > 35% Ph+ metaphases.
	• At any time after the initiation of therapy, loss of CHR, CCyR or PCyR.
	• At any time after the initiation of therapy, detection of new BCR-ABL1 mutations which potentially cause resistance to study treatment (asciminib or bosutinib).
	• At any time after the initiation of therapy, confirmed loss of MMR in 2 consecutive tests.
	• At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cells: CCA/Ph+.
	
	<u>Conditions preventing patients to switch to asciminib:</u>
	• Any Grade 3 or 4 toxicity which has not resolved to Grade 2 or lower within 28 days and before starting asciminib treatment.
	• Asymptomatic (Grade 2) pancreatitis if not resolved within 28 days
	• Disease progression while on bosutinib treatment. The following events are considered disease progression:
	  • Accelerated phase (AP) as defined by any of the following:
	  • ≥ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate.
	  • ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate.
	  • ≥ 20% basophils in the peripheral blood.
	  • Thrombocytopenia (< 100 x 10^9/L) that is unrelated to therapy.
	  • Blast crisis (BC) as defined by any of the following:
	  • ≥ 30% blasts in peripheral blood or bone marrow aspirate

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	• Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma). • QTcF at time of switch > 480 msec or inability to determine QTc interval
Investigational and reference therapy	Asciminib 40 mg BID Bosutinib 500 mg QD
Efficacy assessments	Molecular response (RQ-PCR, mutational analysis) Cytogenetic response (Bone Marrow Aspirate)
Safety assessments	● Physical examination ● Vital Sign ● Height and weight ● ECOG performance status ● Laboratory chemistry and hematology ● Serology ● Electrocardiogram (ECG) ● Echocardiogram ● Pulmonary function tests with DLCO
Other assessments	● PK sampling (full/sparse) ● Bone Marrow Biopsy ● Patient Report Outcomes (MDASI-CML, PGIC, WPAI, EQ--5D-5L, resource utilization)
Data analysis	The primary efficacy variable of the study is the Major Molecular Response (MMR) rate at 24 weeks. A patient will be counted as having achieved MMR at 24 weeks if he meets the MMR criteria (BCR-ABL1 ratio ≤0.1%) at 24 weeks. The MMR rate at 24 weeks will be calculated based on the FAS and according to the Intention To Treat (ITT) principle. MMR rate and its 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. Confidence interval for the difference in MMR rate between treatment groups will be provided using the Wald method. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided. The key secondary endpoint is MMR rate at 96 weeks. Formal statistical testing of the key secondary endpoint will be performed only if the primary endpoint is significant by means of a gatekeeping procedure to control the overall alpha level.
Key words	Phase III, open-label, randomized trial, asciminib, bosutinib, CML-CP, prior treatment with 2 or more TKIs

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Amendment 03-US.01 (05-Aug-2020)

Amendment rationale

As of 25-Jun-2020, 319 patients were screened, 233 patients were randomized in the study. Patient recruitment has been completed on 22-Oct-2019. The study is currently ongoing.

The primary purpose of the amendment is:

Based on FDA request, requirement for male contraception has been reintroduced in the study.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

The requirements for male contraception have been reintroduced in the following sections:

- Section 7.2.2.5.3 Pregnancy and assessments of fertility.
- Section 8.4 Pregnancies.
- Section 11.3 Informed consent procedures.

The enrollment has been completed, thus the eligibility criterion has not been updated.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authority.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

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Amendment 3 (14-Dec-2018)

Amendment rationale

As of 21-Nov-2018, 137 patients were screened and 86 patients were randomized in the study, the study is currently ongoing.

The primary purpose of the amendment is:

Modification of the inclusion criterion of BCR-ABL1 transcript threshold required at study entry from a BCR-ABL1 ratio ≥ 1% IS to BCR-ABL1 ratio > 0.1% IS (i.e. not in MMR) for patients with intolerance to most recent TKI treatment. The threshold presented in this inclusion criteria affects only patients who are intolerant to prior treatment, since patients failing prior treatment must fulfill the criteria defined by ELN guidelines (Baccarani et al 2013). Although the number of treatment options is increasing, especially for patients with imatinib intolerance, alternatives for patients with resistance and/or intolerance to at least two previous TKIs are limited (NCCN 2018, ELN 2013). The reason of reducing the BCR-ABL1 ratio is that in routine clinical practice, physicians do not wait to observe increased BCR-ABL1 levels to switch treatment in patients with intolerance, which may increase the risk of disease progression, especially in patients with only limited further treatment options. This is in line with current CML treatment guidelines where the switch to an alternative therapy in intolerant patients is not linked to a BCR-ABL1 threshold (NCCN 2018, Baccarani et al 2013 and Hochhaus et al 2017).

Therefore, the threshold of ≥ 1% BCR-ABL1 in the current trial is reduced to BCR-ABL1 ratio > 0.1% IS for patients with intolerance to most recent TKI treatment. No more than 66 patients (approximately 30% of the overall trial population) that are intolerant to their most recent TKI therapy with BCR-ABL1 < 1% will be recruited in order to ensure that the CML third line patient population is adequately represented. As the primary endpoint is the rate of MMR at 24 weeks a baseline molecular response level > 0.1 % BCR-ABL1 is needed.

Patients experiencing documented treatment failure on bosutinib treatment will be allowed to switch to asciminib. Patients failing bosutinib treatment will have failed at least their third TKI treatment, with limited remaining treatment options. With this amendment patients who have failed bosutinib will be offered the possibility to continue in the study by receiving asciminib, if investigators consider that this treatment option is in the best interest of the patient. As of 15-Oct-2018, 4 patients could have potentially benefited from this option. Treatment failure during study treatment is assessed by measureable and pre-specified milestones defined by ELN criteria (Baccarani et al 2013), which are also used to define treatment failure as entry criteria for the study. Only documented treatment failure in the bosutinib arm will be considered for a treatment switch. For the purpose of the primary and secondary endpoint analyses, any patient meeting the ELN failure criteria while receiving study treatment, (either before or by the time of conducting the analysis and irrespective of treatment arm), will be considered as non-responders for the specific time point and for any subsequent time point. The switch to asciminib in case of bosutinib treatment failure is not expected to introduce bias as those patients will be regarded as non-responders irrespective of treatment switch and the disease burden will certainly not improve without further treatment. There is no option to switch patients failing on the asciminib treatment arm, as those patients can be offered approved

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therapies outside of the context of the study. The efficacy data collected after the switch from patients switching to asciminib following bosutinib failure will be analyzed separately as exploratory endpoints and will not be included for primary and secondary study endpoints. In addition, safety data from patients receiving asciminib after bosutinib failure will be collected to further characterize asciminib's safety profile.

Potassium increase of up to 6.0 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits. Grade 2 increase of potassium is acceptable in case of normal creatinine clearance as this is not considered to be a risk factor for QTc prolongation. Total calcium (corrected for serum albumin) increase of up to 12.5 mg/dl or 3.1 mmol/L (Grade 2) is acceptable at study entry if associated with creatinine clearance within normal limits as this is not considered to be a risk factor for QTc prolongation.

A change to creatinine clearance instead of GFR is being made in relation to the magnesium inclusion requirement as GFR in this study is expressed by creatinine clearance.

Exclusion criteria #19 is being modified under this amendment in order to define the duration of the use of highly effective methods of contraception after the last dose of bosutinib under this study (one month after last dose of bosutinib). This is being done in order to align with the latest Bosulif® USPI.

Exclusion criteria #21 has also been removed under this amendment. In embryofetal development studies with asciminib, fetal malformations (cardiac malformations) and increased visceral and skeletal variants were observed in rats and increased incidence of resorptions indicative of embryo-fetal mortality and a low incidence of cardiac malformations indicative of dysmorphogenesis were observed in rabbits. Asciminib is not genotoxic. As published in the literature, small molecules can distribute to seminal fluid and the seminal accumulation suggested is semen/plasma ratios up to 11.3 (Klemmt and Scialli 2005). According to the FDA guidance, in general, there is increased concern for reproductive or developmental toxicity in humans for relative exposure ratios (animal: human) that are < 10 and decreased concern for exposure ratios > 25 (FDA Guidance for Industry 2011). The calculations for the asciminib safety margin were done based on Cmax (plasma) seen in patients at a dose of 200 mg BID (Cmax 6843 ng/ml). Safety margin calculation based on the embryo-fetal development study in rats was 768 and safety margin calculation based on the embryo-fetal development study in rabbits was 894. In conclusion, for asciminib, as outlined above, the safety margins are well above 25 and therefore no embryo- and fetotoxicity effects can be anticipated via seminal fluid. Removal of male contraception is in line with the Bosutinib USPI and SmPC.

In addition, patients can be re-screened up to three times for the study, instead of once. The patient population being investigated in this study is heavily pre-treated and patients might not have other treatment options outside the trial. There can be many intolerance-related temporary conditions resulting in ineligibility for the trial.

Recruitment period extension has been reflected in the VES table. Study length has changed with introduction of switch option for patients failing bosutinib treatment.

Patients enrolling in this trial will present a high disease burden after failure of previous therapies. Myelosuppression during TKI targeted treatment is a very common effect observed due to the suppression of the leukemic clone; this effect is also extended to hematopoiesis of

[redacted]

stem cells and progenitors (Steegmann et al 2016). For this reason, the recovery period for cytopenias has been extended from 28 to 42 days in order to allow for sufficient time to recover from suppression and to re-populate the bone marrow.

The biomarker sampling profile has been revised to remove the gene expression profile in leukemic stem cells in both blood and bone marrow due to technical limitations. In addition, there is currently no validated assay available.

A clarification has been made to how the tests for blood urea and Blood Urea Nitrogen (BUN) are noted. The text "blood urea, Blood Urea Nitrogen (BUN)" has been revised to “blood urea or Blood Urea Nitrogen (BUN)” in order to note that either test is permitted.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Change of the purpose of the study by decreasing the requirement of BCR-ABL1 ratio ≥ 1% IS to BCR-ABL1 ratio > 0.1% IS at the time of screening for patients with intolerance:
  - Protocol summary.
  - Section 2.1 Study rationale and purpose.
  - Section 4.1 Description of study.
  - Section 5.2 Inclusion criteria.
  - Section 10.5.2 Other secondary efficacy objectives.
- Change of the study design by introducing the switch to asciminib option for patients experiencing treatment failure on bosutinib treatment:
  - Protocol summary.
  - Section 2.2 Rationale for the study design.
  - Section 4.1 Description of study.
  - Figure 4-1 Schematic of Study Design.
  - Addition of Section 4.1.1 Study treatment switch from bosutinib to asciminib
  - Section 4.3 Definition of end of study.
  - Section 6.1.5 Treatment duration
  - Section 6.7.3.2 Study drug accountability.
  - Section 7 Visit schedule and assessments:
    - Addition of Table 7-2 Visit evaluation schedule (study treatment switch phase).
    - Addition of Section 7.1.2.2 Conditions to be fulfilled for asciminib switch.
    - Section 7.1.5 Visit windows.
    - Section 7.1.6 Discontinuation of study treatment.
    - Section 7.2.1.1 Molecular response.
    - Section 7.2.1.2 Bone marrow analysis and cytogenetics
    - Section 7.2.2.1 Physical examination.

[redacted]

    - Section 7.2.2.2 Vital signs.
    - Section 7.2.2.3 Height and weight.
    - Section 7.2.2.4 Performance status.
    - Section 7.2.2.5 Laboratory evaluations.
    - Section 7.2.2.6 Cardiac assessments.
    - Section 7.2.3 Pharmacokinetics.
    - Section 7.2.4 Biomarkers.
  - Section 10.1.6 Other analysis sets.
  - Section 10.5.3.1 Analysis set and grouping for the analysis
- Addition of new exploratory measure for patients that switch from bosutinib to asciminib:
  - Table 3-1 Objectives and related endpoints.
  - Section 10.1.6 Other analysis sets.
  - Section 10.6 Exploratory objectives:
    - Section 10.6.1 Exploratory efficacy objectives.
    - Section 10.6.1.1 Data analysis of exploratory efficacy objectives.
- Reference for concomitant medications with a "known risk of TdP" has been updated to wwwcrediblemeds.org/
  - Protocol summary
  - Section 5.3 Exclusion criteria
  - Section 6.3.2 Dose adjustments for QTcF prolongation
  - Section 6.4.3 Prohibited concomitant therapy
- [redacted]
- Section 5.2 Inclusion criteria and protocol summary: updated inclusion criteria to reflect the changes below:
  - Inclusion Criteria #3: As referenced above, the requirement of BCR-ABL1 ratio ≥ 1% IS has been decreased to BCR-ABL1 ratio > 0.1% IS at the time of screening for patients intolerant to previous TKI.
  - Inclusion Criteria #10: Potassium increase of up to 6.0 mmol/L is accepted at study entry if associated with creatine clearance within normal limits. Calcium increase of up to 12.5 mg/dl or 3.1 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits. GFR replaced by Creatinine clearance (calculated using Cockcroft-Gault formula) in order to maintain consistency throughout the protocol as creatinine clearance is already calculated based on inclusion criteria #7.
  - Inclusion Criteria #11: As study eligibility is assessed during screening with BCR-ABL1 PCR quantification via international scale this requirement was added as

[redacted]

clarification. Measurement according to international scale is only possible for typical BCR-ABL1 transcripts.

- Section 5.3 Exclusion Criteria and Protocol summary: updated exclusion criteria to reflect the following changes:
  - Exclusion Criteria #14: Removal of P-gp as a moderate or strong inhibitor of CYP3A as P-gp inhibitors are no longer prohibited per updated USPI, and SmPC
  - Exclusion Criteria #19: Duration of the use of highly effective methods of contraception after the last dose of bosutinib has been defined to align with the latest bosutinib USPI.
  - Exclusion Criteria #21 Removal of this criteria in order to align with updated pre-clinical data.
- Section 6.3.1 Dose modification and dose delay: The recovery period for cytopenias has been extended from 28 to 42 days in order to allow for sufficient time to recover from suppression and to re-populate the bone marrow.
- Table 7-1 Visit evaluation schedule: updates due to inadvertent omissions in previous protocols and to reflect extension of study treatment period
  - ECOG Performance status: X has been replaced by “If needed” under Week 6, Week 10 and Week 14.
  - Vital signs: added “If needed” under Week 6, Week 10 and Week 14.
  - Visit name: “W108, W120, W132, W144, W156” has been changed to “Every 12 weeks up to end of study treatment” to align with new extended recruitment timelines.
- Section 7.1.2 Change of patient re-screening allowance from once to up to three times.
- Section 7.1.2.2 Addition of new section with screening eligibility criteria for patients switching from bosutinib to asciminib.
- Section 7.1.4 Change of treatment duration for patients including those patients that switch to asciminib after failure on bosutinib. Patients can remain on asciminib treatment for up to 96 weeks after the last patient received the first dose in the study or up to 48 weeks after the last patient has switched to asciminib whichever is longer.
- Section 7.1.6 Discontinuation of study treatment: updated to specify that the safety follow-up visit can be conducted by telephone and replacement of “after randomization” by “after initiation of therapy” in the event that constitutes a treatment failure.
- Section 7.2.2.5.3 Pregnancy and assessments of fertility: Change in requirement for reporting pregnancies under this study. Pregnancies diagnosed in female partners of male participants are no longer required to be reported to CMO&PS. Contraception use by sexually active males while on study treatment is no longer required.
- Table 7-5 Central clinical laboratory parameters collection plan: Clarification on blood urea and Blood Urea Nitrogen (BUN). The text "blood urea, Blood Urea Nitrogen (BUN)" has been revised to “blood urea or Blood Urea Nitrogen (BUN)”.
- Section 8.4 Pregnancies: removal of male contraception requirement due to new information of asciminib embryo and fetotoxicity.
- Section 10.4.3 Handling of missing values/censoring/discontinuations: imputation rules updated to take in account unscheduled visits close to visit Week 24.

[redacted]

- Section 10.5.1.1. Analysis for key secondary endpoints: imputation rules updated to take in account unscheduled visits close to visit Week 96.
- Section 14 Appendices: updates to reflect that P-gp inhibitors are no longer prohibited
  - Section 14.2 Appendix List of concomitant medications for patients on bosutinib:
    - Removal of P-gp inhibitors from Table 14-3 Prohibited concomitant medications for bosutinib arm.
    - Addition of new medications to Category Torsade de pointe (TdP) TdP/QT risk: Known.
    - Addition of new category, TdP/QT risk: Possible.
    - Addition of new category, TdP/QT risk: Conditional.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 2 (13-Jul-2018)

Amendment rationale

As of 29-Jun-2018, this study has been submitted in 25 and approved in 24 countries. Eighty five (85) sites were initiated, 67 patients were screened and 38 patients were randomized in the study.

The primary purposes of the amendment are:

The frequency of bone marrow aspirate (BMA) to perform cytogenetic analysis has been decreased in accordance with treatment guidelines (European Leukemia Network (ELN) Guidelines (Baccarani et al 2013), National Comprehensive Cancer Network (NCCN) (Clinical Practice Guidelines in Oncology-Chronic Myeloid Leukemia v4.2018). Initially BMAs were foreseen at screening, every 24 weeks thereafter and at end of treatment. With the protocol amendment BMA is no longer needed for patients that have achieved MMR during study, however BMA assessment is requested at the time of end of treatment for biomarker analysis.

Toxicity studies performed in rats, dogs and cynomolgus monkeys identified the pancreas as potential target tissues. Therefore the assessment for laboratory parameters that are associated with pancreatitis were part of the inclusion criteria (amylase, lipase). Serum lipase is the preferred test due to its improved sensitivity, and a threshold concentration of 2-3 x ULN is recommended for the diagnosis of pancreatitis. There are a number of other conditions that can elevate lipase, including TKI pretreatment, thus the screening threshold for lipase is increased from ≤ ULN to ≤ 1.5 x ULN (CTCAE v4.03 grade 1), as patients with history of acute pancreatitis within 1 year of study and history of chronic pancreatitis are excluded. Amylase is not a specific marker for pancreatitis, as up to 60% of total serum amylase originates from non-pancreatic sources. Its short half-life reduces its value as a diagnostic test in the early clinical course. Lipase has replaced amylase as the biochemical test of choice for acute pancreatitis due to its higher specificity (Basnayake 2015), therefore the requirement of amylase ≤ ULN at screening has been removed.

Assessments for visits at weeks 6, 10 and 14 will be limited to the monitoring of the bone marrow function to allow for adjustments of study treatment. Assessments will comprise a complete blood count to detect neutropenia and thrombocytopenia which are among the most frequent adverse reactions [Asciminib Investigator's Brochure, Bosutinib label]. The physical examination must be done at site only in case of previous or newly occurring adverse events.

The concomitant medication section has been updated to reflect the most recent clinical updates on asciminib as well to align with the Bosutinib label.

In addition some minor inconsistencies (discrepancies between sections, typos) have been corrected.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- ABL001 has been replaced by International Nonproprietary Name (INN) asciminib throughout the protocol amendment.

[redacted]

- Protocol Summary and Section 5.2 Inclusion criteria:
  - Inclusion criterion 5: rewording of the reference to previous TKI therapy for more clarity.
  - Inclusion criterion 7: Criteria for amylase removed. Threshold for lipase increased to CTCAEv4.03 grade 1.
  - Inclusion criterion 10: grade 1 increase of magnesium is acceptable in case of normal Glomerular Filtration Rate (GFR) as this is not considered to be a risk factor for QTc prolongation.
- Protocol Summary and Section 5.3 Exclusion criteria:
  - Exclusion criterion 5: adapting the exclusion criteria concerning QT prolonging agents for clarification regarding known, possible or conditional risk for TdP, and adding the external web link to qtdrugs.org.
  - Exclusion criterion 8: deleted to avoid redundancy with inclusion and exclusion criteria 7.
  - Exclusion criterion 14: removal of substrates of CYP3A4/5, CYP2C8, or CYP2C9 with narrow therapeutic index based on most updated PBPK modeling predicting a negligible risk for sensitive CYP3A4/5, CYP2C8, or CYP2C9 substrates. These substrates will be moved under requiring caution and/or action section.
  - Exclusion criteria 19: changed from tubal ligation to bilateral tubal ligation,
  - Exclusion criterion 20: definition of menopausal women should be part of exclusion criterion 19.
- Section 1.2.1 Overview of asciminib (ABL001): updated.
- Section 1.2.1.1 Non-clinical experience/ Non-clinical pharmacokinetics and metabolism:
  - Rephrased to add more clarity on interspecies differences observed and recommendation about sunlight protection.
  - Updated with current available information.
- Section 1.2.1.2 Clinical experience: updated with current available information.
- Section 2.2.1 Rational for biomarker assessment: harmonization of time points for BCR-ABL1 gene mutation analysis.
- [redacted] Addition of the following endpoint: Change in work productivity and activity impairment over time according to WPAI.
- Section 4.3 Definition of end of study: rephrased to add more clarity.
- Section 6.1.1 Dosing regimen: precision on patient fasted state for asciminib dosing.

[redacted]

- Section 6.3.1 Dose modification and dose delay: clarification made on treatment discontinuation.
- Table 6-2 Criteria for dose reduction/interruption and re-initiation of asciminib and bosutinib treatment for adverse drug reactions:
  - Gastro intestinal/ Pancreatitis/Grade 2: precisions provided and treatment delay changed from 7 to 21 days to give investigators sufficient time for re-assessment.
  - Removal of "other adverse event" section which was redundant with the section "non-hematological adverse event reaction except where further specified in individual section".
  - Mandatory instructions for grade 3 and 4 "Non-hematological adverse event reaction except where further specified in individual section" for bosutinib have been aligned with those of asciminib: dose hold until resolved to ≤ grade 1, to handle the patients identically independent of the treatment assigned.
- Section 6.3.2 Dose adjustments for QTcF prolongation: adapting the dose adjustment concerning QT prolonging agents to the classification known, possible or conditional risk for TdP, and adding the external web link to qtdrugs.org.
- Section 6.4.2 Permitted concomitant therapy requiring caution and/or action: updated with the most clinical data available.
- Section 6.4.3 Prohibited concomitant therapy (asciminib):
  - Section on other anticancer agent added,
  - Sections on strong CYP3A4/5 inhibitors and P-gp inhibitors: prohibition on P-gp inhibitors has been removed and moved under requiring caution and/or action section based on CABL001A2102 ADME study,
  - Section on strong CYP3A4/5, UGT1A/2B inducers updated to provide instructions on action to be taken in case these inducers are taken,
  - Section on NTI substrates of CYP3A4/5, CYP2C8 and CYP2C9 removed based on a most updated PBPK modeling predicting a negligible risk for sensitive CYP3A4/5, CYP2C8, or CYP2C9 substrates and moved under requiring caution and/or action section,
  - Section on QT prolonging agents updated to change agents known to prolong QT interval to agents with "known", "possible" or "conditional" risk of Torsades de Pointes.
- Section 6.5.1 Permitted concomitant therapy requiring caution (bosutinib): has been updated to reflect the bosutinib label information regarding the use of QT prolonging agents.
- Section 6.5.2 Prohibited concomitant therapy (bosutinib):
  - Section on other anticancer agent added,
  - Concomitant use with CYP3A4/5 inhibitors/inducers: further clarifications on necessary actions.
- Table 7-1 Visit evaluation schedule:
  - Exploratory BCR-ABL1 mutation analysis (Sanger Sequencing) for patients with mutations at Week 1 Day 1: rephrased to indicate that this assessment will be performed without any dedicated blood collection.

[redacted]

  - [redacted]
  - Removal of PGIC questionnaire at screening: the question should only be completed for patients on treatment.
  - Week 6, 10 and 14: physical examination and extramedullary involvement to be performed only if new or ongoing adverse event since last visit. Chemistry and coagulation testings removed.
- Section 7.1.2 Screening, section 7.2.1.2 Bone marrow analysis and cytogenetics and Table 7-1 Visit evaluation schedule: timeframe for performing bone marrow aspirate and biopsy changed from 42 to 56 days. Historical bone marrow assessments performed before main informed consent form signature allowed if within 56 days of Week 1 Day 1.
- Section 7.1.2.2 Information to be collected on screening failures: correction of screening failure definition.
- Section 7.1.4 Treatment period: treatment failure added as a reason for stopping study treatment.
- Section 7.1.5 Visit windows: correction of the start of visit scheduled every two weeks.
- Section 7.1.6 Discontinuation of study treatment:
  - Has been made mandatory in case of pregnancy.
  - Confirmed loss of MMR in 2 consecutives tests rephrased for consistency with the efficacy assessments.
  - Ineligibility of patient due to detection of T315I or V299L mutations at any time has been added under the section describing the cases when a patient MUST be discontinued to remove any ambiguity.
- Section 7.1.7 Withdrawal of consent and Glossary of terms: these sections were added/updated to incorporate and reflect the European Economic Area (EEA) General Data Protection Regulation (GDPR) requirements.
- Section 7.2.1.1 Molecular response: definition of loss of MMR rephrased and harmonization of time points for BCR-ABL1 gene mutation analysis.
- Table 7.2 Blood samples (efficacy primary endpoint): updated to reflect:
  - [redacted]
  - Exploratory BCR-ABL1 mutation analysis (Sanger Sequencing) for patients with mutations at Week 1 Day 1 will be performed without any dedicated blood collection.
- Section 7.2.1.2 Bone marrow analysis and cytogenetics: bone marrow aspirate for cytogenetic analysis at week 24, 48, 72 and 96 has been limited to patients who have not achieved MMR.
- Section 7.2.2.1 Physical examination: week 6, 10 and 14 assessments must be performed only if new or ongoing adverse event since last visit.
- Section 7.2.2.3 Height and weight and Table 7-1 Visit evaluation schedule: weight to be collected at Week 1 Day 1 and thereafter every 12 weeks.

[redacted]

- Section 7.2.2.5 Laboratory evaluations: was updated to allow on exceptional basis local laboratory evaluations.
- Section 7.2.2.5.1 Hematology: the week 6, 10 and 14 assessments can be performed at site or at any peripheral local laboratory.
- Table 7-4 Central clinical laboratory parameters collection plan and Section 7.2.2.5.2 Clinical chemistry: clarification added for some of the parameters. Parameter naming clarified and total calcium (corrected for albumin) added.
- Table 7-5 Central ECG collection (all patients): clarification for ECG on Week 2 Day 1 for patients treated with bosutinib.
- Section 7.2.4.2 Biomarker assessments in blood samples:
  - Characterization of low level mutations in BCR-ABL1: clarification of time points for Sanger mutation testing.
  - [redacted]
- Table 7-9 Biomarker sample collection plan:
  - Bone marrow samples (exploratory): clarifications added.
  - [redacted]
  - Addition of one time point collection for low level mutation analysis to be consistent with text in Section 7.2.4.2 Biomarker assessment in blood sample.
- Section 7.2.2.5.3 updated to reflect the change of name of the Novartis Drug Safety and Epidemiology (DS&E) department to the present name, Chief Medical Office and Patient Safety (CMO&PS).
- Section 7.2.2.6.1 Electrocardiogram (ECG): additional instruction given if ECG and blood samples for PK scheduled at the same time point.
- Section 7.2.5 Resource utilization and Section 10.6.4.1 Resource Utilization: precision of the reasons for resource utilization.
- Section 7.2.6 Patient reported outcome: precision that completion of questionnaires is mandatory.
- Section 8.4 Pregnancies: updated to reflect the change of name of the Novartis Drug Safety and Epidemiology (DS&E) department to the present name, Chief Medical Office and Patient Safety (CMO&PS) and the change in collection of pregnancy outcomes from "must" to "should".
- Section 10 Statistical methods and data analysis: precisions provided regarding the cut-off dates for the primary and end of study treatment phase analysis.
- Section 10.1.5 Pharmacokinetic analysis set: precision provided on the post and pre-dose samples and vomiting.
- Section 10.1.6 Other analysis sets: precision of MMR and CCyR responder sets.
- Section 10.5.1.1 Analysis of key secondary objectives: adding an imputation rule for the secondary objective at 96 weeks and clarification concerning the analysis of the key secondary endpoint at week 96 if statistical significance is not reached for primary endpoint at week 24.

[redacted]

- Section 10.5.2 Other secondary efficacy objectives: update of descriptive statistics definition and removal of presentation of p value as no formal statistical testing will be performed.
- Section 10.6.1 Exploratory efficacy objectives and Section 10.6.3 Exploratory biomarker objectives:
  - Correction of time points for BCR-ABL1 mutation characterization (baseline corrected to Week 1 Day 1, adding "upon confirmed loss of MMR, and changed "and" to "and/or" End of treatment).
  - [redacted]
- Section 10.6.4.1 Resource utilization: correction on duration of resource utilization reporting.
- Section 10.7 Interim analysis: clarification concerning the analysis of the key secondary endpoint at week 96 if statistical significance is not reached for primary endpoint at week 24.
- Section 14 Appendices: the lists of concomitant medications for patients on asciminib and bosutinib have been updated based on the internal Pharmacokinetic Sciences memorandum on Drug-Drug Interaction (release date: January 2018).
- Some minor inconsistencies (discrepancies between sections, typos) have been corrected.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 1 (10-Apr-2017)

Amendment rationale

This study is currently in the protocol submission phase. The protocol was submitted to the FDA only. The submissions to the other HA and IRB/EC will be performed once the amended protocol is available. As of 30 Mar 2017, no sites were initiated nor any patients screened for this study.

The primary purpose of this amendment is:

Patients with a mutation V299L are excluded from the study, due to the known inactivity of the comparator drug bosutinib. The designation of the mutation was inadvertently identified incorrectly throughout the protocol as V229L instead of V299L. The purpose of this amendment is to correctly identify the exclusionary mutation as "V299L" throughout the document.

In addition some inconsistencies that were discovered after the finalization of the initial protocol are corrected.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Protocol summary: The wrongly designated mutation V229L was corrected to V299L
- Protocol summary: The missing exclusion criteria number 18 "Pregnant or nursing (lactating) women" was added, to be consistent with Section 5.3.
- Section 1.2.2- Overview of bosutinib: The wrongly designated mutation V229L was corrected to V299L
- Section 2.5- Rationale for choice of comparators drug bosutinib: The wrongly designated mutation V229L was corrected to V299L
- [redacted]
- Section 5.1- Patient population: The wrongly designated mutation V229L was corrected to V299L
- Section 5.3- Exclusion criteria: The wrongly designated mutation V229L was corrected to V299L
- Section 6.4.4- Other concomitant medications: The duration of contraception was corrected to "3 days" after treatment discontinuation. Highly effective contraception needs to be continued until 3 days post-treatment discontinuation.
- Table 7-1-Visit evaluation schedule: X for weight removed from Visit Week 1 Day 1, to be consistent with Section 7.2.2.3.
- Table 7-1-Visit evaluation schedule: X for antineoplastic therapies since discontinuation of study treatment added to survival follow-up phase to be consistent with Section 7.1.6.

[redacted]

- Section 7.1.6- Discontinuation of study treatment: The criteria for study treatment discontinuation "documented lack of efficacy, disease progression" was removed. All patients (excluding patients that died, withdrew consent or are lost to follow-up), are followed up for survival after the treatment phase.
- Section 7.1.6- Discontinuation of study treatment: clarification added to distinguish between discontinuation of study treatment versus discontinuation of study.
- Section 7.2.2.1- Physical examination: clarification of methodology to assess extramedullary involvement.
- [redacted]
- Section 7.2.6- Patient reported outcomes: The statement "The original questionnaire will be kept with the patient's file as the source document." was removed. Questionnaires will be completed electronically; no paper copies will be kept in the source documents.
- Section 10.1.5- Pharmacokinetic analysis set: The number of consecutive days required for PK concentration evaluability was corrected to "3" days. ABL001 should be taken at least 3 consecutive days without interruption or dose modification prior to full PK day.

IRBs/IECs

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[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Chronic myeloid leukemia (CML) is a hematological stem cell disorder characterized by a specific chromosomal translocation leading to the Philadelphia (Ph) chromosome which is detected in 95% of patients (Nowell and Hungerford 1960; Rowley 1973). The molecular consequence of the translocation is the fusion of the *ABL1* proto-oncogene to the *BCR* gene resulting in the production of an activated form of the ABL1 protein tyrosine kinase (TK) (Bartram et al 1983; Heisterkamp et al 1983). BCR-ABL1 drives the growth factor independence, increased proliferation, genomic instability, suppression of apoptosis and alteration of the adhesive properties of CML cells (Hochhaus 2009) and the expression of BCR-ABL1 in mice results in the development of a CML-like disease (Daley et al 1990; Kelliher et al 1990). This evidence that BCR-ABL1 is a genetic driver of CML was subsequently confirmed by the clinical efficacy of imatinib in patients [IRIS Study STI571A0106].

Clinically, CML is characterized by overproduction of immature myeloid cells and mature granulocytes in the spleen, bone marrow and peripheral blood. Most patients, however, present in the CP, characterized by splenomegaly and leukocytosis with generally few symptoms. CML progresses through three distinct phases of increasing refractoriness to therapy: chronic phase (CP), accelerated phase (AP), and blast crisis (BC). With conventional chemotherapy, such as busulfan or hydroxyurea, the median survival time commonly reported for CML was about 4 years, but progression to AP and BP was only slightly delayed. Interferon-alfa delayed progression significantly, with a median survival of approximately 6 years. However, during the last decade, TK inhibitor (TKI) therapy became the standard treatment for most patients with CML, with complete cytogenetic response rates of 70% to 90% and 5-year progression-free survival and overall survival of 80% to 95% commonly reported (Vardiman 2009).

The National Comprehensive Cancer Network (NCCN) guideline on CML (NCCN guideline v 1.2014) and the European Leukemia Net (ELN) (Baccarani et al 2013) recommend continuing TKI treatment indefinitely in all responding patients. The first TKI, imatinib mesylate (imatinib, STI571, Gleevec™/Glivec™), an adenosine triphosphate (ATP)-competitive TKI with selectivity towards BCR-ABL1, revolutionized treatment of CML and significantly improved the prognosis of patients since its approval in 2001. It is effective in most patients with CML at well-tolerated doses, and is indicated as frontline therapy for Ph+ CML-CP and in patients with Ph+ CML in blast crisis (BC), accelerated phase (AP), or in CP after failure of interferon-alpha therapy. However, despite the remarkable efficacy of imatinib, some patients are either intolerant to the drug or can develop resistance (O'Hare 2006). Imatinib resistance is primarily due to nucleotide substitutions in BCR-ABL1, which encode mutant forms of protein's tyrosine kinase domain that impair imatinib binding. Over-expression of the BCR-ABL1 protein may also cause resistance. Rates of resistance increase with each stage of progression of CML (CP < AP < BC) (Branford 2003).

Multiple agents, including nilotinib, dasatinib, ponatinib, bosutinib, radotinib (Korea) and omacetaxine (USA, Canada) are able to combat various forms of imatinib-resistant CML and are currently approved for patients with CML-CP previously treated with prior therapy. With the exception of omacetaxine, which is a cytotoxic chemotherapeutic agent, all of these drugs

[redacted]

are ATP-competitive TKIs. Like imatinib, nilotinib, dasatinib and most recently bosutinib are also indicated for the treatment of patients with newly diagnosed CML. The activity of nilotinib or dasatinib in patients previously treated with a second generation TKI is not known. In contrast to the ATP-competitive TKIs, asciminib inhibits the enzymatic activity of BCR-ABL1 through an allosteric mechanism.

There remains an unmet need for new compounds in patients with CML who have failed at least two prior TKIs. Current practice suggests that a second generation TKI will have been used for first line therapy for about one half of patients with CML, meaning that most patients who have failed at least two prior TKIs will have failed at least one if not two second generation TKIs: dasatinib and/or nilotinib. Potentially, such patients may also have failed bosutinib and/or ponatinib (Soverini 2014). Patients having failed at least two TKIs may have limited sensitivity to the remaining available agents and, thus, there exists a need for new safe and effective therapy. In addition, mutations will have developed in 21 to 33% of patients that prevent the use of specific TKIs, increasing the need for a better and alternative compound (Soverini 2014). Omacetaxine, a chemotherapeutic agent, is available for patients who have failed at least two prior TKIs under these conditions but only in the US and Canada. This agent is not available for most patients globally, where a bigger unmet medical need is present. Thus, there remains an unmet need for active and safe drugs in patients with CML who have failed at least two prior tyrosine kinase inhibitors (TKI), even in the presence of approved drugs, as described below.

1.2 Introduction to investigational treatment

1.2.1 Overview of asciminib (ABL001)

Asciminib is an orally bioavailable specific BCR-ABL1 inhibitor with a novel mechanism of action. In contrast to inhibitors such as imatinib, nilotinib, dasatinib and bosutinib that bind within the ATP-binding site of the ABL kinase domain, asciminib inhibits ABL tyrosine kinase activity by binding to a particular allosteric site on the kinase domain, which has only been identified on ABL1, ABL2 and BCR-ABL1. Consequently, asciminib is specific for the latter three enzymes.

Asciminib potently and selectively inhibits the proliferation of cell lines that express BCR-ABL1. By virtue of asciminib not interacting with the ATP-binding site, the drug maintains activity against cells expressing clinically observed ATP-binding TKI resistance mutations.

1.2.1.1 Non-clinical experience

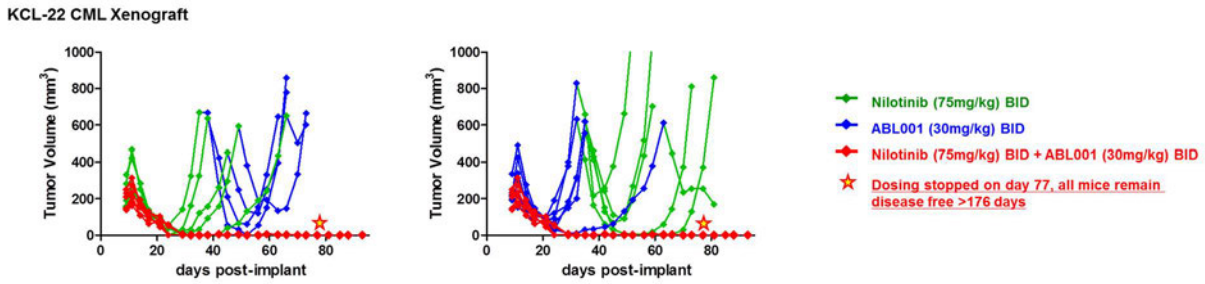
In vitro and in vivo pharmacology data

Asciminib displays potent anti-tumor activity *in vivo* with a clear pharmacokinetic (PK)/pharmacodynamic (PD)/Efficacy relationship [RD-2013-50145]. In a KCL-22 CML blast crisis (CML-BC) cell line mouse subcutaneous xenograft model, tumor regression was observed at doses of 7.5 mg/kg BID and above when asciminib was administered alone. Efficacy in the KCL-22 xenograft model correlated with stable inhibition of the downstream PD marker phospho-STAT5, consistent with finding that ABL1 inhibits STAT5 phosphorylation in KCL22 cells with an IC_{90} value of approximately 20 nM.

[redacted]

The KCL-22 xenograft model was also used to assess the activity of asciminib and nilotinib as single agents and in combination (Figure 1-1). In these experiments, when each agent was administered as monotherapy in sequence, initial sensitivity of the tumor was observed to each agent, but relapse occurred in each case. The mutations observed were as expected based on clinical experience (T315I for nilotinib) or modeling (A337V) for asciminib. In contrast, animals treated upfront with the combination of asciminib and nilotinib achieved sustained tumor regression with no evidence of disease relapse during the 70 days of treatment or for 80 days following discontinuation of treatment. Note that in this KCL-22 model, the cells (derived from a blast crisis CML patient) were grown as a solid tumor rather than as disseminated disease. Also, this model is much more aggressive than chronic phase CML in patients.

Figure 1-1 KCL-22 CML Xenograft



These data are consistent with asciminib being active against nilotinib-resistant mutations and nilotinib being active against asciminib-resistant mutations. Consequently, the findings support development of asciminib both as single agent as well as in combination with TKIs as initial therapy of CML as well as therapy after progression on nilotinib.

In addition, due to asciminib specifically targeting the ABL kinase family (ABL1, ABL2, BCR-ABL1), asciminib offers the potential for improved safety and tolerability when administered as monotherapy when compared to TKIs binding to the ATP site of BCR-ABL1, which are less specific towards ABL. Thus, there is the potential for an improved safety profile of asciminib in comparison to other TKIs.

Safety pharmacology and toxicology

An extensive toxicology safety evaluation program (subchronic, chronic, reproductive toxicology, phototoxicity and genotoxicity studies) was conducted.

Safety pharmacology studies indicate that asciminib is not expected to cause effects on the vital functions of the CNS, and the respiratory systems. The IC50 for asciminib in the hERG patch clamp is 11.4 µM (4498 ng/mL). No cardiovascular effects were observed in a single dose jacketed telemetry study in dogs at doses up to 600 mg/kg or the invasive telemetry cardiovascular safety study up to 60 mg/kg. Furthermore, no changes in cardiovascular parameters related to QTc prolongation were observed using standard electrocardiography in the 4-week dog toxicity study and in cynomolgus monkey toxicity studies (up to 39 weeks of treatment).

Asciminib does not show mutagenic, clastogenic, or aneugenic potential in the *in vitro* assays or the MNT assessment *in vivo*; therefore, no potential risk for human is perceived.

[redacted]

As determined by the results of the phototoxicity assessment (*in vitro* and *in vivo*), phototoxic potential was identified in the mouse UV-LLNA assay. Given these data, patients should be advised to avoid prolonged exposure to sunlight (sunbathing), to avoid sunbed and to use sunscreen.

Toxicity studies performed in rats, dogs and cynomolgus monkeys (up to 26, 4 and 39 weeks of treatment, respectively) identified the pancreas, liver, hematopoietic system, adrenal and gastro-intestinal tract as potential target tissues.

Fetal malformations and increased visceral and skeletal variants were observed in the rat embryo-fetal development study. There was no evidence of effects on reproductive function in the fertility study; however there was a slight effect on male sperm motility and/or sperm count in individual animals. Phototoxic potential was identified in the phototoxicity (*in vitro* and *in vivo*) assessment.

Please refer to the latest [Asciminib Investigator's Brochure] for more details.

Non-clinical pharmacokinetics and metabolism

The preclinical pharmacokinetic profile of asciminib has been investigated in three species: mouse, rat and dog. In these species, asciminib exhibited low to moderate clearance, a moderate volume of distribution and a short apparent terminal half-life. Bioavailability was found to be low in rodents and moderate to high in dog.

Asciminib displayed high plasma protein binding across all tested species (2-6% free fraction).

The metabolite profile of asciminib has been examined in vitro using rat, dog, monkey and human hepatocytes. Interspecies differences were observed in the *in vitro* metabolism of asciminib in hepatocytes, with direct glucuronidation occurred more readily in human, to a lesser extend in dog and monkey, and was noticeably absent in rat. However, no unique, major metabolites were identified in human hepatocytes. The overall metabolic turnover was low.

The metabolite profile of asciminib has also been examined *in vivo* in rats. Following intravenous and oral administration of [^{14}C-asciminib] to intact rats, asciminib was found to be the predominant component of plasma, accounting for ~86 - 91% of radioactivity from 0 - 8 h. Asciminib was excreted primarily in the feces, with ~90% of radioactivity detected in the feces from 0 - 48 h. Renal elimination represented a minor route, with ~2.4% of radioactivity detected in the urine from 0 - 72 h. In the feces, ~58% (intravenous) and ~71% (oral) of the dose was associated with unchanged asciminib, with several oxidative metabolites accounting for the remaining radioactivity. The metabolites formed *in vivo* were consistent with those observed *in vitro*. Similar observations were noted in bile-duct cannulated rats.

To assess for potential drug-drug interactions (DDI), studies have been conducted with cytochrome P450 (CYP) enzymes and several transporters *in vitro*.

In human liver microsomes, the major metabolic route of asciminib was found to be glucuronidation, followed by oxidative metabolism, consistent with findings from human hepatocytes. Several Uridin diPhospho-glucuronosyltransferase (UGT) enzymes were found to be capable of asciminib glucuronidation (UGT1A3, UGT1A4, UGT2B7, and UGT2B17). The oxidative metabolism of asciminib was also catalyzed by several CYP enzymes. CYP3A4/5 appears to contribute the most, followed by CYP2C8, CYP4F12, and potentially CYP2D6.

[redacted]

Though the DDI risk with inhibitors of these enzymes is likely to be minimal, inhibitors of CYP3A4/5 still have the potential to increase asciminib concentration. Therefore, strong inhibitors of CYP3A4/5 should be avoided and are prohibited in this study. Strong inducers of CYP3A4/5 have the potential to reduce asciminib concentrations. Therefore, the use of strong inducers of CYP3A4/5 or UGT1A/2B is prohibited in this trial.

In recombinant cellular expression systems, asciminib was identified as a substrate of Breast Cancer Resistant Protein (BCRP) (Michaelis-Menten constant (Km) ≈ 4 μM) and permeability glycoprotein (P-gp) (Km could not be estimated due to insufficient saturation of efflux activity). Late fecal metabolite analysis in the human Absorption, Distribution, Metabolism, and Excretion (ADME) study [CABL001A2102] and estimated contributions of different enzyme pathways (CYP vs. UGT) by use of in vitro enzyme phenotyping methods, do suggests that at least 24% of the parent drug in the feces is due to conversion of a glucuronide (M30.5) metabolite back to parent drug (absorption then being maximally 57%). However, this late fecal metabolite analysis could also suggest that the 24% could be active secretion by P-gp (Drug Metabolism and Pharmacokinetics [DMPK R1700912]. This is a small percentage (< 25% of the clearance by this pathway) with a weak expected impact on asciminib concentrations. Overall, inhibitors of BCRP and P-gp may increase asciminib concentration. Therefore, BCRP and P-gp inhibitors should be administered with caution.

Based on *in vitro* phenotyping studies and human ADME study outcome, the physiologically based pharmacokinetic (PBPK) model was updated and predicted minimal to no DDI for sensitive substrates of CYP3A4, CYP2C8 and CYP2C9 (Drug Metabolism and Pharmacokinetics [DMPK-DDI-R1700912]. Indeed, the effect of asciminib 40 mg BID is expected to result in increased area under the curve (AUC) of CYP3A4, CYP2C8 and CYP2C9 probe substrate by 1.21, 1.09 and 1.07. Therefore, the effect of asciminib is expected to be weak and hence substrates of CYP2C8, CYP2C9 and CYP3A4 with narrow therapeutic index (NTI) would be used with caution.

Please refer to the latest [Asciminib Investigator's Brochure] version for more details.

1.2.1.2 Clinical experience

Asciminib is undergoing evaluation in a first-in-human (FIH) phase I clinical study, study [CABL001X2101].

This study evaluates patients with 1) CML who have been treated with at least 2 prior TKIs, or 2) who have the T315I mutation and have been treated with at least 1 prior TKI, or 3) who have Acute Lymphoblastic Leukemia (ALL) and have been treated with at least 1 prior TKI. The study evaluates administration of asciminib in a BID single agent dosing schedule, as well as in a QD single agent schedule, and in combination with nilotinib, imatinib, and dasatinib. In the present document, discussion will focus on data from CML patients treated with asciminib BID single agent only.

As of 01-Sep-2017, a total of 239 CML or Ph+ ALL patients have been treated with either single agent oral asciminib or in combination cohorts. 150 CML patients have been treated with asciminib monotherapy. Based on the preliminary efficacy, safety and tolerability in patients with CML-CP or CML-AP treated with asciminib as a single agent on a BID schedule in study [CABL001X2101] and the results of a population PK/PD exposure-response model, the

[redacted]

dose of 40 mg BID has been selected as the recommended dose to be used in future studies in patients with CML-CP who do not harbor T315I mutations.

Efficacy:

Preliminary data from the ongoing Phase I FIH study [CABL001X2101] indicate that asciminib exhibits single-agent activity in patients with CML who have failed at least two prior TKIs or are intolerant to TKIs, as demonstrated by major molecular response and reduction in the BCR-ABL1 % IS. Asciminib has demonstrated anti-tumor activity at doses greater or equal to 10 mg BID as well as daily higher doses.

To date, efficacy data in 141 patients with chronic-phase CML treated with single agent asciminib therapy (10-200 mg BID and 80-200 mg QD) are available (113 patients without T315I mutation and 28 with T315I mutation).

Of the 62 patients with BCR-ABL1 no greater than 10 % IS at screening and without T315I mutation, 1-log reduction of BCRABL1 % IS was achieved in 16 of 62 (25.8%) patients by 6 months and 19 of 62 (30.6%) patients by 12 months. For asciminib 40 mg BID dose, of the 17 patients studied, 1-log reduction of BCRABL1 % IS was achieved in 5 of 17 (29.4%) patients by 6 months, and 12 months.

Please refer to the latest [Asciminib Investigator's Brochure] for more details.

Safety:

Asciminib was generally well tolerated in heavily pre-treated CML patients resistant to or intolerant of prior TKIs. All 239 patients were evaluable for safety. Seventy six study discontinuations have been reported; the most frequent reason for discontinuation was progressive disease, reported in 38 patients (15.9%). Adverse events leading to treatment discontinuation were reported in 15 patients (6.3%). Death leading to treatment discontinuation was reported in 3 patients (1.3%) (one patient in asciminib 20 mg BID due to aspiration pneumonia after bypass procedure and two patients with ALL with 80 mg and 160 mg BID due to progressive disease).

Among the 150 patients treated with asciminib monotherapy, almost all (94.7%) patients reported at least one AE, including 49.3% reported grade 3/4 AEs. The most common AEs (> 10%) among patients treated with 40 mg BID (n=35), regardless of study drug-relationship, were increased lipase, fatigue, diarrhea, thrombocytopenia, neutropenia, arthralgia, rash, headache, increased amylase, nausea, vomiting, abdominal pain, pyrexia, upper respiratory tract infection, back pain, hypertension, cough, pruritus, pain in extremity, dyspnea, bone pain, peripheral oedema, non-cardiac chest pain and insomnia. The most common reported grade 3/4 event was increased lipase (17.1%).

Forty-seven of 150 patients with CML-CP or CML-AP treated with asciminib single agent (31.3%) were reported with serious adverse events (SAE).

Electrocardiogram (ECG) data shows no reported QT prolongation (increase > 60 msec or new > 500 msec) in 40 mg BID asciminib monotherapy group. There was no reports of QT prolongation (increase > 60 msec) and two reports of new >500 msec (one each in 80 mg QD and 120 mg QD) among all asciminib monotherapy group.

[redacted]

Please refer to the latest [Asciminib Investigator's Brochure] for more details.

Pharmacokinetics:

PK data from 190 patients were available from the [CABL001X2101] study, as of 01-Sep-2017. When given as a single agent on a twice daily schedule, patients received escalating doses of asciminib ranging from 10 to 200 mg.

Based on the available PK data, asciminib, administered orally is rapidly absorbed with a median time to maximum plasma concentration (Tmax) of 2 to 3 hours, independent of dose. Systemic exposure of asciminib, following oral administration of single and multiple doses, as measured by Cmax and AUC, increased in an approximately dose proportional manner. The variability of exposure is low to moderate with inter-patient variability (geometric mean CV %) ranging from approximately 25 to 70% for both Cmax and AUClast. With the twice daily dosing regimen, median plasma asciminib accumulation ratios ranged from 1.3 to 2.5. The median accumulation half-life was estimated to be 7 to 15 hours.

The data of the hADME study [CABL001A2102] show that the relative contribution of the glucuronidation pathway to the total clearance of asciminib via metabolism is estimated to range from 30% to 61%, whereas the relative contribution of the oxidative pathway is estimated to range from 35% to 63%. CYP3A4 was the main contributor for the clearance of asciminib via the oxidative pathway while UGT2B7 and UGT2B17 were responsible for the clearance of asciminib via the glucuronidation pathway. There was no metabolite detected with mean contribution to plasma radioactivity AUC0-24hours ≥ 10%. Asciminib was the predominant drug-related component in plasma at all time points analyzed, ranging from 91.9 to 94.2% of the total radioactivity AUC0-24 hours AUC, with an average value of 92.7%.

Please refer to the latest [Asciminib Investigator's Brochure] for more details.

Exposure-response relationship:

Exposure-efficacy

A preliminary population PKPD model has been developed using data from the [CABL001X2101] study (cut-off 02-May-2016). The time course of molecular response (change in BCR-ABL1 ratio % IS levels from baseline) was described using a semi-physiological model accounting for cell maturation, disease progression and existing resistance.

Simulations performed using an asciminib population PK model revealed that a dose of 40 mg BID maintains Ctroughs above the clinical (0.07 to 61 ng/mL) threshold in ≥95% of chronic phase CML patients without T315I mutation having failed ≥ 2 TKI or intolerant to TKIs. The estimates from this clinical study were found to be similar to the threshold trough concentration required for 90% inhibition of pSTAT5 derived from a preclinical PK-PD KCL-22 mouse xenograft model (free IC90: 30 to 121 ng/mL, after correction for protein binding) and *in vitro* gIC50 assessed in the KCL-22 cell line (1 ng/mL = 2.1 nM after correction for protein binding).

Simulations performed using asciminib population PKPD model revealed that chronic phase CML patients having failed ≥ 2 TKI or intolerant to TKIs are likely to exhibit a 1 log10 reduction of (%) BCR-ABL1 mRNA transcript levels from baseline of ~33% (CI95%: 24-42%) at 6 months, and ~42% (CI95%: 32-52%) at 12 months at a dose of 20 mg BID and ~41%

[redacted]

(CI95%: 31-51%) at 6 months, and ~53% (CI95%: 43-63%) at 12 months at a dose of 40 mg BID.

Additional preliminary exposure response analyses (i.e. exploring the relationship between PK and both safety and efficacy) support the selected dose.

Food effect

The effect of food on asciminib PK was characterized in a Phase I study [CABL001A2101] in healthy volunteers. Food was found to influence the pharmacokinetics of asciminib. When administered with a low-fat meal, the exposure (AUC) decreased by approximately 30%. The overall exposure decreased by approximately 65% when administered with a high-fat meal. Therefore, asciminib will be administered in a fasted state.

1.2.2 Overview of bosutinib

Bosutinib (Bosulif®) is indicated for the treatment of adult patients with newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) and for the treatment of patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy (500 mg QD) [Bosulif® USPI] as well as for newly-diagnosed CML-CP (400 mg QD), and in Europe for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options [EU Summary of Product Characteristics (SmPC)]. Bosutinib has been evaluated in patients treated with one or more prior TKIs.

For patients treated with bosutinib after prior imatinib only, the MMR rate is approximately 15% at 24 weeks overall, and approximately 10% in imatinib-resistant patients and 20% in imatinib-intolerant patients (Gambacorti-Passerini 2014). The cytogenetic, molecular, and hematological response rates did not appear to differ greatly between patients who were imatinib-resistant or imatinib-intolerant (Gambacorti-Passerini 2014).

Twenty seven percent of patients treated with bosutinib after at least 2 previous TKIs achieved MCyR rate by Week 24 [Bosulif® USPI]. For patients previously treated with imatinib and either dasatinib or nilotinib, after a median of 28.5 months follow-up, the cumulative rate of Major Molecular Response (MMR) is 15% (Khoury 2012). The cytogenetic, molecular, and hematological response rates appeared to be lower in patients who were resistant to dasatinib after imatinib treatment as compared to patients who were intolerant to dasatinib after imatinib treatment (Khoury 2012). In a small (30 patient) compassionate use trial of patients previously treated with imatinib, dasatinib and nilotinib, after a median duration of treatment of 9.3 months, the cumulative MMR rate was 14% (García-Gutiérrez 2015). Based on these data, the MMR rate at 6 month with bosutinib treatment in patients treated with at least 2 prior TKIs is estimated to be approximately 10-15%.

Bosutinib has no activity against the T315I and V299L mutant form of BCR-ABL1. Accordingly, the pivotal trial leading to the registration in the 3rd line setting excluded patients with a known history of the T315I or V299L mutation [Bosulif® USPI].

[redacted]

2 Rationale

2.1 Study rationale and purpose

Asciminib is an agent intended to be evaluated for the treatment of patients with CML. In the ongoing study [CABL001X2101] study, asciminib was found to produce clinically meaningful and durable responses in patients who have had treatment failure after a minimum of 2 prior ATP-binding site TKIs, with an acceptable safety and tolerability profile.

The purpose of this pivotal study is to compare the efficacy of asciminib with that of bosutinib in the treatment of patients with CML-CP having previously been treated with a minimum of two prior ATP-binding site TKIs. Patients with intolerance to most recent TKI therapy must have BCR-ABL1 ratio > 0.1% IS at screening and patients experiencing failure to most recent therapy must meet the definition of treatment failure as per the 2013 ELN guidelines (Baccarani et al 2013).

Imatinib, nilotinib and dasatinib are indicated for the treatment of patients with newly diagnosed CML. Multiple agents, including nilotinib, dasatinib, ponatinib, bosutinib, radotinib (Korea) and omacetaxine (USA, Canada) are approved for patients with CML-CP previously treated with prior therapy. Imatinib is a first generation TKI; nilotinib, dasatinib, bosutinib, ponatinib and radotinib are considered second generation TKIs and have activity in patients previously treated with imatinib. The activity of nilotinib or dasatinib in patients previously treated with a second generation TKI is not known. All the currently approved BCR-ABL1 TKIs are enzymatic site inhibitors, in distinction to asciminib which is an allosteric TKI. Omacetaxine is a cytotoxic chemotherapeutic agent.

2.2 Rationale for the study design

Asciminib is an orally bioavailable specific BCR-ABL1 inhibitor with a novel mechanism of action. In contrast to other TKIs that bind within the ATP-binding site of the ABL kinase domain, asciminib inhibits ABL tyrosine kinase activity by binding to a particular allosteric site on the kinase domain that is utilized by a myristate group to auto-regulate the native ABL1 kinase. With allosteric inhibition of BCR-ABL1 being a novel mechanism of action, asciminib produces clinically meaningful and durable responses in patients who have had treatment failure after a minimum of 2 prior ATP-binding site TKIs, with an acceptable safety and tolerability profile as demonstrated in study [CABL001X2101].

The development of asciminib, presents an opportunity to evaluate the beneficial effects of inhibition of BCR-ABL1 in the treatment of patients with CML. The proposed study design is expected to adequately allow an assessment of the efficacy, safety and tolerability of asciminib in a population of patients with continuing medical need i.e., patients who have been treated with at least two prior TKIs and are in the need for further therapeutic intervention.

Bosutinib is one of the TKIs with proven clinical benefit in CP-CML patients previously treated with one or more tyrosine kinase inhibitor(s) and is currently approved for this indication in many countries, including the European Union. The proposed study will evaluate asciminib in comparison to bosutinib at the approved doses in the targeted population.

[redacted]

This study is not being conducted as a blinded study; the conditions for drug administration being distinct for the two treatments arms makes blinding complex and increases the likelihood of dosing errors. Bosutinib needs to be taken with food, whereas asciminib needs to be taken fasted. The difference in administration of the two treatments, requiring double dummy treatments, makes blinding difficult to put in place in practice and carries inherent risks of dosing errors and reduces patient compliance. Additionally, the characteristic adverse event profile of bosutinib (frequent gastrointestinal AEs of diarrhea and vomiting in 78.5% and 37.1% patients, respectively) further preclude effective blinding. Randomization and use of objective efficacy endpoints mitigate the risks of an open label study design.

The study design incorporates a 2:1 randomization, allocating more patients to the asciminib arm in order to learn more about the safety profile of the experimental therapy, whereas the safety of bosutinib therapy is well documented.

Patients randomized to the bosutinib arm who have documented treatment failure as defined by the 2013 ELN Guidelines at any time point will have the option to receive asciminib at the investigator's discretion and if it is in the patient's best interest. The purpose of the option to switch to asciminib is to provide this investigational treatment option to eligible patients who will have limited available therapeutic options outside of the study.

Treatment duration for each patient in the present study is up to 96 weeks after the last patient received the first dose in the study (which should be an adequate timeframe to address both the primary objective of the study, i.e. determination of the MMR rate at 24 weeks, as well as the secondary efficacy and safety objectives) or up to 48 weeks after the last bosutinib failure patient has switched to asciminib during the treatment period, whichever is longer unless the patient discontinues treatment earlier. Blood samples will be taken in this study from all patients randomized to asciminib in order to describe the pharmacokinetics and possibly identify the sources of variabilities. Exploratory analysis may be performed to establish the relationship between exposure and efficacy or safety.

2.2.1 Rationale for Biomarker Assessment

The primary goal of the biomarker assessments for this study is to evaluate potential mechanisms of resistance to asciminib.

Exploratory endpoints involving biomarker assessments for patients treated with asciminib, in comparison to those treated with bosutinib, will focus on 1) the PK/PD relationship; 2) BCR-ABL1 gene mutations that could influence the outcome of treatment regimens; and 3) the underlying biology of CML.

In order to evaluate tumor kinetics on a molecular level and to explore the role of mutations with respect to response to treatment, exploratory endpoints include assessment of mutations in the BCR-ABL1 gene at Week 1 Day 1, upon confirmed loss of molecular response and/or at end of treatment. Mutational status will be characterized in peripheral blood.

[redacted]

[redacted]

2.3 Rationale for dose and regimen selection

The dose and regimen of asciminib selected for this study is 40 mg BID. This dose is supported by pharmacokinetic, efficacy and safety data available from the ongoing [CABL001X2101] study.

During escalating doses of asciminib 10 mg to 200 mg on a continuous BID schedule in study [CABL001X2101], the 40 mg BID dose was shown to be active and well tolerated in CML-CP patients.

With respect to efficacy, no clear evidence of dose-response relationship was observed across dose levels when considering Complete Cytogenetic Response (CCyR) or MMR. However, as described below, PK-PD population modeling using change from baseline of BCR-ABL1 mRNA levels as a PD endpoint suggest a higher probability of achieving ≥1 log reduction at 6 and 12 months with 40 mg BID versus 20 mg BID.

With respect to safety, although no MTD (maximum tolerated dose) has been formally characterized, there is an increased toxicity observed at doses ≥ 80 mg BID (pancreatitis occurred at the dose of 80 mg in two patients who had an intra-patient escalation to 80 mg from 40 mg, and in one patient at the dose of 150 mg BID). Generally there is a trend for higher rates of discontinuation due to AE, DLT (dose limiting toxicity) and grade 3/4 AE with increasing doses.

With respect to overall exposure, the dose of 40 mg BID is expected to result in concentrations consistently above IC90 *in vitro* concentrations. The estimates from study [CABL001X2101] were found to be above the threshold trough concentration required for 90% inhibition of pSTAT5 derived from a preclinical PK-PD KCL-22 mouse xenograft model (free IC90: 30 to 121 ng/mL, after correction for protein binding) and *in vitro* gIC50 assessed in the KCL-22 cell line (1 ng/mL = 2.1 nM after correction for protein binding).

A preliminary population PK-PD model has been developed using data from the [CABL001X2101] study (cut-off 2 May 2016). The time course of molecular response (change in BCR-ABL1 ratio % IS levels from baseline) was described using a semi-physiological model accounting for cell maturation, disease progression and existing resistance. Simulations performed (with 100 patients) using asciminib population PK-PD model revealed that at a dose of 40 mg BID, ~41% (CI95%: 31-51%) of chronic phase CML patients having failed ≥ 2 TKI or intolerant to TKIs are likely to exhibit a 1 log10 reduction of (%) BCR-ABL1 mRNA transcript levels from baseline at 6 months, and 53% (CI95%: 43-63%) at 12 months, and predicting higher probability of achieving BCR-ABL1 mRNA ≥ 1 log reduction at 6 and 12 months with 40 mg BID versus 20 mg BID.

[redacted]

Additional preliminary PK-efficacy and PK-safety analyses to assess the exposure-response relationship for asciminib were conducted (Section 1.2.1.2). The efficacy measure used was Molecular Response (MR) which is defined as a decline in BCR-ABL1 transcript levels in clinical blood samples of patients with Chronic Myeloid Leukemia (CML). MR was evaluated as both a continuous variable (BCR-ABL1 transcript levels) and categorical variable (whether or not adequate decline in BCR-ABL1 was achieved). The safety measures used were occurrence of Common Toxicity Criteria (CTC) grade 2, 3 or 4 laboratory values for lipase and amylase.

Reviewing the totality of the efficacy, safety, and pharmacokinetic data derived from the [CABL001X2101] study, the recommended dose for asciminib in this phase 3 study is 40 mg BID. Of note, the dose of asciminib single agent BID is further being evaluated in patients with the T315I mutation. At present the recommended dose of 40 mg BID is for patients without the T315I mutation. For this reason, patients with the T315I mutation are excluded from this study.

2.4 Rationale for choice of combination drugs

Not Applicable.

2.5 Rationale for choice of comparators drug bosutinib

The guidance provided by the NCCN and the ELN (Baccarani et al 2013), recommends bosutinib as a treatment in CML-CP patients who fail first-line or second-line treatment with imatinib or nilotinib or dasatinib. Consistent with these recommendations and clinical practice, bosutinib was selected to be an appropriate comparator in a study of 3rd line CML-CP patients after failure of at least 2 prior TKIs, and is the comparator that will be used in the present study.

It is to be noted that bosutinib has no activity against the T315I and V299L mutant form of BCR-ABL1. Patients who have the T315I or V299L mutations documented in their medical record will already be excluded from this study. Bosutinib is known to be active against E255K/V, F317L/V/I/C, F359V/C/I, T315A, and Y253H and therefore, these mutations are not considered in the exclusion criteria for the current study.

Ponatinib is not selected as the comparator in the present clinical trial, because the comparator in this study needs to be an approved agent administered at the approved dose. Currently, the ponatinib dose is being evaluated in a randomized trial as a post-approval commitment due to the occurrence of vascular risks at the current approved dose of ponatinib. The dose of ponatinib that will be approved and will be used in practice at the completion of the present study may not be the approved dose at the time of initiation of the present study.

2.6 Risks and benefits

Appropriate eligibility criteria, as well as specific dose modification and stopping rules in the event of expected toxicities, are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events are provided in Section 6.3. Patients who have failed 2 prior TKIs are at increased risk of progression to more advanced phases of CML such as CML-AP and CML-BC. Currently available therapeutic agents in this setting are non-curative and patients remain at risk of progressing after short duration of remissions (Khoury 2012).

[redacted]

An important potential risk for patients enrolling on the experimental arm of the study with asciminib will be that this agent may be ineffective. However, the evidence to date at the doses to be administered in a similar population of patients in the study [CABL001X2101] suggests that asciminib is an active agent. Further, the adverse event profile of asciminib is similar qualitatively to that observed with other TKIs targeting BCR-ABL1 (Section 1.2.1.2). The risk of asciminib not being effective has been mitigated in that patients will be observed closely for evidence of efficacy, based on assessment of hematologic, cytogenetic and molecular response data, which will permit rapid decision making as to discontinuation of therapy if necessary.

Other risks to subjects in this trial will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, and adherence to dose modification and interruption guidance provided in the protocol.

The currently available information suggests that there is equivalence between the two arms with respect to benefit / risk to enable inclusion of patients in this study.

There may be unforeseen risks with asciminib which could be serious. Refer to the latest [Asciminib Investigator's Brochure] for additional details.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To compare the MMR rate at 24 weeks of asciminib versus bosutinib	Major Molecular Response (MMR) rate at 24 weeks	Refer to Section 10.4
Key secondary		
To compare additional parameters of the efficacy of asciminib versus bosutinib	MMR rate at 96 weeks	Refer to Section 10.5.1
Other secondary		
To compare additional parameters of the efficacy of asciminib versus bosutinib	• Cytogenetic response rate (Complete, Partial, Major, Minor, Minimal, no response) at and by all scheduled data collection time points including 24, 48 and 96 weeks • MMR rate at all scheduled data collection time points (except 24 and 96 weeks which are already covered by primary and key secondary endpoints) • MMR rate by all scheduled data collection time points including 24, 48 and 96 weeks • Time to MMR • Duration of MMR • Time to CCyR • Duration of CCyR • Time to treatment failure • Progression free survival • Overall survival	Refer to Section 10.5.2
To compare the safety and tolerability profile of asciminib versus bosutinib	Type, frequency and severity of adverse events, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG and other safety data (vital signs, physical examination)	
To characterize the PK of asciminib in the CML-CP population	Trough plasma concentrations, PK parameters in full PK group: Cmax, Tmax, AUC0-12h, CL/F	
To assess the safety of asciminib when administered as treatment after bosutinib failure according to the 2013 ELN Guidelines	Type, frequency and severity of adverse events, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG and other safety data (vital signs, physical examination)	Refer to Section 10.6

[redacted]

Objective	Endpoint	Analysis
Exploratory		
To evaluate the influence of factors such as cytogenetic response at baseline, failure/intolerance to prior TKIs, line of therapy, gender, race and age on the effect of asciminib with respect to the primary efficacy endpoint	Major Molecular Response (MMR) rate at 24 weeks	Refer to Section 10.6
To explore the exposure-response relationships of asciminib; evaluate the effect of population covariates	Exposure-safety and exposure-PD analyses	
To characterize mutations in the BCR-ABL1 gene at Week 1 Day 1, upon confirmed loss of molecular response and/or at end of treatment and examine their association with molecular and cytogenetic response for asciminib vs. bosutinib	BCR-ABL1 gene mutations at Week 1 Day 1, upon confirmed loss of molecular response and/or at end of treatment as determined by Sanger Sequencing	
[redacted]	[redacted]	
To assess clonal evolution during treatment with asciminib vs. bosutinib	Low level BCR-ABL1 mutation profiles assessed by mass spectrometry at Week 1 Day 1, upon confirmed loss of MMR and/or at EOT. Clonal evolution of several genes implicated in CML assessed by Next Generation Sequencing (NGS) methods	
[redacted]	[redacted]	
To compare the impact of treatment on patient reported outcomes (PRO) including CML-specific symptoms, patient quality of life, and impact on work productivity and activity impairment from baseline and EOT between treatment arms in all patients	Change in symptom burden and interference from baseline over time according to the MDASI-CML PRO instrument Change in patient's impression of CML symptoms according to Patient Global Impression of Change (PGIC) Change in health utility from baseline over time according to EQ-5D-5L Change in work productivity and activity impairment over time according to WPAI	
To compare the impact of treatment on health care resource utilization between treatment arms in all patients	Health care resource burden over time	
To assess the efficacy of asciminib when administered as treatment after bosutinib failure according to the 2013 ELN Guidelines	• Cytogenetic response rate (Complete, Partial, Major, Minor, Minimal, no response) at and by all scheduled data collection time points • MMR rate at and by all scheduled data collection time points	Refer to Section 10.6

[redacted]

Objective	Endpoint	Analysis
	• Time to MMR • Duration of MMR • Time to CCyR • Duration of CCyR • Time to treatment failure	

[redacted]

4 Study design

4.1 Description of study design

The study is a phase 3, multi-center, open-label randomized study of oral asciminib versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors.

The trial is designed to compare the efficacy and safety of asciminib with that of bosutinib in the treatment of patients with CML-CP having previously been treated with a minimum of two prior ATP-binding site TKIs. Patients intolerant to the most recent TKI therapy must have BCR-ABL1 ratio > 0.1% IS at screening and patients failing their most recent TKI therapy must meet the definition of treatment failure as per the 2013 ELN guidelines (Baccarani et al 2013). No more than 66 patients (approximately 30% of the overall trial population) that are intolerant to their most recent TKI therapy with BCR-ABL1 < 1% will be recruited in order to ensure that the CML third line patient population is adequately represented.

The study will also investigate secondary endpoints for efficacy, safety and PK of single-agent asciminib compared to bosutinib. Tolerability, PK, PRO and exploratory biomarker activities will also be assessed. Safety and efficacy data for patients switching to asciminib will be collected and analyzed separately.

Patients meeting all of the inclusion and none of the exclusion criteria will be randomized into one of the 2 treatment arms, based on a 2:1 randomization between the asciminib arm and the bosutinib arm.

The randomization will be stratified to ensure the study population is balanced between the arms with respect to cytogenetic response status (See Section 7.2.1.2) at screening as follows:

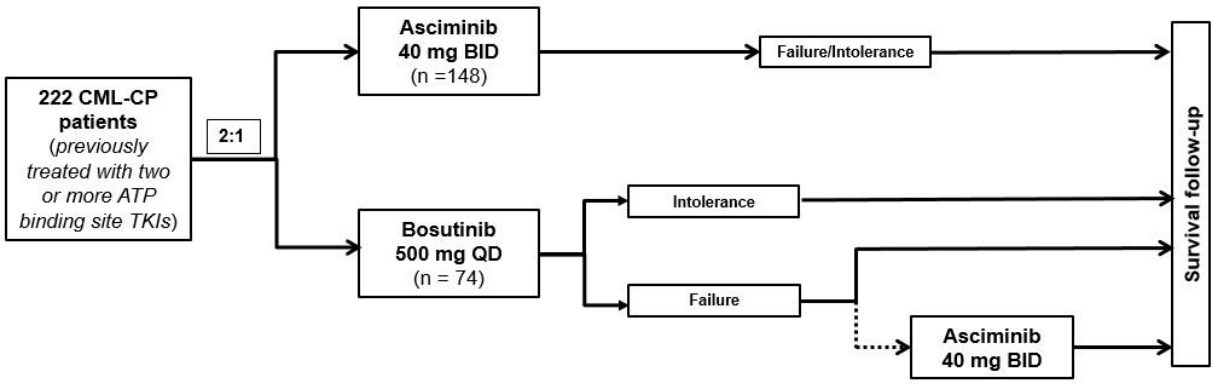
- Major cytogenetic response (complete or partial)
- No major cytogenetic response (minor, minimal or none)

Patients will continue to receive the assigned study treatments (asciminib or bosutinib) until the end of study treatment period as defined in Section 4.3. Patients who discontinue their study treatment at any time during the study will be followed up for survival and for progression to AP/BC for up to 5 years from the date the last randomized patient receives the first dose (irrespective of treatment switch for patients failing bosutinib).

Serial PK samples over 12 hours will be collected on Week 2 Day 1 from at least 20 CML-CP patients (full PK group) on the asciminib arm, in addition to trough PK samples. These patients will be identified sequentially at selected sites that are capable of serial PK sampling over 12 hours. In the remaining patients in the asciminib arm and in patients that have switched to asciminib, sparse post-dose PK samples on Week 1 Day 1 and trough PK samples will be collected (sparse PK group).

[redacted]

Figure 4-1 Schematic of Study Design



4.1.1 Study treatment switch from bosutinib to asciminib

Patients with documented treatment failure (as per the 2013 ELN guidelines; Baccarani et al 2013) while on bosutinib treatment will have the option to switch to asciminib treatment within 96 weeks after the last patient has been randomized on study. The patients who switch to asciminib will be able to receive asciminib up to end of study treatment period. At the end of the treatment period for patients who, in the opinion of the investigator still derive clinical benefit, asciminib treatment will be made available through alternative options including, but not limited to, an expanded access/compassionate use/managed access program or access to commercial supplies in applicable countries. Discontinuation of asciminib for patients who have switched over from bosutinib must follow the guidelines provided in Section 7.1.6. Eligibility criteria for patients switching to asciminib are described in Section 7.1.

4.2 Timing of interim analyses and design adaptations

Not applicable. There are no formal interim analyses or design adaptations planned for this study. See Section 8.6 for documentation of safety DMC.

4.3 Definition of end of study

The patients are treated in the study up to end of study treatment period defined as up to 96 weeks after the last patient receives the first dose or up to 48 weeks after the last patient has switched to asciminib treatment whichever is longer unless patients have discontinued treatment earlier. The end of the study, concluding the survival follow-up, will occur 5 years from the date when the last patient enrolled into the study receives the first dose of the randomized treatment.

The primary analysis (cut-off date) is defined as the date when all randomized patients have been on study treatment for 24 weeks (Section 10.4) or discontinued earlier. Subsequent to this

[redacted]

analysis, the primary clinical study report (CSR) will be developed. Following the cut-off date for the primary CSR, the study will remain open. Patients who are ongoing at the time of the primary analysis will continue to receive the assigned study treatments (asciminib or bosutinib) during the study treatment period as defined above. The end of study treatment analysis will be conducted with a cut-off date 30 days after the end of study treatment period to ensure all available treatment data from all patients in the study is analyzed and summarized in a CSR.

After the end of the study treatment period the assigned study treatment will be made available to patients who in the opinion of the Investigators are still deriving clinical benefit. This may be outside of this study through alternative options including, but not limited to, an expanded access/compassionate use /managed access program or access to commercial supplies in applicable countries.

Patients will be followed for survival and progression for up to 5 years from the date the last randomized patient receives the first study dose (irrespective of treatment switch for patients failing bosutinib). Information on subsequent treatments will also be collected. An updated analysis of OS and PFS will be performed at the end of the follow-up period in the final study CSR.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be contacted as soon as possible and instructed to stop taking study medication. The end of treatment visit should be scheduled and the same assessments should be performed as described in Section 7 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

Two-hundred and twenty-two (222) patients with CML-CP who had prior treatment with two or more ATP binding site TKIs will be randomized in a 2:1 fashion to receive either asciminib or bosutinib. No patients with a medical history of the T315I or V299L mutation at study entry will be included in the trial. Previous medical records should be used to confirm the patient's mutational status/history.

The definition of CML-CP will be according to the European Leukemia Network (ELN) criteria (Baccarani et al 2013), and is outlined below in the inclusion criteria.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Male or female patients with a diagnosis of CML-CP ≥ 18 years of age

[redacted]

2. Patients must meet all of the following laboratory values at the screening visit:
   - < 15% blasts in peripheral blood and bone marrow
   - < 30% blasts plus promyelocytes in peripheral blood and bone marrow
   - < 20% basophils in the peripheral blood
   - ≥ 50 x 10^9/L (≥ 50,000/mm^3) platelets
   - Transient prior therapy related thrombocytopenia (< 50,000/mm^3 for ≤ 30 days prior to screening) is acceptable
   - No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly

3a. BCR-ABL1 ratio > 0.1% IS according to central laboratory at the screening examination, for patients intolerant to the most recent TKI therapy

4. Prior treatment with a minimum of 2 prior ATP-binding site TKIs (i.e. imatinib, nilotinib, dasatinib, radotinib or ponatinib)
5. Failure (adapted from the 2013 ELN Guidelines; Baccarani et al 2013) or intolerance to the most recent TKI therapy at the time of screening
   - Failure is defined for CML-CP patients (CP at the time of initiation of last therapy) as follows. Patients must meet at least 1 of the following criteria.
     - Three months after the initiation of therapy: No CHR or > 95% Ph+ metaphases
     - Six months after the initiation of therapy: BCR-ABL1 ratio > 10% IS and/or > 65% Ph+ metaphases
     - Twelve months after initiation of therapy: BCR-ABL1 ratio > 10% IS and/or > 35% Ph+ metaphases
     - At any time after the initiation of therapy, loss of CHR, CCyR or PCyR
     - At any time after the initiation of therapy, the development of new BCR-ABL1 mutations which potentially cause resistance to current treatment
     - At any time after the initiation of therapy, confirmed loss of MMR in 2 consecutive tests, of which one must have a BCR-ABL1 ratio ≥ 1% IS
     - At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cells: CCA/Ph+
   - Intolerance is defined as:
     - Non-hematologic intolerance: Patients with grade 3 or 4 toxicity while on therapy, or with persistent grade 2 toxicity, unresponsive to optimal management, including dose adjustments (unless dose reduction is not considered in the best interest of the patient if response is already suboptimal)
     - Hematologic intolerance: Patients with grade 3 or 4 toxicity (absolute neutrophil count [ANC] or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by manufacturer
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2
7. Adequate end organ function as defined by (as per central laboratory tests):
   - Total bilirubin ≤ 1.5 x ULN except for patients with Gilbert's syndrome who may only be included if total bilirubin ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN

[redacted]

- Aspartate transaminase (AST) ≤ 3.0 x ULN
- Alanine transaminase (ALT) ≤ 3.0 x ULN
- Serum lipase ≤ 1.5 x ULN. For serum lipase > ULN - ≤ 1.5 x ULN, value must be considered not clinically significant and not associated with risk factors for acute pancreatitis
- Alkaline phosphatase ≤ 2.5 x ULN
- Creatinine clearance ≥ 50 mL/min as calculated using Cockcroft-Gault formula

8. Patients must avoid consumption of grapefruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.
9. Written informed consent obtained prior to any screening procedures.

10a. Patients must have the following electrolyte values (as per central laboratory tests) within normal limits or corrected to be within normal limits with supplements prior to first dose of study medication:

- Potassium (potassium increase of up to 6.0 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits)
- Total calcium (corrected for serum albumin); (calcium increase of up to 12.5 mg/dl or 3.1 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits)
- Magnesium, with the exception of magnesium increase > ULN – 3.0 mg/dL; > ULN - 1.23 mmol/L associated with creatinine clearance (calculated using Cockcroft-Gault formula) within normal limits.

11. Evidence of typical BCR-ABL1 transcript [e14a2 and/or e13a2] at the time of screening which are amenable to standardized RQ-PCR quantification.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Known presence of the T315I or V299L mutation at any time prior to study entry
2. Known second chronic phase of CML after previous progression to AP/BC
3. Previous treatment with a hematopoietic stem-cell transplantation
4. Patient planning to undergo allogeneic hematopoietic stem cell transplantation
5. Cardiac or cardiac repolarization abnormality, including any of the following:
   - History within 6 months prior to starting study treatment of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG)
   - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)
   - QTcF at screening ≥450 msec (male patients), ≥460 msec (female patients)
   - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:

[redacted]

- Risk factors for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
- Concomitant medication(s) with a "Known risk of Torsades de Pointes" per wwwcrediblemeds.org/ that cannot be discontinued or replaced 7 days prior to starting study drug by safe alternative medication.
- Inability to determine the QTcF interval

6. Severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol (e.g. uncontrolled diabetes, active or uncontrolled infection, pulmonary hypertension)
7. History of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis
9. History of acute or chronic liver disease
10. Known presence of significant congenital or acquired bleeding disorder unrelated to cancer
11. History of other active malignancy within 3 years prior to study entry with the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively
12. Known history of Human Immunodeficiency Virus (HIV), chronic Hepatitis B (HBV), or chronic Hepatitis C (HCV) infection. Testing for Hepatitis B surface antigen (HBs Ag) and Hepatitis B core antibody (HBcAb / anti HBc) will be performed at screening
13. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or gastric bypass surgery)

14a. Treatment with medications that meet one of the following criteria and that cannot be discontinued at least one week prior to the start of treatment with study treatment

- Moderate or strong inducers of CYP3A
- Moderate or strong inhibitors of CYP3A

15. Previous treatment with or known/ suspected hypersensitivity to asciminib or any of its excipients.
16. Previous treatment with or known/ suspected hypersensitivity to bosutinib or any of its excipients.
17. Participation in a prior investigational study within 30 days prior to randomization or within 5 half-lives of the investigational product, whichever is longer
18. Pregnant or nursing (lactating) women

19a. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 days after last dose of asciminib and one month after last dose of bosutinib. Highly effective contraception methods include:

[redacted]

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy) total hysterectomy or bilateral tubal ligation at least six weeks before taking study treatment). In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking study medication. In the case of oophorectomy alone, women are considered post-menopausal and not of child bearing potential only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

6 Treatment

6.1 Study treatment

The investigational treatments for this study are asciminib (40 mg BID) and bosutinib (500 mg QD). Novartis will supply asciminib to the investigational site as 20 mg and 40 mg tablets. Bosutinib will be supplied to the investigational site as 100 mg and 500 mg tablets.

6.1.1 Dosing regimen

Asciminib

Asciminib 20 or 40 mg strength tablets will be administered orally twice-daily (BID), without food. Asciminib tablets should be ingested as follows:

- Asciminib should be administered in the fasted state: avoid food for at least 2 hours before the dose is taken and for at least 1 hour after the dose is taken. Water is permitted during this period.
- Asciminib should be taken with approximately 8 ounces (240 mL) of water.
- Asciminib should be swallowed whole and not chewed or crushed.
- If vomiting occurs within the first hour after taking the drug, re-dosing is allowed before the next scheduled dose

[redacted]

- If the patient does not take asciminib within 6 hours after the approximate time of the usual dosing time, that dose should be skipped and treatment should continue with the next daily dose at the prescribed level

Bosutinib

Bosutinib 500 mg or 100 mg tablets will be administered orally once daily (QD) with food. If a dose is missed beyond 12 hours, the patient should skip the dose and take the usual dose on the following day.

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen	Fasting Condition
Asciminib	Tablet for oral use	20 mg[a]	Twice-daily	Fasting
Asciminib	Tablet for oral use	40 mg	Twice-daily	Fasting
Bosutinib	Tablet for oral use	100 mg[b]	Once-daily	Non-fasting
Bosutinib	Tablet for oral use	500 mg	Once-daily	Non-fasting

[a] 20 mg tablets will be dispensed to patients in the instance of dose reduction.
[b] 100 mg tablets will be dispensed to patients in the instance of dose modifications.

On days when serial blood samples are collected for asciminib PK analysis, patients will be instructed to bring their drug supply to the site, and take the dose in the clinic, under supervision of the site personnel. The exact time for dose administration and meal intake must be recorded in the electronic Case Report Form (eCRF).

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.1.2 Ancillary treatments

Not applicable.

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

Not applicable. See Section 6.3.

6.1.5 Treatment duration

There is no fixed duration of treatment planned per patient. The patients are treated in the study up to end of study treatment period defined as up to 96 weeks after the last patient receives the first dose or up to 48 weeks after the last patient has switched to asciminib treatment whichever is longer unless patients have discontinued treatment earlier. Patients may be discontinued from treatment with the study drug at any time due to unacceptable toxicity, disease progression and/or at the discretion of the investigator or the patient.

[redacted]

6.2 Dose escalation guidelines

Dose escalation beyond the standard doses of 40 mg BID for asciminib is not permitted.

Dose escalation above 500 mg QD for bosutinib is permitted in this study. Bosutinib escalation guidelines are as follows:

Consider dose escalation to 600 mg once daily in patients who are currently taking 500 mg daily, did not have Grade 3 or higher adverse events and who:

- Did not reach complete hematological response (CHR) by week 8
- Did not reach complete cytogenetic response (CCyR) by week 12

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to allow the patient to continue the study treatment.

These dose modifications are summarized in Table 6-2. The dose reduction indicated as "recommendations" are provided to assist investigators in the event the patient experiences toxicity. However, deviations from "mandatory" dose interruptions and/or reductions are not allowed and mandatory interruptions or reductions must be strictly followed. Re-escalation to asciminib 40 mg BID is permitted if a change in the patient's individual benefit/risk assessment at the lower dose level is seen. Re-escalation will be allowed only once for any given patient on the asciminib arm per protocol. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-2. Any dose changes must be recorded on the Dosage Administration Record eCRF.

A patient must discontinue treatment with either asciminib or bosutinib if, after treatment is resumed at a lower dose level, the toxicity recurs with the same or worse severity, except for recurrence of cytopenias (Table 6-2). If a patient requires a dose interruption of > 28 days for each non-hematologic toxicity, then the patient must be discontinued from the study treatment. If a hematologic toxicity (cytopenia Grade 3 or 4) lasts for more than 42 days without recovery to at least a Grade 2, despite TKI interruption and adequate management (including hematopoietic growth factors), then the patient must be discontinued from the study treatment.

[redacted]

Table 6-2 Criteria for dose reduction/interruption and re-initiation of asciminib and bosutinib treatment for adverse drug reactions

Dose modifications for both asciminib and bosutinib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**		
Worst toxicity **CTCAE Grade 4.03**	**Asciminib**	**Bosutinib**
Investigations (Hematologic) If a hematologic toxicity (cytopenia Grade 3 or 4) lasts for more than 42 days without recovery to at least a Grade 2, despite TKI interruption and adequate management (including hematopoietic growth factors), then the patient must be discontinued from the study treatment.		
Neutropenia (ANC)		
Grade 1 (ANC < LLN – 1.5 x 10^9/L)	**Recommendation**: Maintain dose level	**Recommendation**: Maintain dose level
Grade 2 (ANC < 1.5 – 1.0 x 10^9/L)	**Recommendation**: Maintain dose level	**Recommendation**: Maintain dose level
Grade 3 (ANC < 1.0 – 0.5 x 10^9/L)	**Mandatory**: Hold dose until resolved to ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, then reduce dose ↓ 1 dose level	**Mandatory**: Hold dose until resolved to ≤ Grade 2 and platelets ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, reduce dose ↓ 1 dose level
Grade 4 (ANC < 0.5 x 10^9/L)	**Mandatory**: Hold dose until resolved to ≤ Grade 2, (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved to ≤ Grade 2 and platelets ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level
Febrile neutropenia (ANC < 1.0 x 109/L, fever ≥ 38.5°C)	**Mandatory:** Hold dose until resolved, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved, then reduce dose ↓ 1 dose level
Thrombocytopenia		
Grade 1 (PLT < LLN – 75 X 10^9/L)	**Recommendation**: Maintain dose level	**Recommendation:** Maintain dose level
Grade 2 (PLT < 75 - 50 x 10^9/L)	**Recommendation**: Maintain dose level	**Recommendation:** Maintain dose level

Dose modifications for both asciminib and bosutinib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**		
Worst toxicity **CTCAE Grade 4.03**	**Asciminib**	**Bosutinib**
Grade 3 (PLT < 50 - 25 x 10^9/L)	**Mandatory:** Hold dose until resolved to ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved to ≤ Grade 2 and neutrophils ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	**Mandatory:** Hold dose until resolved to ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved to ≤ Grade 2 and neutrophils ≤ Grade 2 (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level
Recurrence of all cytopenias	**Recommendation:** Hold dose until resolved to ≤ Grade 2, then maintain current dose level.	**Recommendation:** Hold dose until resolved to ≤ Grade 2, then reduce dose ↓ 1 additional level
Non-hematologic adverse reactions except where further specified in individual sections		
Grade 1	**Recommendation**: Maintain dose level	**Recommendation:** Maintain dose level
Grade 2	**Recommendation:** Hold dose until resolved to ≤ Grade 1, then maintain dose level	**Recommendation:** Maintain dose level
Grade 3	**Mandatory:** Hold dose until resolved to ≤ Grade 1, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved to ≤ Grade 1, then reduce dose ↓ 1 dose level, If clinically appropriate, re-escalation of the dose back to baseline dose level (500 mg) should be considered
Grade 4	**Mandatory**: Permanently discontinue patient from study drug treatment.	**Mandatory:** Hold dose until resolved to ≤ Grade 1, then reduce dose ↓ 1 dose level; If clinically appropriate, re-escalation of the dose back to baseline dose level (500 mg) should be considered
Investigations (Renal)		
Serum creatinine		
Grade 1 (> ULN - 1.5 x ULN)	**Recommendation:** Maintain dose level	**Recommendation:** Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN)	**Recommendation:** Hold dose until resolved to ≤ Grade 1 or baseline, then maintain dose level	**Recommendation:** Hold dose until resolved to ≤ Grade 1 or baseline, then maintain dose level
Grade 3 (> 3.0 - 6.0 x ULN)	**Mandatory:** Permanently discontinue patient from study drug treatment.	**Mandatory:** Permanently discontinue patient from study drug treatment.
Grade 4 (> 6.0 x ULN)	**Mandatory:** Permanently discontinue patient from study drug treatment.	**Mandatory:** Permanently discontinue patient from study drug treatment.

[redacted]

Dose modifications for both asciminib and bosutinib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**		
Worst toxicity **CTCAE Grade 4.03**	**Asciminib**	**Bosutinib**
Investigations (Hepatic)		
Isolated total Bilirubin elevation		
> ULN – 1.5 x ULN	**Recommendation:** Maintain dose level	**Recommendation:** Maintain dose level
> 1.5 - 3.0 x ULN	**Recommendation:** Hold dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level	**Recommendation:** Hold dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓ 1 dose level
> 3.0 - 10.0 x ULN*	**Mandatory:** Hold dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: if resolved in ≤ 14 days, then reduce dose ↓ 1 dose level if resolved in > 14 days, then discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.	**Mandatory:** Hold dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: if resolved in ≤ 14 days, then reduce dose ↓ 1 dose level if resolved in > 14 days, then discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
> 10.0 x ULN*	**Mandatory:** Permanently discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.	**Mandatory:** Permanently discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
Isolated AST or ALT elevation		
> ULN - 3.0 x ULN	**Recommendation:** Maintain dose level	**Recommendation:** Maintain dose level
> 3.0 - 5.0 x ULN	**Recommendation:** Maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN	**Recommendation:** Maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN

[redacted]

Dose modifications for both asciminib and bosutinib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**		
Worst toxicity **CTCAE Grade 4.03**	**Asciminib**	**Bosutinib**
> 5.0 - 10.0 x ULN	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN: Then If resolved in ≤ 14 days, maintain dose level If resolved in > 14 days, reduce dose ↓ 1 dose level	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 2.5 x ULN: Then **Recommendation:** If resolved in ≤ 28 days, reduce dose ↓ 1 dose level **Recommendation**: If resolved in > 28 days, Discontinue patient from study drug treatment
> 10.0 - 20.0 x ULN	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ baseline. Then reduce dose ↓ 1 dose level.	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 2.5 x ULN. Then **Recommendation:** If resolved in ≤ 28 days, reduce dose ↓ 1 dose level maintain dose level **Recommendation:** If resolved in > 28 days, Discontinue patient from study drug treatment.
> 20.0 x ULN	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3 x ULN (or ≤ 5 x ULN for patients with baseline value > 3.0 -5.0 x ULN), then resume treatment at reduce dose ↓ 1 dose level. Only 1 dose reduction is allowed; if reoccurs at > 5 x ULN, discontinue patient from study drug treatment.	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 2.5 x ULN (then **Recommendation:** If resolved in ≤ 28 days, reduce dose ↓ 1 dose level maintain dose level **Recommendation:** If resolved in > 28 days, Discontinue patient from study drug treatment

[redacted]

Dose modifications for both asciminib and bosutinib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**		
Worst toxicity **CTCAE Grade 4.03**	**Asciminib**	**Bosutinib**
Combined [c] elevations of AST or ALT and total bilirubin		
For patients with normal baseline ALT and AST and total bilirubin value: AST or ALT >3.0 x ULN combined with total bilirubin >2.0 x ULN without evidence of cholestasis[d] For patients with elevated baseline AST or ALT or total bilirubin value [AST or ALT>2 x baseline AND > 3.0 x ULN]	**Mandatory:** Permanently discontinue patient from study drug treatment. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b]), or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Refer to Section 6.3.3.1 for additional follow-up evaluations as applicable.	**Mandatory:** Permanently discontinue patient from study drug treatment. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTsb), or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Refer to Section 6.3.3.1 for additional follow-up evaluations as applicable.
Investigation (metabolic)		
Asymptomatic amylase and/or lipase elevation		
Grade 1 (> ULN - 1.5 x ULN)	**Recommendation:** Maintain dose level, measure 2x week	**Recommendation:** Maintain dose level, measure 2x week
Grade 2 (> 1.5 - 2.0 x ULN)	**Recommendation:** Maintain dose level, measure 2x week	**Recommendation:** Maintain dose level, measure 2x week
Grade 3 (> 2.0 - 5.0 x ULN)	**Mandatory:** Hold dose until resolved to Grade ≤ 1 or baseline, then: If resolved in ≤ 7 days, then reduce dose ↓ 1 dose level If resolved in > 7 days, then discontinue treatment and obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).	**Mandatory:** Hold dose until resolved to Grade ≤ 1 or baseline, then: If resolved in ≤ 7 days, then reduce dose ↓ 1 dose level If resolved in > 7 days, then discontinue treatment and obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).
Grade 4 (> 5.0 x ULN)	**Mandatory:** Permanently discontinue patient from study drug treatment. Obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).	**Mandatory:** Permanently discontinue patient from study drug treatment. Obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).

[redacted]

Dose modifications for both asciminib and bosutinib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**		
Worst toxicity **CTCAE Grade 4.03**	**Asciminib**	**Bosutinib**
Vascular disorders		
Hypertension		
CTCAE Grade 3	**Mandatory:** Hold dose until resolved ≤ Grade 1, then reduce dose ↓ 1 dose level	**Mandatory:** Hold dose until resolved ≤ Grade 1, then reduce dose ↓ 1 dose level
CTCAE Grade 4	**Mandatory:** Permanently discontinue patient from study drug treatment.	**Mandatory:** Permanently discontinue patient from study drug treatment.
Gastro intestinal		
Pancreatitis		
Grade 2 (radiologic findings for pancreatitis as per CTCAE v4.03, for increased enzymes please see table for asymptomatic amylase and/or lipase elevation)	**Mandatory:** If asymptomatic radiologic pancreatitis, hold treatment until recovery of the radiologic findings. If treatment delay is ≤ 21 days, then reduce dose ↓ 1 dose level. If treatment delay > 21 days, discontinue treatment and keep monitoring with appropriate imaging (i.e., MRI, CT scan or ultrasound).	**Mandatory**: If asymptomatic radiologic pancreatitis, hold treatment until recovery of the radiologic findings. If treatment delay is ≤ 21 days, then reduce dose ↓ 1 dose level. If treatment delay > 21 days, discontinue treatment and keep monitoring with appropriate imaging (i.e., MRI, CT scan or ultrasound).
Grade ≥ 3	**Mandatory:** Permanently discontinue patient from study drug treatment. Obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).	**Mandatory:** Permanently discontinue patient from study drug treatment. Obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).
Diarrhea***		
Grade 1	**Recommendation:** Maintain dose level but, initiate anti-diarrhea treatment	**Recommendation:** Maintain dose level but, initiate anti-diarrhea treatment
Grade 2	**Recommendation:** Hold dose until resolved to ≤ grade 1, then maintain dose level. If diarrhea returns as ≥ grade 2, then hold dose until resolved to ≤ grade 1, then reduce dose ↓ 1 dose level	**Recommendation:** Hold dose until resolved to ≤ grade 1, then maintain dose level. If diarrhea returns as ≥ grade 2, then hold dose until resolved to ≤ grade 1, then reduce dose ↓ 1 dose level
Grade 3	**Recommendation:** Hold dose and discontinue patient from study drug treatment	**Mandatory:** Hold dose until recovery to ≤ grade 1. **Recommendation:** Bosutinib may then be resumed at ↓ 1 dose level
Grade 4	**Mandatory:** Permanently discontinue patient from study drug treatment	**Mandatory**: Hold dose until recovery to ≤ grade 1. **Recommendation:** Bosutinib may then be resumed at ↓ 1 dose level

[redacted]

Dose modifications for both asciminib and bosutinib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**		
Worst toxicity **CTCAE Grade 4.03**	**Asciminib**	**Bosutinib**
Skin and subcutaneous tissue disorders		
Rash/photosensitivity		
Grade 1	**Recommendation:** Maintain dose level. Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)	**Recommendation:** Maintain dose level. Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
Grade 2	**Recommendation**: Maintain dose level, but initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)	**Recommendation:** Maintain dose level, but initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
Grade 3, despite skin toxicity therapy	**Recommendation:** Hold dose until resolved to Grade ≤ 1, then: If resolved in ≤ 7 days, then reduce dose ↓ 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then discontinue patient from study drug treatment	**Recommendation:** Hold dose until resolved to Grade ≤ 1, then: If resolved in ≤ 7 days, then reduce dose ↓ 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then discontinue patient from study drug treatment
Grade 4, despite skin toxicity therapy	**Mandatory:** Permanently discontinue patient from study drug treatment.	**Mandatory:** Permanently discontinue patient from study drug treatment.
General disorders and administration site conditions		
Fatigue/ Asthenia		
Grade 1 or 2	**Recommendation:** Maintain dose level	**Recommendation:** Maintain dose level
Grade 3	**Recommendation:** Hold dose until resolved to ≤ grade 1, then : If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then reduce dose ↓ 1 dose level	**Recommendation:** Hold dose until resolved to ≤ grade 1, then : If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then reduce dose ↓ 1 dose level
All dose modifications should be based on the worst preceding toxicity. [a] Common Toxicity Criteria for Adverse Events (CTCAE Version 4.03) [b] Core LFTs consist of ALT, AST, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.) [c] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold		

[redacted]

Dose modifications for both asciminib and bosutinib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**		
Worst toxicity **CTCAE Grade 4.03**	**Asciminib**	**Bosutinib**
If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when hold dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction [d] "Cholestasis" defined as ALP elevation (>2.0 x ULN and R value <2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury * Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator. ** Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study treatment. *** Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea		

Table 6-3 Dose reduction steps for asciminib and bosutinib

Dose reduction*			
	Starting dose level – 0	Dose level – 1	
Asciminib BID	40 mg tablet BID (total daily dose 80 mg)	20 mg tablet BID (total daily dose 40 mg)	
*Dose reduction should be based on the worst toxicity demonstrated at the last dose.			
Asciminib dose reduction below total daily 40 mg is not allowed. 20 mg tablets will be dispensed to patients in the instance of dose reduction.			
Dose reduction*			
	Starting dose level – 0	Dose level – 1	Dose level – 2
Bosutinib QD	500 mg (1-500 mg tablet QD)	400 mg (4-100 mg tablets QD)	300 mg (3-100 mg tablets QD)
* Dose reduction should be based on the worst toxicity demonstrated at the last dose.			
Bosutinib dose reduction below total daily 300 mg is not allowed. 100 mg tablets will be dispensed to patients in the instance of dose reduction.			

6.3.2 Dose adjustments for QTcF prolongation

If QTcF >500 msec or QTcF prolongation >60 msec from baseline is observed at any point during study treatment, and confirmed, the below guidance must be followed:

1. Assess the quality of the ECG recording and the QT value and repeat if needed
2. Interrupt study treatment until confirmed resolution of QTcF and as per dose reduction guidelines for non-hematological AEs.
3. Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment.
4. Review concomitant medication associated with QT prolongation, including drugs with a "Known", "Possible", or "Conditional risk of Torsades de Pointes" (refer to wwwcrediblemeds.org/), and drugs with the potential to increase the risk of study drug exposure related QT prolongation.
5. Check study drug dosing schedule and treatment compliance.

After confirming ECG reading at site, if QTcF > 500 msec

- Interrupt study treatment
- Repeat ECG and confirm ECG diagnosis by a cardiologist or central ECG lab
- If QTcF confirmed > 500 msec:
  - Correct electrolytes, eliminate culprit concomitant treatments, and identify and address clinical conditions that could potentially prolong the QT as per the ECG and QTc Clinical Safety Standards Guidelines Section 3.3.1.
  - Consult with a cardiologist (or qualified specialist)
  - Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 msec.
- After resolution to ≤ 480 msec, consider re-introducing treatment at reduced dose, and increase ECG monitoring for the next treatment(s), (e.g. pre-dose and 2 hours post dose after one week and two weeks of treatment re-introduction):

[redacted]

- If QTcF remains ≤ 500 msec after dose reduction, continue planned ECG monitoring during subsequent treatment
- If QTcF > 500 msec recurs after dose reduction, discontinue patient from trial.

6.3.3 Follow-up for toxicities

Patients whose treatment is permanently discontinued due to a study drug related adverse event or clinically significant laboratory value, must be followed up at least once a week for 4 weeks, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary. All patients must be followed up for adverse events and serious adverse events for 30 days following the last dose of study treatment.

6.3.3.1 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatinine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2 . A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.

[redacted]

4. Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.3.4 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e., hyperglycemia, skin toxicity and diarrhea are provided in Table 6-2. Refer to preclinical toxicity and or clinical data found in the [Asciminib Investigator's Brochure] or bosutinib label.

6.4 Concomitant medications for patients on asciminib

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug and including over-the-counter treatment and nutritional or vitamin supplements) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the "Concomitant Medications/Significant non-drug therapies" section of the eCRF.

Chronic medication should be maintained at the same dose and schedule throughout the study period, as medically feasible.

All prior antineoplastic surgery, chemotherapy, biologic, immunologic and radiation therapy must be recorded in the "Prior antineoplastic therapy" section of the eCRF.

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records and on the appropriate case report form, including the medication's duration (start and end dates or if continuing at final exam). These include blood and platelet transfusions for patients with anemia and with thrombocytopenia.

6.4.1 Permitted concomitant therapy

Drugs that affect gastric pH

Asciminib does not have a pH-dependent solubility. Drugs that elevate gastric pH will not affect asciminib absorption. All acid reducing agents are allowed.

[redacted]

6.4.2 Permitted concomitant therapy requiring caution and/or action

The *in vivo* potential of asciminib to interact with sensitive CYP3A4/5, CYP2C8 and CYP2C9 substrates has been evaluated and would indicate a minimal or negligible risk (Section 1.2.1.1). Therefore CYP3A4/5, CYP2C8 and CYP2C9 substrates with narrow therapeutic index (NTI) should be used with caution.

In recombinant cellular expression systems, asciminib was identified as a substrate of BCRP (Km ≈ 4 μM) and P-gP (Km could not be estimated due to insufficient saturation of efflux activity). Inhibitors of BCRP and P-gP may increase asciminib concentration. Based on human ADME study, P-gp may represent maximally 24% of the total clearance resulting in modest increase in AUC. Therefore, both BCRP and P-gp inhibitors should be administered with caution. If a medication listed in Section 14 appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.

6.4.3 Prohibited concomitant therapy

Other anticancer agents

The administration of any other anticancer agents including chemotherapy and biologic agents is not permitted except for anti-cancer treatments of newly diagnosed solid cancers (e.g. prostate cancer) that would not impact the level of minimal residual disease of patients. These patients may remain in the current study after consultation with Novartis. The administration of other tyrosine kinase inhibitors indicated for treatment of CML is **not** allowed.

Strong CYP3A4/5 inhibitors

Every effort should be made NOT to concomitantly administer strong CYP3A4/5 inhibitors. CYP3A4/5 inhibitors may decrease the metabolism of asciminib and resulting in increased serum concentrations and increased exposure. If administration of a strong CYP3A4/5 inhibitor cannot be avoided during the study and cannot be switched to an alternative therapy that does not strongly inhibit CYP3A4/5, asciminib must be interrupted.

A list of cytochrome P450 isoenzymes and CYP3A4/5inhibitors may be found at medicine.iupui.edu/CLINPHARM/ddis/clinical-table.

A classification of CYP3A4/5 SmPC can be found in Section 14-Appendices.

Further information can also be found in the following reference (Venkatakrishnan et al 2001).

Strong CYP3A4/5, and UGT1A/2B inducers

Every effort should be made NOT to concomitantly administer strong CYP3A4 inducers during the study.

Additionally, the use of strong inducers of UGT1A/2B is prohibited during the study.

If administration of a strong CYP3A4/5 inducer or UGT1A/2B inducer cannot be avoided during the study and cannot be switched to an alternative therapy, temporary interruption of study treatment is NOT needed.

[redacted]

QT prolonging agents

As far as possible avoid co-administering drugs with a "Known", "Possible" or "Conditional" risk of Torsades de Pointes (per wwwcrediblemeds.org/) during the course of the study:

- If concomitant administration of drugs with a "Known risk of Torsades de Pointes" is required and cannot be avoided, study drug must be interrupted. If, based on the investigator assessment and clinical need, study treatment is resumed, close ECG monitoring is advised.
- If during the course of the study, concomitant administration of a drug with "Possible risk" or "Conditional risk of Torsades de Pointes" is required, based on the investigator assessment and clinical need, study treatment may be continued under close ECG monitoring to ensure patient safety.

A list of drugs associated with QT prolongation and/or Torsades de Pointes is available online at wwwcrediblemeds.org/.

Herbal medications

Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

6.4.4 Other concomitant medications

Anti-emetics

Use of anti-emetics is allowed. Prophylactic anti-emetics should be started only once the patient experiences nausea or vomiting, at the discretion of the investigator. It is recommended that patients use drugs that do not cause QT prolongation. Please note that some anti-emetics have a known risk for Torsade de Pointes and are prohibited (refer to Section 6.4.2 and Section 14.1 Appendix 1).

Bisphosphonates

The use of bisphosphonates regardless of indication is allowed.

Contraceptives

Hormonal contraceptives are allowed as contraception methods. Highly effective contraception should be maintained throughout the study and for 3 days after study treatment discontinuation.

Anticoagulation agents

All anticoagulants or anti-aggregation agents may be administered under the discretion of the investigator.

Therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants should be used with caution and fully avoided whenever possible because of its known interaction with many commonly used medications and certain foods. As warfarin has a narrow therapeutic range, and asciminib is possibly an inhibitor of CYP2C9, the major

[redacted]

metabolizing enzyme of S-warfarin (R-warfarin is metabolized by multiple CYP enzymes), warfarin should be carefully monitored whenever used.

Caution is also advised when asciminib is co-administered with anti-platelet pro-drugs such as clopidogrel, ticlopidine and prasugrel, which require metabolic activation by CYP3A4 and CYP2C9. While the weak reversible *in vitro* inhibition potential of asciminib is unlikely to translate into clinical significance as the steady-state plasma concentrations at the maximum therapeutic doses are significantly lower than the experimentally determined inhibition constants, patients using anti-platelet pro-drugs should still be carefully monitored.

Direct Thrombin inhibitors (DTIs) and Factor Xa inhibitors are allowed as anticoagulants. Individual medications from each of the classes should be checked if they are not prohibited due to other drug-drug-interactions with asciminib. Alternatively, therapeutic anticoagulation may be accomplished using low-molecular weight heparin.

6.5 Concomitant medications for patients on bosutinib

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug and including over-the-counter treatment and nutritional or vitamin supplements) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the "Concomitant Medications/Significant non-drug therapies" section of the eCRF.

Chronic medication should be maintained at the same dose and schedule throughout the study period, as medically feasible.

All prior antineoplastic surgery, chemotherapy, biologic, immunologic and radiation therapy must be recorded in the "Prior antineoplastic therapy" section of the eCRF.

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records and on the appropriate case report form, including the medication's duration (start and end dates or if continuing at final exam). These include blood and platelet transfusions for patients with anemia and with thrombocytopenia

6.5.1 Permitted concomitant therapy requiring caution

Bosutinib should be used with caution in patients who have or may develop prolongation of QT, including those patients who are taking medicinal products that are known to prolong the QTc (e.g., anti-arrhythmic medicinal products such as amiodarone, disopyramide, procainamide, quinidine and sotalol and other substances that may prolong QTc) (in accordance with EU SmPC dated 05/2018).

If a medication listed in Section 14-Appendices appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.

[redacted]

6.5.2 Prohibited concomitant therapy

Other anticancer agents

The administration of any other anticancer agents including chemotherapy and biologic agents is not permitted except for anti-cancer treatments of newly diagnosed solid cancers (e.g. prostate cancer) that would not impact the level of minimal residual disease of patients. These patients may remain in the current study after consultation with Novartis. The administration of other tyrosine kinase inhibitors indicated for treatment of CML is **not** allowed.

Concomitant use with CYP3A inhibitors

Avoid the concomitant use of strong or moderate CYP3A inhibitors as an increase in bosutinib plasma concentration is expected. Strong CYP3A inhibitors include boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole.

Moderate CYP3A inhibitors include amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit products, imatinib and verapamil) [Bosulif® USPI]. If administration of a strong or moderate CYP3A4/5 inhibitor cannot be avoided during the study and cannot be switched to an alternative therapy, bosutinib must be interrupted.

Concomitant use with CYP3A inducers

Avoid the concomitant use of strong or moderate CYP3A inducers as a large reduction in exposure is expected (strong CYP3A inducers include carbamazepine, phenytoin, rifampin and St. John's Wort. Moderate CYP3A inducers include bosentan, efavirenz, etravirine, modafinil and nafcillin) [Bosulif® USPI]. However, if administration of a strong or moderate CYP3A4/5 inducer cannot be avoided during the study and cannot be switched to an alternative therapy, temporary interruption of bosutinib is NOT required.

pH Altering Medications

Bosutinib displays pH-dependent aqueous solubility, in vitro. In a cross-over trial in 23 healthy volunteers, a single oral dose of 400 mg of bosutinib was either administered alone or in combination with multiple-oral doses of 60 mg of lansoprazole (PPI) under fasting conditions. Lansoprazole decreased bosutinib Cmax and AUC by 46% and 26%, respectively.

Concomitant administration with PPIs is not allowed.

Consider using short-acting antacids or H2 blockers instead of PPIs to avoid a reduction in bosutinib exposure. Separate antacid or H2 blocker dosing by more than 2 hours [Bosulif® USPI].

6.6 Patient numbering, treatment assignment or randomization

6.6.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient

[redacted]

throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Screening Disposition page. IRT must be notified within 2 days that the patient was not randomized.

6.6.2 Treatment assignment or randomization

Patients will be assigned to one of the 2 treatment arms (Section 4.1 and Section 6.1) in a ratio of 2:1. Randomization will be stratified by cytogenetic response status at screening.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

6.6.3 Treatment blinding

Not applicable.

6.7 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

[redacted]

6.7.1 Study treatment packaging and labeling

Study treatment, asciminib and bosutinib tablets, will be provided as global clinical open-label supply and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

Study treatment labels will comply with the legal requirements of each country and will include storage conditions, a unique medication number (corresponding to study treatment and strength). Responsible site personnel will identify the study treatment package(s) to dispense by the medication number(s) assigned by IRT to the patient. Site personnel will add the patient number on the label. If the label has 2-parts (base plus tear-off label), immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document.

Table 6-4 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
asciminib (20 mg and 40 mg)	Tablets in bottle	Labeled as 'ABL001 20 mg/ABL001 40 mg'(BID)
bosutinib (100 mg or 500 mg)	Tablets in bottle or tablets in blister	Labeled as 'bosutinib 100 mg or bosutinib 500 mg'(QD)

6.7.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, asciminib and bosutinib should be stored according to the instructions specified on the drug labels.

6.7.3 Study drug compliance and accountability

6.7.3.1 Study drug compliance

Total daily dose of study treatment administered with start and end date will be collected on the Dosage Administration Record eCRF page. Name, start and end dates of any Concomitant Medications and Surgical and Medical procedures will be collected on the Prior and Concomitant medications and Surgical and Medical procedures eCRFs respectively.

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each dispensing patient visit.

6.7.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study treatment or at the time of study treatment discontinuation during the treatment period as well as during the switch treatment period with asciminib.

[redacted]

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.3.3 Handling of other study treatment

Not applicable.

6.7.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, or at the site only if permitted by local regulations and authorized by Novartis in a prior agreement.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. Patients can be consented for study participation prior to study day -21.

Table 7-2 lists all of the assessments required by patients that switch treatment from bosutinib to asciminib after documented treatment failure of bosutinib.

No eCRF will be used as a source document.

(S) is defined as "Source"

(D) is defined as "Data Based"

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section 7	Screening Phase	Treatment Phase																	
Visit name			Screening/ Baseline (Day -21 to -1)	Week 1 Day 1	Week 2 Day 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Obtain Informed Consent	D		X (Screening window - 56 days)																		
IRT																					
Eligibility checklist/registration	D		X																		
Randomization	D			X																	
Demography	D	7.1.2.4	X																		
Inclusion/exclusion criteria	D		X																		
Medical History	D	7.1.2.4	X																		
Disease History	D	7.1.2.4	X																		
Mutation status	D	7.1.2.4	X																		
Prior antineoplastic therapy	D	7.1.2.4	X																		
Prior TKI therapy	D	7.1.2.4	X																		

[redacted]

	Category	Protocol Section 7	Screening Phase	Treatment Phase																	
Visit name			**Screening/ Baseline (Day -21 to -1)**	**Week 1 Day 1**	**Week 2 Day 1**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**
Prior/concomitant medications	D	7.1.2.4	X	Continuous																	
Physical examination	S	7.2.2.1	X	X		X	If needed	X	If needed	X	If needed	X	X	X	X	X	X	X	X	X	X
Extramedullary Involvement	D	7.2.2.1	X	X		X	If needed	X	If needed	X	If needed	X	X	X	X	X	X	X	X	X	X
ECOG Performance status	D	7.2.2.4	X	X		X	If needed	X	If needed	X	If needed	X	X	X	X	X	X	X	X	X	X
Height	D	7.2.2.3	X																		
Weight	D	7.2.2.3	X	X						X				X			X			X	
Vital signs	D	7.2.2.2	X	X	X	X	If needed	X	If needed	X	If needed	X	X	X	X	X	X	X	X	X	X
Laboratory assessments		7.2.2.5																			
Hematology	D	7.2.2.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	D	7.2.2.5.2	X	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X
Chemistry-Hemoglobin A1c	D	7.2.2.5.2	X	Week 12 and as clinically indicated																	
Coagulation	D	7.2.2.5.2	X	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X

[redacted]

	Category	Protocol Section 7	Screening Phase	Treatment Phase																	
Visit name			**Screening/ Baseline (Day -21 to -1)**	**Week 1 Day 1**	**Week 2 Day 1**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**
Serum Pregnancy test (if applicable)	D	7.2.2.5.3	X			X		X		X		X	X	X	X	X	X	X	X	X	X
Hepatitis markers	D	7.2.2.5.2	X																		
Liver assessments	D			as clinically indicated																	
Efficacy assessments		7.2.1																			
Blood collection for BCR-ABL1 quantification by RQ-PCR	D	7.2.1.1	X			X		X		X		X		X			X			X	
Blood collection for exploratory BCR-ABL1 mutation analysis by Sanger Sequencing	D	7.2.1.1		X																	

[redacted]

	Category	Protocol Section 7	Screening Phase	Treatment Phase																	
Visit name			Screening/ Baseline (Day -21 to -1)	Week 1 Day 1	Week 2 Day 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Exploratory BCR-ABL1 mutation analysis (Sanger Sequencing) for patients with mutations at Week 1 Day 1	D	7.2.1.1								X				X			X			X	
Bone Marrow Aspirate/Cytogenetics -scheduled	D	7.2.1.2	X (Screening window - 56 days)											X						X	
Cardiac Assessments		7.2.2.6																			
ECG	D	7.2.2.6.1	X	X	X	X				X				X							
Cardiovascular risk factor assessments (including Family History)	D	7.2.2.6.2	X																		
Echocardiogram	D	7.2.2.6.3	X										X								
Pulmonary Function Test	D	7.2.2.6.4	X										X								

[redacted]

	Category	Protocol Section 7	Screening Phase	Treatment Phase																	
Visit name			**Screening/ Baseline (Day -21 to -1)**	**Week 1 Day 1**	**Week 2 Day 1**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**
Adverse events / SAE	D		X	Continuous																	
Biomarker Assessments		7.2.4																			
[redacted]	D	7.2.4.1	X (Screening window -56 days)											X							
[redacted]	D	7.2.4.1	X (Screening window -56 days)																		
Blood collection for Low level mutation analysis	D	7.2.4.2		X	Upon visit to confirm loss of MMR																
[redacted]	D	7.2.4.2		X																X	
[redacted]	D	7.2.4.2		X																	

[redacted]

	Category	Protocol Section 7	Screening Phase	Treatment Phase																	
Visit name			Screening/ Baseline (Day -21 to -1)	Week 1 Day 1	Week 2 Day 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Patient reported Outcomes		7.2.6																			
MDASI-CML	D	7.2.6	X			X		X		X		X		X			X			X	
EQ 5D 5L	D	7.2.6	X			X		X		X		X		X			X			X	
PGIC	D	7.2.6				X		X		X		X		X			X			X	
WPAI	D	7.2.6	X			X				X				X						X	
Resource Utilization Assessments	D	7.2.5	X	Continuous																	
Asciminib Drug administration	D			Continuous																	
Bosutinib Drug administration	D			Continuous																	
PK sampling (asciminib arm only)		7.2.3																			
Sparse PK blood collection	D	7.2.3		X	X	X				X				X							
Full PK blood collection (at least 20 patients)	D	7.2.3		X	X	X				X				X							
Meal record	D			X	X	X				X				X							

[redacted]

	Category	Protocol Section 7	Treatment Phase											EOT/Early Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	**Week 76**	**Week 80**	**Week 84**	**Week 88**	**Week 92**	**Week 96**	**Every 12 weeks up to end of study treatment**			
Prior/concomitant medications	D		Continuous														
Physical examination	S	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X		
Extramedullary	D	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance status	D	7.2.2.4	X	X	X	X	X	X	X	X	X	X	X	X	X		
Weight	D	7.2.2.3		X			X			X			X	X	X		
Vital signs	D	7.2.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory assessments		7.2.2.5															
Hematology	D	7.2.2.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry	D	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry-Hemoglobin A1c	D	7.2.2.5.2	as clinically indicated														
Coagulation	D	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum Pregnancy test (if applicable)	D	7.2.2.5.3	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urine Pregnancy test (if applicable	D	7.2.2.5.3											Monthly between visits				
Liver assessments	D		as clinically indicated														

[redacted]

	Category	Protocol Section 7	Treatment Phase											EOT/Early Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	**Week 76**	**Week 80**	**Week 84**	**Week 88**	**Week 92**	**Week 96**	**Every 12 weeks up to end of study treatment**			
Efficacy assessments		7.2.1														
Blood collection for BCR-ABL1 quantification by RQ-PCR	D	7.2.1.1		X			X			X			X	X	X		
Exploratory BCR-ABL1 Mutation analysis by Sanger sequencing	D	7.2.1.1													X		
Exploratory BCR-ABL1 Mutation analysis by Sanger sequencing for patients with mutations at Week 1 Day 1	D	7.2.1.1		X			X			X			X	X			
Bone Marrow Aspirate/Cytogenetics - scheduled	D	7.2.1.2					X						X		X		
Cardiac Assessments		7.2.2.6															
ECG	D	7.2.2.6.1											X				
Cardiovascular risk factor assessments (including Family History)	D	7.2.2.6.2													X		
Echocardiogram	D	7.2.2.6.3													X		
Pulmonary Function Test	D	7.2.2.6.4													X		

[redacted]

	Category	Protocol Section 7	Treatment Phase											EOT/Early Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	**Week 76**	**Week 80**	**Week 84**	**Week 88**	**Week 92**	**Week 96**	**Every 12 weeks up to end of study treatment**			
Adverse events / SAE	D		Continuous													
Biomarker Assessments		7.2.4														
Blood collection for Low level mutation analysis	D	7.2.4.2	Upon visit to confirm loss of MMR											X		
[redacted]	D	7.2.4.2												X		
[redacted]	D	7.2.4.1												X		
[redacted]	D	7.2.4.1												X		
Patient reported Outcomes		7.2.6														
MDASI-CML	D	7.2.6											X			
EQ 5D 5L	D	7.2.6											X			
PGIC	D	7.2.6											X			
WPAI	D	7.2.6											X			
Resource Utilization Assessments	D	7.2.5	Continuous													
Asciminib Drug administration	D		Continuous													
Bosutinib Drug administration	D		Continuous													

[redacted]

	Category	Protocol Section 7	Treatment Phase											EOT/Early Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96	Every 12 weeks up to end of study treatment			
PK sampling (asciminib arm only)		7.2.3															
Sparse PK blood collection	D	7.2.3											X				
Full PK blood collection (at least 20 patients)	D	7.2.3											X				
Survival follow-up	D																X
Antineoplastic therapies since discontinuation of study treatment	D															X	X
Stem Cell Transplant status	D																X
Progression status	D																X
Meal Record	D												X				

[redacted]

Table 7-2 Visit evaluation schedule (study treatment switch phase)

	Category	Protocol Section 7	Switch Screening Phase	Treatment Switch Phase																	
Visit name			EOT (Bosutinib) / S-Screening/ S-Baseline	S-Week 1 Day 1	S-Week 2 Day 1	S-Week 4	S-Week 6	S-Week 8	S-Week 10	S-Week 12	S-Week 14	S-Week 16	S-Week 20	S-Week 24	S-Week 28	S-Week 32	S-Week 36	S-Week 40	S-Week 44	S-Week 48	S-Week 52
IRT																					
Treatment Switch Eligibility checklist	D		X																		
Treatment switch criteria	D		X																		
Mutation status	D	7.1.2.4	X																		
Prior/concomitant medications	D	7.1.2.4	X	Continuous																	
Physical examination	S	7.2.2.1	X	X		X	If needed	X	If needed	X	If needed	X	X	X	X	X	X	X	X	X	X
Extramedullary Involvement	D	7.2.2.1	X	X		X	If needed	X	If needed	X	If needed	X	X	X	X	X	X	X	X	X	X
ECOG Performance status	D	7.2.2.4	X	X		X	If needed	X	If needed	X	If needed	X	X	X	X	X	X	X	X	X	X
Weight	D	7.2.2.3	X	X						X				X			X			X	
Vital signs	D	7.2.2.2	X	X	X	X	If needed	X	If needed	X	If needed	X	X	X	X	X	X	X	X	X	X
Laboratory assessments		7.2.2.5																			

[redacted]

	Category	Protocol Section 7	Switch Screening Phase	Treatment Switch Phase																	
Visit name			**EOT (Bosutinib) / S-Screening/ S-Baseline**	**S-Week 1 Day 1**	**S-Week 2 Day 1**	**S-Week 4**	**S-Week 6**	**S-Week 8**	**S-Week 10**	**S-Week 12**	**S-Week 14**	**S-Week 16**	**S-Week 20**	**S-Week 24**	**S-Week 28**	**S-Week 32**	**S-Week 36**	**S-Week 40**	**S-Week 44**	**S-Week 48**	**S-Week 52**
Hematology	D	7.2.2.5.1	X (if not done at EOT)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	D	7.2.2.5.2	X (if not done at EOT)	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X
Chemistry-Hemoglobin A1c	D	7.2.2.5.2	X (if not done at EOT)	Week 12 and as clinically indicated																	
Coagulation	D	7.2.2.5.2	X (if not done at EOT)	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X
Serum Pregnancy test (if applicable)	D	7.2.2.5.3	X (if not done at EOT)			X		X		X		X	X	X	X	X	X	X	X	X	X
Liver assessments	D			as clinically indicated																	

[redacted]

	Category	Protocol Section 7	Switch Screening Phase	Treatment Switch Phase																	
Visit name			EOT (Bosutinib) / S-Screening/ S-Baseline	S-Week 1 Day 1	S-Week 2 Day 1	S-Week 4	S-Week 6	S-Week 8	S-Week 10	S-Week 12	S-Week 14	S-Week 16	S-Week 20	S-Week 24	S-Week 28	S-Week 32	S-Week 36	S-Week 40	S-Week 44	S-Week 48	S-Week 52
Efficacy assessments		7.2.1																			
Blood collection for BCR-ABL1 quantification by RQ-PCR	D	7.2.1.1	X			X		X		X		X		X			X			X	
Exploratory BCR-ABL1 Mutation analysis by Sanger sequencing	D	7.2.1.1		X (if not done at EOT)																	
Exploratory BCR-ABL1 Mutation analysis by Sanger sequencing for patients with mutations at Week 1 Day 1	D	7.2.1.1								X				X			X			X	
Bone Marrow Aspirate/Cytogenetics -scheduled	D	7.2.1.2												X						X	

[redacted]

	Category	Protocol Section 7	Switch Screening Phase	Treatment Switch Phase																	
Visit name			EOT (Bosutinib) / S-Screening/ S-Baseline	S-Week 1 Day 1	S-Week 2 Day 1	S-Week 4	S-Week 6	S-Week 8	S-Week 10	S-Week 12	S-Week 14	S-Week 16	S-Week 20	S-Week 24	S-Week 28	S-Week 32	S-Week 36	S-Week 40	S-Week 44	S-Week 48	S-Week 52
Cardiac Assessments		7.2.2.6																			
ECG	D	7.2.2.6.1	X	X	X	X				X				X							
Cardiovascular risk factor assessments (including Family History)	D	7.2.2.6.2	X																		
Adverse events / SAE	D		X	Continuous																	
Biomarker Assessments		7.2.4																			
[redacted]	D	7.2.4.1	X (if not done at EOT)																		
[redacted]	D	7.2.4.1	X (if not done at EOT)																		
Blood collection for Low level mutation analysis	D	7.2.4.2		X (if not done at EOT)	Upon visit to confirm loss of MMR																

[redacted]

	Category	Protocol Section 7	Switch Screening Phase	Treatment Switch Phase																	
Visit name			EOT (Bosutinib) / S-Screening/ S-Baseline	S-Week 1 Day 1	S-Week 2 Day 1	S-Week 4	S-Week 6	S-Week 8	S-Week 10	S-Week 12	S-Week 14	S-Week 16	S-Week 20	S-Week 24	S-Week 28	S-Week 32	S-Week 36	S-Week 40	S-Week 44	S-Week 48	S-Week 52
[redacted]	D	7.2.4.2		X (if not done at EOT)																	
[redacted]	D	7.2.4.2		X (if not done at W1D 1)																	
Asciminib Drug administration	D			Continuous																	
PK sampling		7.2.3																			
Sparse PK blood collection	D	7.2.3		X	X	X				X				X							
Meal record	D			X	X	X				X				X							

[redacted]

	Category	Protocol Section 7	Treatment Switch Phase											S-EOT/Early S-Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			S-Week 56	S-Week 60	S-Week 64	S-Week 68	S-Week 72	S-Week 76	S-Week 80	S-Week 84	S-Week 88	S-Week 92	S-Week 96	Every 12 weeks up to end of study treatment			
Prior/concomitant medications	D		Continuous														
Physical examination	S	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X		
Extramedullary	D	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance status	D	7.2.2.4	X	X	X	X	X	X	X	X	X	X	X	X	X		
Weight	D	7.2.2.3		X			X			X			X	X	X		
Vital signs	D	7.2.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory assessments		7.2.2.5															
Hematology	D	7.2.2.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry	D	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry-Hemoglobin A1c	D	7.2.2.5.2	as clinically indicated														
Coagulation	D	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum Pregnancy test (if applicable)	D	7.2.2.5.3	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urine Pregnancy test (if applicable	D	7.2.2.5.3											Monthly between visits				
Liver assessments	D		as clinically indicated														

[redacted]

	Category	Protocol Section 7	Treatment Switch Phase											S-EOT/Early S-Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			S-Week 56	S-Week 60	S-Week 64	S-Week 68	S-Week 72	S-Week 76	S-Week 80	S-Week 84	S-Week 88	S-Week 92	S-Week 96	Every 12 weeks up to end of study treatment			
Efficacy assessments		7.2.1															
Blood collection for BCR-ABL1 quantification by RQ-PCR	D	7.2.1.1		X			X			X			X	X	X		
Exploratory BCR-ABL1 Mutation analysis by Sanger sequencing	D	7.2.1.1													X		
Exploratory BCR-ABL1 Mutation analysis by Sanger sequencing for patients with mutations at Week 1 Day 1	D	7.2.1.1		X			X			X			X	X			
Bone Marrow Aspirate/Cytogenetics – scheduled	D	7.2.1.2					X						X		X		
Cardiac Assessments		7.2.2.6															
ECG	D	7.2.2.6.1											X				
Cardiovascular risk factor assessments (including Family History)	D	7.2.2.6.2													X		
Adverse events / SAE	D		Continuous														
Asciminib Drug administration	D		Continuous														

[redacted]

	Category	Protocol Section 7	Treatment Switch Phase											S-EOT/Early S-Discontinuation	Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name			S-Week 56	S-Week 60	S-Week 64	S-Week 68	S-Week 72	S-Week 76	S-Week 80	S-Week 84	S-Week 88	S-Week 92	S-Week 96	Every 12 weeks up to end of study treatment			
PK sampling		7.2.3															
Sparse PK blood collection	D	7.2.3											X				
Survival follow-up	D																X
Antineoplastic therapies since discontinuation of study treatment	D															X	X
Stem Cell Transplant status	D																X
Progression status	D																X
Meal Record	D												X				

[redacted]

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 Screening

Written informed consent must be obtained before any study specific medical procedures are performed. All screening/baseline assessments (with the exception of Bone Marrow Aspirates) should occur within 21 days before Week 1 Day 1.

The screening visit window for bone marrow assessments is 56 days prior to Week 1 Day 1. Should bone marrow assessments have been performed before the main informed consent is signed but within 56 days of Week 1 Day 1, no further bone marrow sampling will be required at screening. At end of treatment, a bone marrow exploratory aspirate and/or biopsy must be collected even if the screening/baseline bone marrow exploratory aspirate and/or biopsy samples were not collected. During the screening visit, inclusion and exclusion criteria will be assessed. Screening assessments to confirm eligibility must be performed prior to randomization. The results of the real time quantitative polymerase chain reaction (RQ-PCR) and the bone marrow aspirate must be available prior to randomization and first dose of study treatment.

For details of assessments required during screening please refer to Table 7-1.

Laboratory baseline assessments (including hematology, chemistry, coagulation and serum pregnancy test), physical examination including extramedullary involvement, performance status, ECG, height, weight and vital signs, evaluation of all relevant medical history including cardiovascular risk factors, CML disease history, including prior TKI therapy and antineoplastic medication and prior and concomitant medication must be performed prior to the first dose of study treatment. Patients with potassium, and/or magnesium and/or total calcium levels that are < LLN at screening, must have their potassium, and/or magnesium, and/or calcium replenished through supplementation and the levels must be within normal limits prior to the first dose of study drug.

A patient who has a laboratory test (peripheral blood test) results that do not satisfy the entrance criteria may have the tests repeated. These tests may be repeated as soon as the investigator believes the re-test results are likely to be within the acceptable range to satisfy the entrance criteria, but should be completed within approximately 2 weeks of the original screening visit date. In this case, the subject will not be required to sign another Informed Consent Form (ICF), and the original patient ID number assigned by the investigator will be used. In the event that the laboratory tests cannot be performed within the screening visit window, or the re-tests do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the patient is considered a screen failure, and must be discontinued from the study.

A new ICF will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed, however, the patient ID number will remain the same. All required screening activities must be performed when the patient is re-screened for participation in the study. No further bone marrow sampling will be done at re-screening if a previous assessment was done within 56 days of Week 1 Day 1. After 56 days, new bone marrow biopsy and aspirates samples for cytogenetic assessment and exploratory biomarker purpose should be re-

[redacted]

collected at the time of the bone marrow assessment. An individual patient may be re-screened up to three times for the study. Once the number of patients screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the patients who screen failed will not be permitted to re-screen.

7.1.2.1 Eligibility screening

Following registering in the IRT for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be managed via IRT system. Please refer and comply with detailed guidelines in the IRT manual.

7.1.2.2 Conditions to be fulfilled for asciminib switch

The eligibility assessments of patients who are candidates for asciminib switch will start with the bosutinib EOT visit. Assessments conducted during the EOT visit will be used to evaluate if all conditions for asciminib switch are fulfilled and there are no conditions preventing patients from receiving asciminib treatment. Therefore all efforts **MUST** be made to ensure that all EOT assessments are completed per Table 7-1. In the event that all EOT assessments cannot be completed during the EOT visit, they must be completed within 42 days (6 weeks) after the bosutinib EOT visit. For details of assessments required for patients that switch treatment from bosutinib to asciminib, please refer to Table 7-2. The maximum allowed time frame for patients failing bosutinib to start treatment with asciminib is 42 days after bosutinib EOT.

In case a patient presents with a grade 3 or 4 adverse event at the time of the EOT visit or develops it after the EOT visit, the adverse event must be resolved to grade 2 or lower before starting asciminib treatment and within 28 days of the date of occurrence of the adverse event as outlined in the criteria listed below.

However, a patient who has laboratory test (peripheral blood test) results or ECG results that do not satisfy the treatment switch conditions may have the tests repeated multiple times during the treatment switch screening period. The last test performed before start of asciminib dosing must meet the conditions for treatment switch as listed below.

If a patient does not meet the conditions for treatment switch, they should enter the survival follow-up phase.

The conditions for treatment switch will be checked via the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

Conditions to fulfill to allow the switch to asciminib:

1. Failure to bosutinib treatment up to 96 weeks after the last patient received the first dose (adapted from the 2013 ELN Guidelines; Baccarani et al 2013). Patients must meet at least 1 of the following criteria. Failure is defined as follows:
   - Three months after the initiation of therapy or thereafter: No CHR or > 95% Ph+ metaphases.
   - Six months after the initiation of therapy or thereafter: BCR-ABL1 ratio > 10% IS and/or > 65% Ph+ metaphases.
   - Twelve months after initiation of therapy or thereafter: BCR-ABL1 ratio > 10% IS and/or > 35% Ph+ metaphases.

[redacted]

- At any time after the initiation of therapy, loss of CHR, CCyR or PCyR.
- At any time after the initiation of therapy, detection of new BCR-ABL1 mutations which potentially cause resistance to study treatment (asciminib or bosutinib).
- At any time after the initiation of therapy, confirmed loss of MMR in 2 consecutive tests.
- At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cells: CCA/Ph+.

Conditions preventing patients to switch to asciminib

- Any Grade 3 or 4 toxicity which has not resolved to Grade 2 or lower within 28 days and before starting asciminib treatment.
- Asymptomatic (Grade 2) pancreatitis if not resolved within 28 days
- Disease progression while on bosutinib treatment. The following events are considered disease progression:
  - Accelerated phase (AP) as defined by any of the following:
    - ≥ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate.
    - ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate.
    - ≥ 20% basophils in the peripheral blood.
    - Thrombocytopenia (< 100 x 10^9/L) that is unrelated to therapy.
  - Blast crisis (BC) as defined by any of the following:
    - ≥ 30% blasts in peripheral blood or bone marrow aspirate
    - Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e. chloroma).
- QTcF at time of switch > 480msec or inability to determine QTc interval

7.1.2.3 Information to be collected on screening failures

Patients who sign an informed consent but fail to be randomized for any reason will be considered a screen failure. The reason for not being randomized will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details). If the patient fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

7.1.2.4 Patient demographics and other baseline characteristics

Patient demographics and baseline characteristics collected will include the following: date of birth, gender (and child bearing potential for female), race and ethnicity, height, weight, all relevant medical history including cardiovascular disease history, CML disease history,

[redacted]

including mutation status, and prior and concomitant medication including prior TKI therapy and antineoplastic medication.

Physical examination including extramedullary involvement, performance status, vital signs, ECGs, and laboratory assessments will be performed at screening.

Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the subject's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the patient's eCRF.

The central reading of the screening ECGs as well as the results of the RQ-PCR and the bone marrow aspirate must be available prior to randomization and first dose of study treatment to evaluate eligibility and to stratify the patient.

7.1.2.5 Local recruitment procedures-Japan

Given the limited safety data available in Japanese patients, specific recruitment and data monitoring procedures will be put in place for Japanese patients randomized to asciminib. Randomization of these patients will be staggered to avoid enrollment of more than one patient on the same day. Safety parameters from a minimum of 2 patients treated on the asciminib arm will be reviewed for determining the appropriateness of continuing patient enrollment in Japan.

7.1.3 Run-in period

Not applicable.

7.1.4 Treatment period

There is no fixed duration of treatment planned per patient. All patients will be given the opportunity to receive study treatment until the end of study treatment period as defined in (Section 4.3).

During the treatment phase, the patients will receive either asciminib treatment 40 mg BID or bosutinib 500 mg QD according to randomization. The dose can be modified, if required from the perspective of tolerance, following the guidance in Section 6.2 and Section 6.3. Treatment will be administered until patient experiences treatment failure, unacceptable toxicity, disease progression, death, lost to follow-up and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent.

The patients are advised to adhere to the food restrictions during the treatment (fasting status regarding study treatment administration, avoidance of prohibited concomitant medication).

7.1.5 Visit windows

Study visits from Week 1 Day 1 to Week 2 Day 1 / S-Week 1 Day 1 to S-Week 2 Day 1 should be completed on the designated date [with an allowed "visit window" of +/- 1 day for Week 2 Day 1 / S-Week 2 Day 1]

Study visits from Week 4 to Week 16 / S-Week 4 to S-Week 16 should be completed every 2 weeks on the designated date [with an allowed "visit window" of +/- 1 day]

[redacted]

Study visits from Week 20 to Week 96 / S-Week 20 to S-Week 96 should be completed every 4 weeks on the designated date [with an allowed "visit window" of +/- 2 days]

Study visits from Week 108 to EOT / S-Week 108 to S-EOT should be completed every 12 weeks on the designated date [with an allowed "visit window" of +/- 7 days]

A delayed visit will have no impact on the next planned visit. The next visit should be completed as scheduled in order to avoid accumulation of additional weeks.

7.1.6 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate eCRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if, he/she believes that continuation would be detrimental to the patient's well-being. Patients who discontinue study treatment should undergo an end of treatment visit.

For patients who discontinue treatment in treatment period or switch treatment period for reasons other than death, lost to follow-up, or withdrawal of consent, the patient should enter the survival follow-up phase. Survival visit assessments (survival, antineoplastic therapies, stem cell transplant and progression) should be performed every 12 weeks until documented death, lost to follow-up, withdrawal of consent or until the end of the study. This visit can be conducted by telephone.

Patients who discontinue the study treatment for an adverse event suspected to be related to study drug or an abnormal laboratory value suspected to be related to study drug must be followed as described in Section 8

Patients may also be discontinued from the study treatment if any of the following occurs:

- discovery of patient ineligibility
- errors in treatment compliance [study treatment, other prescribed or non-prescribed medications]
- missed/unscheduled/off schedule/incomplete/incorrect assessments
- major protocol deviation
- use of prohibited treatment refer to Section 14-Appendices
- any other protocol deviation that results in a significant risk to the patient's safety

In addition to the general discontinuation criteria, the following study specific criteria will also require discontinuation of study treatment:

- In the event of detection of T315I or V299L mutations at any time the patient **must** be discontinued from the study treatment.
- In the event of a pregnancy during study, if a patient wants to pursue the pregnancy then patient **must** be discontinued from the study treatment. However, in the event of a

[redacted]

spontaneous miscarriage or in the event of elective abortion, the patient is permitted to continue study treatment.

- In the event of treatment failure the patient must be discontinued from the study treatment. Patients randomized to bosutinib treatment experiencing treatment failure may switch to asciminib treatment. The following events will constitute 'treatment failure', and are based on the ELN criteria (Baccarani et al 2013) defining failure of a second line treatment:
  - No CHR or > 95% Ph+ metaphases at three months after initiation of therapy or thereafter
  - BCR-ABL1 ratio > 10% IS and/or > 65% Ph+ metaphases at six months after initiation of therapy or thereafter
  - BCR-ABL1 ratio > 10% IS and/or > 35% Ph+ metaphases at 12 months after initiation of therapy or thereafter
  - Loss of CHR, CCyR or PCyR at any time after initiation of therapy
  - Detection of new BCR-ABL1 mutations which potentially cause resistance to study treatment (asciminib or bosutinib) at any time after initiation of therapy
  - Confirmed loss of MMR in 2 consecutive tests (Section 7.2.1.1)
  - New clonal chromosome abnormalities in Ph+ cells: CCA/Ph+: at any time after initiation of therapy
- In the event of disease progression the patient must be discontinued from the study treatment. The following events are considered disease progression.

1. CML-related death (any death during treatment or follow-up if the principal cause of death is marked as "study indication" in the eCRF by the investigator, or if the death occurred subsequent to documented progression to AP/BC and the cause of death is reported as "unknown" or not reported by the investigator)
2. Accelerated phase (AP) as defined by any of the following:
   - ≥ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate
   - ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate
   - ≥ 20% basophils in the peripheral blood
   - Thrombocytopenia (<100 x 109/L) that is unrelated to therapy
3. Blast crisis (BC) as defined by any of the following:
   - ≥ 30% blasts in peripheral blood or bone marrow aspirate
   - Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma).

7.1.7 Withdrawal of consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

[redacted]

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and Rest of World: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 Molecular response

Molecular response (MR) will be assessed in all patients randomized to each treatment arm as well as in patients that switch study treatment from bosutinib to asciminib.

Levels of BCR-ABL1 transcripts will be determined by real-time quantitative PCR (RQ-PCR) testing of peripheral blood and analyzed at a central testing laboratory. Log reduction in BCR-ABL1 transcripts levels from the standardized baseline value, or the percent ratio of BCR-ABL1 transcripts versus control gene (ABL) transcripts converted to a reference standard, international scale (Hughes and Branford 2006), will be calculated for each sample.

Major molecular response and related variables are defined as the following:

- Rate of Major Molecular Response (MMR) where MMR is defined as a ≥ 3.0 log reduction in BCR-ABL1 transcripts compared to the standardized baseline equivalent to ≤ 0.1 % BCR-ABL1/ABL % by international scale as measured by RQ-PCR, confirmed by duplicate analysis of the same sample
- Time to MMR defined as the time from the date of randomization to the date of the first documented MMR,
- Duration of MMR defined as the time from the date of first documented MMR to the earliest date of loss of MMR, progression to AP or BC, or CML-related death.

[redacted]

Loss of MMR is defined as increase of BCR-ABL1/ABL to > 0.1% by international scale (IS) in association with a ≥ 5-fold rise in BCR-ABL1 from the lowest value achieved on study treatment and replicated by a second analysis of the same sample. Loss of MMR must be confirmed by subsequent sample analysis within 4 to 6 weeks showing loss of MMR associated with a ≥ 5-fold rise in BCR-ABL1 from the lowest value achieved on study treatment, unless it is associated with confirmed loss of CHR or loss of CCyR or progression to AP/BC or CML-related death. Mutational analysis will be performed at a Novartis designated laboratory by Sanger sequencing at Week 1 Day 1, upon confirmed loss of MMR and/or at end of treatment. If the result at Week 1 Day 1 is positive for a mutation, analysis will be performed every 12 weeks.

The blood samples will be taken as described in Table 7-1, Table 7-2 and Table 7-3.

Table 7-3 Blood samples (efficacy primary endpoint)

Sample Type	Volume	Visit	Time point
Blood for BCR-ABL1 quantification by RQ-PCR	20 mL	Screening/Baseline / S-Screening/S-Baseline*	Pre-dose
	20 mL	Week 4 / S-Week 4	Pre-dose
	20 mL	Week 8 / S-Week 8	Pre-dose
	20 mL	Week 12 / S-Week 12	Pre-dose
	20 mL	Week 16 / S-Week 16	Pre-dose
	20 mL	Week 24 / S-Week 24	Pre-dose
	20 mL	Week 36 / S-Week 36	Pre-dose
	20 mL	Week 48 / S-Week 48	Pre-dose
	20 mL	Week 60 / S-Week 60	Pre-dose
	20 mL	Week 72 / S-Week 72	Pre-dose
	20 mL	Week 84 / S-Week 84	Pre-dose
	20 mL	Week 96 / S-Week 96	Pre-dose
	20 mL	Every 12 weeks thereafter up to end of study treatment	Pre-dose
	20 mL	End of Treatment / S-End of Treatment	Anytime
Blood for BCR-ABL1 Mutation analysis by Sanger Sequencing	5 mL	Week 1 Day 1 /S-Week 1 Day 1*	Pre-dose
	No sample collected - testing is performed on the "Blood for BCR-ABL1 quantification by RQ-PCR" sample	Upon confirmed loss of MMR and/or End of Treatment/ S-End of Treatment	Anytime
Blood for BCR-ABL1 Mutation analysis **only** for patients with mutations at Week 1 Day 1	No sample collected - testing is performed on the "Blood for BCR-ABL1 quantification by RQ-PCR" sample	Week 12 and every 12 weeks thereafter up to end of study treatment	Anytime
*Assessment does not need to be completed during the visit for patients in the treatment switch if already collected during the EOT or the treatment switch screening visit.			

[redacted]

During the study, peripheral blood samples will be collected into PAXgene™ Blood RNA tubes for all RQ-PCR assessments. Detailed instructions for the collection, handling, and shipment of RQ-PCR and mutation samples are outlined in the [CABL001A2301 Laboratory Manual].

7.2.1.2 Bone marrow analysis and cytogenetics

Cytogenetic response will be assessed locally as the percentage of Ph+ metaphases in the bone marrow and is defined as the following (a review of a minimum of 20 metaphases is required):

- Complete (CCyR) - 0% Ph+ metaphases
- Partial (PCyR) - >0 to 35% Ph+ metaphases
- Major (MCyR) - 0 to 35% Ph+ metaphases
- Minor (mCyR) - >35 to 65% Ph+ metaphases
- Minimal - >65 to 95% Ph+ metaphases
- None - >95 to 100% Ph+ metaphases.

Bone marrow aspirate for cytogenetic analyses will be performed at screening/baseline (performed up to 56 days prior to Week 1 Day 1), at Week 24/S-Week 24, 48/S-48, 72/S-72, 96/S-96 as long as patient has not achieved MMR and at end of treatment (S-end of treatment as specified in Table 7-1 and Table 7-2. For patients on the bosutinib arm an unscheduled bone marrow assessment at week 12 may be performed to evaluate cytogenetic response in consideration for potential dose escalation.

Quantification of the percentage of Ph+ chromosome metaphases, number of metaphases, number positive for Ph chromosome, additional chromosomal abnormalities as well as data from cytologic evaluation (microscopic analysis) of percentage of blasts and promyelocytes will be recorded on the Bone Marrow eCRF. These exams will be performed and analyzed locally. Fluorescent In-situ hybridization (FISH) analysis will not be accepted.

7.2.1.3 Hematologic response

A complete hematologic response (CHR) is defined as all of the following present for ≥ 4 weeks:

- WBC count <10 x 10^9/L
- Platelet count <450 x 10^9/L
- Basophils <5%
- No blasts and promyelocytes in peripheral blood
- Myelocytes + metamyelocytes < 5% in peripheral blood
- No evidence of extramedullary disease, including spleen and liver

7.2.2 Safety and tolerability assessments

Safety will be monitored by the assessments described below as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8. Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the patient's eCRF.

[redacted]

7.2.2.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. Information about the physical examination must be present in the source documentation at the study center and will be collected on the following visits as specified in Table 7-1 and Table 7-2:

- Screening /S-Screening
- Week 1 Day 1 / S-Week 1 Day 1
- Every 2 weeks from Week 4 to Week 16 / S-Week 4 to S-Week 16. Week 6, 10 and 14 / S-Week 6, 10 and 14 assessments must be performed in case of previous or newly occurring adverse events.
- Every 4 weeks from Week 16 to Week 96 / S-Week 16 to S-Week 96
- Every 12 weeks from Week 96 to EOT / S-Week 96 to S-EOT
- End of treatment / S-End of treatment visit or early discontinuation / S-early discontinuation visit in case of premature discontinuation.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF. Presence of extramedullary leukemic involvement will be checked with each physical examination as outlined above. Findings on physical examination consistent with extra-medullary leukemic involvement will be recorded (e.g. liver and spleen size, any other organ involvement).

7.2.2.2 Vital signs

Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature and must be performed at the following visits as specified in Table 7-1 and Table 7-2:

- Screening / S-Screening
- Week 1 Day 1 / S-Week 1 Day 1
- Week 2 Day 1 / S-Week 2 Day 1
- Every 2 weeks from Week 4 to Week 16 / S-Week 4 to S-Week 16
- Every 4 weeks from Week 16 to Week 96 / S-Week 16 to S-Week 96
- Every 12 weeks from Week 96 to EOT/ S-Week 96 to S-EOT
- End of treatment / S-End of treatment visit or early discontinuation / S-early discontinuation visit in case of premature discontinuation.

7.2.2.3 Height and weight

Height in centimeters (cm) will be measured at screening only.

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1 and Table 7-2:

- Screening / S-Screening

[redacted]

- Week 1 Day 1 / S-Week 1 Day 1
- Every 12 weeks from Week 12 to EOT / S-Week 12 to S-EOT
- End of treatment visit / S-End of treatment or early discontinuation / S-early discontinuation visit in case of premature discontinuation.

7.2.2.4 Performance status

ECOG Performance status scale (Table 7-4) will be used as described in the Table 7-1, Table 7-2 and Table 7-4:

- Screening / S-Screening
- Week 1 Day 1 / S-Week 1 Day 1
- Every 2 weeks from Week 4 to Week 16 / S-Week 4 to S-Week 16
- Every 4 weeks from Week 16 to Week 96 / S-Week 16 to S-Week 96
- Every 12 weeks from Week 96 to EOT / S-Week 96 to S-EOT
- End of treatment / S-End of treatment visit or early discontinuation / S-early discontinuation visit in case of premature discontinuation.

More frequent examinations may be performed at the investigator's discretion, if medically indicated.

Table 7-4 ECOG Performance status scale

Description	Grade
Fully active, able to carry on all pre-disease activities without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light housework, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead.	5

7.2.2.5 Laboratory evaluations

Central laboratory will be used for analysis of hematology, biochemistry, coagulation, serum pregnancy and hepatitis marker specimens collected (safety monitoring) as specified in Table 7-1, Table 7-2 and Table 7-5. Details on the collections, shipment of the samples and reporting of results by the central laboratory are provided to investigators in the [CABL001A2301 Laboratory Manual]. The time windows granted for laboratory evaluations are identical with the corresponding visit time windows for each visit (see Section 7.1.5).

Local laboratory analysis are allowed if there is a clinical suspicion of abnormal laboratory values which is supported by a reported adverse event and for hematology assessments at Week 6, 10 and 14.

[redacted]

Table 7-5 Central clinical laboratory parameters collection plan

Test Category	Test Name	Frequency
Hematology	Hemoglobin, platelets, red blood cells, white blood cells, WBC morphology with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils, promyelocytes, myelocytes, metamyelocytes, blast and other)	Screening/baseline, Week 1 Day 1, Week 2 Day 1, every 2 weeks from week 4 up to week 16, every 4 weeks up to week 96, and every 12 weeks thereafter, EOT and as clinically indicated / S-Screening/S-baseline*, S-Week 1 Day 1, S-Week 2 Day 1, every 2 weeks from S-week 4 up to S-week 16, every 4 weeks up to S-week 96, and every 12 weeks thereafter, S-EOT and as clinically indicated
Chemistry	Hemoglobin A1c	Screening/baseline, Week 12 and as clinically indicated / S-Screening/S-baseline*, S-Week 12 and as clinically indicated
Chemistry	Creatinine clearance	Screening/baseline / S-Screening/S-baseline*
Chemistry	Albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), total calcium, total calcium (corrected for albumin), creatinine, creatine kinase, potassium, magnesium, sodium, phosphate (inorganic phosphorus), direct bilirubin, indirect bilirubin, total bilirubin, total cholesterol, LDL cholesterol, HDL cholesterol, total protein, triglycerides, blood urea or Blood Urea Nitrogen (BUN), uric acid, amylase, lipase, glucose (fasting)	Screening/baseline, Week 1 Day 1, Week 2 Day 1, every 4 weeks from week 4 up to week 96, and every 12 weeks thereafter, EOT, and as clinically indicated / S-Screening/S-baseline*, S-Week 1 Day 1, S-Week 2 Day 1, every 4 weeks from S-week 4 up to S-week 96, and every 12 weeks thereafter, S-EOT, and as clinically indicated
Coagulation	International Normalized Ratio (INR)	
Hepatitis markers	HbsAg, HbcAb /anti-Hbc	Screening/baseline**
Serum Pregnancy test (if applicable)	Serum ß-HCG testing	Screening/baseline, every 4 weeks up to week 96, and every 12 weeks thereafter, EOT, unscheduled / S-Screening/S-baseline*, every 4 weeks up to S-week 96, and every 12 weeks thereafter, S-EOT, unscheduled

*Assessment does not need to be completed during the screening visit for patients in the treatment switch if already collected during the EOT.

**Not applicable for patients being assessed for treatment switch as part of the treatment switch screening/baseline visit.

7.2.2.5.1 Hematology

Hematology labs are to be analyzed at each scheduled visit by a central laboratory (Week 6, 10 and 14 assessments can be performed at site or at any peripheral local laboratory) as specified in Table 7-1 and Table 7-2. Hematology includes assessment of hemoglobin, platelets count, red blood cells, total white blood cell count (WBC) and a full manual differential count including basophils, eosinophils, lymphocytes, monocytes, neutrophils, promyelocytes, myelocytes, metamyelocytes, blast and other cells (Table 7-5).

[redacted]

7.2.2.5.2 Clinical chemistry

Blood chemistry labs are to be analyzed at each scheduled visits by a central laboratory as specified in Table 7-1 and Table 7-2. Chemistry includes albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), total calcium, total calcium (corrected for albumin), creatinine, creatinine clearance, creatine kinase, potassium, magnesium, sodium, phosphate (inorganic phosphorus), direct bilirubin, indirect bilirubin, total bilirubin, total cholesterol, LDL cholesterol, HDL cholesterol, total protein, triglycerides, blood urea, Blood Urea Nitrogen (BUN), uric acid, amylase, lipase and fasting glucose. In addition the coagulation parameter INR is analyzed at each scheduled visit.

HbA1c is analyzed at screening/baseline, week 12 and as clinically indicated.

The hepatitis markers HbsAg, HbcAb/anti-Hbc are analyzed at screening/baseline (Table 7-5).

7.2.2.5.3 Pregnancy and assessments of fertility

All women of childbearing potential have to complete a serum pregnancy test at the screening visit, at every monthly visit until end of treatment visit. Pregnancy testing is not required for patients who are determined to be post-menopausal. The time windows granted for pregnancy testing are identical with the corresponding visit time windows for each visit. Refer to Table 7-1 and Table 7-2 of the Visit evaluation schedules. Serum pregnancy test will be performed by a central laboratory.

After Week 96 / S-Week 96, monthly urine pregnancy test must be performed by all women of child-bearing potential between the three monthly visits (beginning at Week 100 / S-Week 100). Urine pregnancy tests may be performed at the investigational site or at home. Test results performed at home should be recorded onto a patient diary and brought to each scheduled visit for the site to review. If a test result indicates a pregnancy, the patient must contact the investigator immediately.

Pregnancies diagnosed in female patients participating in the study (including female partners of male patients) should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the Oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) Department.

During the whole study, women of childbearing potential should employ the use of highly effective contraception. Highly effective contraception methods are defined in Section 5.3.

Sexually active males on asciminib treatment must use a condom during intercourse while taking the drug and for at least 3 days after stopping treatment and should not father a child within this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. In addition, male participants must not donate sperm for the time period specified above.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

After the subject has rested approximately 10 minutes in a semi-supine position, standard 12-lead ECGs must be obtained in triplicate with a recommended minimal interval of 5 minutes

[redacted]

between each ECG at the time points specified in Table 7-1, Table 7-2, Table 7-6 and Table 7-7. ECGs should be taken before blood samples for PK if both assessments are scheduled at the same time point. In this case recording of ECGs should be planned according to the true time of blood sample for PK rather than to the scheduled time point.

Table 7-6 Central ECG collection (all patients)

Week (or Day)	Number of ECGs (per visit)	Time of ECG
Screening/Baseline Day -21 to -1 / S-Screening/S-Baseline Day -42 to -1 (all patients)	3	3 serial ECGs at the screening visit
Week 1 Day 1 / S-Week 1 Day 1 (all patients)	3	3 serial ECGs at 2 h post dose
Week 2 Day 1 / S-Week 2 Day 1 (asciminib/asciminib switch patients)	12	3 serial ECGs pre-dose and at 2, 3, 4 h post-dose
Week 2 Day 1 / S-Week 2 Day 1 (bosutinib)	3	3 serial ECGs pre-dose
Week 4 / S-Week 4 (all patients)	3	3 serial ECGs pre-dose
Week 12 / S-Week 12 (all patients)	3	3 serial ECGs pre-dose
Week 24 / S-Week 24 (all patients)	3	3 serial ECGs pre-dose
Week 96 / S-Week 96 (all patients)	3	3 serial ECGs 30 min* post-dose
Unscheduled (all patients)	3	3 serial ECGs
* 30 min +/- 5min allowed		

Table 7-7 Central ECG collection plan for patients in full PK asciminib group

Week (or Day)	Number of ECGs (per visit)	Time of ECG
Day -21 to -1	3	3 serial ECGs at the screening visit
Week 1 Day 1	3	3 serial ECGs at 2 h post dose
Week 2 Day 1	24	3 serial ECGs pre-dose and at 1, 2, 3, 4, 6, 8, 12 h post-dose
Week 4	3	3 serial ECGs pre-dose
Week 12	3	3 serial ECGs pre-dose
Week 24	3	3 serial ECGs pre-dose
Week 96	3	3 serial ECGs 30 min* post-dose
Unscheduled	3	3 serial ECGs
* 30 min +/- 5min allowed		

All ECGs performed will be independently reviewed. Instructions for the collection and transmission of these ECGs to the independent central reader (ERT (Electronic Research Technology, Inc.)) will be provided in the [CABL001A2301 ECG Manual].

Three serial ECGs (triplicate) should be performed ½ hour prior to dosing for pre-dose assessment. The serial ECGs should be taken approximately 5 minutes apart. All 3 ECGs for each time point should be sent to ERT. Readings for QTc prolongation will be based on the

[redacted]

average seen in the scans for each time point. The enrollment of patients has to be based on centrally assessed QTcF time. If one of the 3 serial ECGs prior to dosing on day 1 shows a QTcF ≥ 450 msec (male) or ≥ 460 msec (female) by automated reading, an immediate manual central reading must be requested by calling ERT. The patient may not be dosed if the average of the manually read ECGs confirms a QTcF ≥ 450 msec (male) or ≥ 460 msec (female).

Dose adjustments in case of QT prolongation should be performed per Section 6.3.2.

Additional unscheduled ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator.

All ECGs, including unscheduled triplicate safety ECGs with clinically relevant findings, collected during the study should be transmitted to the central core ECG laboratory for review.

The results of the centrally assessed ECGs are automatically transferred into the clinical database.

Clinically significant ECG abnormalities present at screening should be reported on the Medical History eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

7.2.2.6.2 Cardiovascular risk factor assessment

Cardiovascular events (CVE) including ischemic heart disease, peripheral arterial occlusive disease and ischemic cerebrovascular events have been reported in CML patients receiving TKI therapies as specified in Table 7-1 and Table 7-2. As both study treatments in the trial are TKIs (asciminib and bosutinib), the cardiovascular risk factors (hypertension, tobacco use, raised blood glucose (diabetes), physical inactivity, unhealthy diet, cholesterol/lipids, overweight and obesity) of each patient will be collected prior to randomization and end of treatment. This will also include the patient's Family History.

7.2.2.6.3 Echocardiogram

Echocardiograms will be performed to monitor cardiac safety. Assessments are scheduled at screening/baseline, Week 20 and end of treatment visits. The echocardiogram will be performed and evaluated locally to assess the left ventricular ejection fraction. Any clinically significant findings will be collected and reported in the database (i.e. reported as adverse events). For patients that switch from bosutinib to asciminib treatment, an echocardiogram will no longer be required.

7.2.2.6.4 Pulmonary function test

Pulmonary function test will be performed to monitor cardio-pulmonary safety. Assessments are scheduled at screening/baseline, Week 20 and end of treatment visits. The pulmonary function test with the plethysmograph includes the assessment of the lung volumes FEV1, FVC, FEV1/FVC, TLC and VC. In addition the DLCO to evaluate the gas exchange will be assessed at the same time points. Any clinically significant findings will be collected and reported in the

database (i.e. reported as adverse events). For patients that switch from bosutinib to asciminib treatment, the pulmonary function testing will no longer be required.

7.2.3 Pharmacokinetics

Blood samples for asciminib pharmacokinetics will be collected on all study subjects allocated to the asciminib treatment arm. Blood samples for full PK profiles will be collected from at least 20 patients. These patients will be identified sequentially at selected sites that are capable of serial PK sampling over 12 hours. Asciminib should be taken for at least 3 consecutive days without interruption or dose modification prior to full PK day.

Blood samples for asciminib pharmacokinetics will also be collected on patients switching from bosutinib to asciminib (see Table 7-8).

For the assessment of asciminib pharmacokinetics in plasma, serial blood samples will be collected following asciminib administration at several time-points (see Table 7-1, Table 7-2, Table 7-8 and Table 7-9 below for further details). Remaining plasma samples may be used for identification and/or measurement of metabolites of asciminib.

Refer to the [CABL001A2301 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

Table 7-8 Pharmacokinetic blood collection log (Sparse PK-group-asciminib arm/ asciminib treatment switch patients)

Week / S-Week	Day	Scheduled Time Point	Dose Reference ID	PK Sample No	Blood Volume (mL)
1	1	2 h (± 10 min)	101	101	2
2	1	0 h (Pre-dose)[a]	102/2001[b]	102	2
	1	2 h (± 10 min)	102	103	2
	1	3 h (± 15 min)	102	104	2
	1	4 h (± 15 min)	102	105	2
4	Any	0 h (Pre-dose)[a]	103/3001[b]	106	2
12	Any	0 h (Pre-dose)[a]	104/4001[b]	107	2
24	Any	0 h (Pre-dose)[a]	105/5001[b]	108	2
96	Any	0 h (Pre-dose)[a]	106/6001 [b]	109	2
		Unscheduled		1001+	

[a] Pre-dose PK sample should be taken immediately prior to the next administration of asciminib. PK samples on Week 2 Day 1 should be taken before and after the morning dose (i.e. 1st dose of the day). PK samples on other weeks may be taken immediately prior to the morning dose (i.e. 1st dose of the day) or the evening dose (i.e. 2nd dose of the day).
[b] The first dose reference ID refers to the first dose administered after PK sampling and the second dose reference ID refers to the last dose administered prior to the PK sampling.

[redacted]

Table 7-9 Pharmacokinetic blood collection log (Full PK group-asciminib arm)

Week	Day	Scheduled Time Point	Dose Reference ID	PK Sample No	Blood Volume (mL)
1	1	2 h (± 10 min)	1	1	2
2	1	0 h (Pre-dose)[a]	2/201[b]	2	2
	1	0.5 h (± 10 min)	2	3	2
	1	1 h (± 10 min)	2	4	2
	1	2 h (± 10 min)	2	5	2
	1	3 h (± 15 min)	2	6	2
	1	4 h (± 15 min)	2	7	2
	1	6 h (± 30 min)	2	8	2
	1	8 h (± 60 min)	2	9	2
	1	12 h (± 60 min) (Pre-dose)[a]	3/2[b]	10	2
4	Any	0 h (Pre-dose)[a]	4/401[b]	11	2
12	Any	0 h (Pre-dose)[a]	5/501[b]	12	2
24	Any	0 h (Pre-dose)[a]	6/601[b]	13	2
96	Any	0 h (Pre-dose)[a]	7/701[b]	14	2
		Unscheduled		2001+	

[a] Pre-dose PK sample should be taken immediately prior to the next administration of asciminib. PK samples on Week 2 Day 1 should be taken before and after the morning dose (i.e. 1st dose of the day). PK samples on other weeks may be taken immediately prior to the morning dose (i.e. 1st dose of the day) or the evening dose (i.e. 2nd dose of the day).
[b] The first dose reference ID refers to the first dose administered after PK sampling and the second dose reference ID refers to the last dose administered prior to the PK sampling.

7.2.3.1 Analytical method

Plasma asciminib concentrations will be measured at the designated laboratory using a validated high-performance liquid chromatography/tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) was 1.00 ng/mL.

[redacted]

[redacted]

[redacted]

[redacted]

7.2.4.2 Biomarker assessments in blood samples

Blood samples will be requested from all patients participating in the study.

Characterization of low level mutations in BCR-ABL1 gene

A 10 mL blood sample to be collected at Week1 Day 1 pre-dose, to confirm loss of MMR and/or end of treatment to assess whether there are low level mutations undetected by Sanger Sequencing in BCR-ABL1 gene at Week 1 Day 1 or new mutations appearing during treatment and at time of disease progression which potentially cause resistance to asciminib or bosutinib treatment as specified in Table 7-1, Table 7-2 and Table 7-10.

[redacted]

Table 7-10 Biomarker sample collection plan

Sample Type	Volume	Visit	Time point
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
Blood samples (exploratory)			
Blood for low level mutation analysis	10mL	Week 1 Day 1/ S-Week 1 Day 1*	Pre-dose
	10mL	Upon visit to confirm loss of MMR and/or End of Treatment	Anytime
[redacted]			
[redacted]			
[redacted]			
[redacted]			

*Assessment does not need to be completed during the S-Week 1 Day 1 visit for patients in the treatment switch if already collected during the EOT.

**Assessment does not need to be completed during the S-Week 1 Day 1 visit for patients in the treatment switch if already collected during the Week 1 Day 1 visit.

[redacted]

7.2.5 Resource utilization

The measures of healthcare Resource Utilization (RU) to be collected include: hospitalization (H), emergency room (ER) visit, general practitioner (GP) visits, specialist (Sp) visit and urgent care (UC) visit. These measures will be used to derive the economic impact of asciminib and bosutinib.

Hospitalization visits will also record the number of days in ward and the type of ward (hospital unit) and the discharge status. At each RU collection, the reason for the visit (i.e. related to CML, AE related to CML therapy or other reason) will be collected in order to quantify the impact of asciminib and bosutinib on healthcare resources.

The RU assessment will be completed at each scheduled clinical trial visit as specified in Table 7-1; the RU will be completed by the investigator however information with respect to the number of GP, UC, Sp or ER visits will be ascertained from the patient.

All attempts to collect as much information from the patient as possible should be made in order to minimize selection bias.

7.2.6 Patient reported outcomes

The MDASI CML, PGIC, WPAI along with EQ-5D-5L (EuroQol Group (1990), Brooks (1996), Herdman et al (2011)) will be used to compare data on the patient's disease-related symptoms and health-related quality of life from baseline to EOT between the treatment arms. The WPAI will be used to assess work productivity and activity impairment related to the patient's CML. All measures will assess differences between the treatment arms. All tools require patient's direct completion and will be administered utilizing an electronic device for data collection.

Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses. Missing data items in a scale will be handled according to the manual for each instrument. No imputation will be applied if the total or subscale scores are missing at a visit.

The patient should be given the questionnaire(s) to be completed at the scheduled visit before any clinical assessments are conducted as specified in Table 7-1. Completion of all questionnaires is mandatory; they cannot be skipped. In the event a patient refuses to complete the questionnaire(s), the patient's refusal should be documented in the study data capture system and should not be captured as a protocol deviation. Patient questionnaires should be completed in the language most familiar to the patient.

The patient should be given sufficient space and time to complete the questionnaires and the administered questionnaire should be reviewed for completeness. If missing responses are noted, patients should be encouraged to complete any missing responses.

Completed questionnaire(s) and any unsolicited comments written by the patient should be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the patient to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 8 (e.g. reference "Adverse Events" Section) of the study protocol.

[redacted]

MDASI-CML

The M.D. Anderson Symptom Inventory – Chronic Myeloid Leukemia (MDASI-CML) is a 26 item self-administered questionnaire for adult CML patients. Twenty of the items measure the severity of disease-related symptoms and are scored from 0 (Not present) to 10 (As Bad as you can imagine) and 6 items that measure symptom interference with daily life scored from 0 (Did not interfere) to 10 (Interfered completely). Descriptive statistics will be provided for the MDASI-CML symptom score and interference score, and the change in the MDASI-CML symptom score and interference score from baseline to all available time points to the end of study. Additional analysis may be performed and details will be described in the analysis plan.

EQ-5D-5L

EQ-5D-5L is a two-part standardized instrument for measuring health outcomes in a wide range of health conditions and treatments. It consists of a descriptive system and a visual analogue scale (EQ VAS). The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems (or unable to perform the activity). The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'worst imaginable health state'. The health states derived from the descriptive system can be summarized into a single index score that provides a simple measure of health for clinical and economic appraisal. Descriptive statistics will be provided for EQ-5D-5L health index score and for the EQ VAS, at each scheduled assessment time point. There should be only ONE response for each dimension. Missing values can be coded as '9'. Ambiguous values (e.g. 2 boxes are ticked for a single dimension) should be treated as missing values. Additional analysis may be performed and details will be described in a separate analysis plan.

WPAI

The Work Productivity and Activity Impairment Questionnaire (WPAI) is a four-item questionnaire which is intended to measure work and activity impairment associated with CML for those who self-identify as currently employed for pay. This questionnaire measures self-reported productivity loss associated with CML during the past seven days. It consists of questions about absence from work due to CML, hours spent at work, the reduction in productivity at work attributed to CML, and the reduction in productivity while performing regular activities. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, Scoring will be done according to WPAI instrument guidance resulting in four scores including: Percent work time missed due to problem; percent impairment while working due to problem; Percent overall work impairment due to problem; and, percent activity impairment due to problem. Change from baseline in WPAI at each visit, where measured, will be done for each of the four derived scores.

PGIC

The Patient Global Impression of Change is comprised of a single question intended to measure a patient's perspective of improvement or deterioration over time relative to treatment. The

[redacted]

PGIC uses a seven-point scale where one (1) equals very much improved and seven (7) equals very much worse. A summary of Patient Global Impression of Change (PGIC) at each visit, where measured will be provided.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)

[redacted]

5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)

If the event worsens the event should be reported a second time in the eCRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the eCRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Natural progression or deterioration of the malignancy under treatment (including loss of response, progression to accelerated phase or blast crisis and death due to disease progression), will be recorded as part of the efficacy evaluation and should NOT be reported as an AE/SAE.

Signs and symptoms clearly associated with the disease under study should NOT be reported as AEs unless they are newly emergent (i.e. not previously observed in the patient), judged by the Investigator to be unusually severe or accelerated, or if the Investigator considers deterioration of disease-related signs and symptoms to be caused directly by the study drug. If there is any uncertainty about an AE being due solely to the disease under study, it should be reported as an AE or SAE as appropriate.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by

[redacted]

the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the [Asciminib Investigator's Brochure].

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time

[redacted]

interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcome should be collected for the female partners of any male who received asciminib treatment in this study. Consent to report information regarding pregnancy outcome should be obtained from the mother.

[redacted]

For all pregnancies with live birth and/or unknown outcome the newborn has to be followed up to obtain infant health status and development up to twelve months after delivery.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided asciminib Investigator's Brochure or bosutinib label. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

This study will institute a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will be constituted prior to the randomization of the first patient. The DMC will be responsible to review safety data at approximately 6 months after the first randomized patient has started study treatment. Subsequent reviews will be conducted approximately every 6 months on an as and when needed basis thereafter (i.e. if significant safety findings are noted). This includes but does not limit the role of the DMC to evaluate these data and to provide recommendations to the sponsor to continue, modify or stop the study early. The DMC will be in place at least until the conduct of the primary analysis.

It is expected that the DMC will consist at a minimum of two physicians with appropriate disease area qualifications and one statistician. There will be a meeting with the DMC describing their roles and responsibilities and discussing potential data format and process issues prior to the finalization of DMC charter.

It is envisioned that the DMC may make certain types of recommendations, namely:

- No safety concerns, ethical to continue the study as planned
- Serious safety concerns precluding further study treatment, regardless of efficacy
- Recommendation to continue the study but proposing an amendment to the protocol (e.g., incorporate an additional safety assessments)

8.7 Steering Committee

In order to monitor study conduct, a Steering Committee (SC) will be established comprising investigators participating in the trial. Additionally two sponsor representatives (a physician and a statistician) will be active members of this committee.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. Novartis will make final decisions on trial conduct based on SC recommendations. Together with the clinical trial team, the SC will review protocol amendments as appropriate, and also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

[redacted]

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

[redacted]

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Data collected by third parties (biochemistry, PCR assessments, biomarkers, PK) will be sent electronically to Novartis.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using the Novartis Interactive Response Technology.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

The data will be analyzed by Novartis and/or designated CRO. It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis.

[redacted]

Study data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant PK and PD measurements.

The cut-off date for the primary analysis is defined as the date when all patients have been on study treatment for 24 weeks or discontinued earlier. The cut-off date for the end of study treatment analysis is defined as 30 days after the end of study treatment period (see Section 4.3) to ensure that all available treatment phase data from all patients up to the last dose of study drug taken in this study, will be analyzed and summarized in the end of study treatment phase CSR. Patients will be further followed for survival and progression for up to 5 years from the date the last randomized patient receives the first study dose. An update analysis of OS and PFS will be performed at the end of the follow-up period in the final study CSR.

10.1 Analysis sets

10.1.1 Full Analysis Set

The **Full Analysis Set (FAS)** comprises all patients to whom study treatment has been assigned by randomization. According to the intention to treat principle, patients will be analyzed according to the treatment and stratum they have been assigned to during the randomization procedure.

10.1.2 Safety set

The **Safety Set** includes all patients who received at least one dose of study treatment. Patients will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

10.1.3 Per-Protocol set

The **Per-Protocol Set (PPS)** consists of a subset of the patients in the FAS who are compliant with requirements of the CSP. The PPS will be used for sensitivity analyses on the primary endpoint only.

Oncology standards for protocol deviations potentially leading to exclusion from the PPS are:

- Type of indication different from those required by the CSP
- If prior therapy does not match with CSP requirements in terms of number and types of previous therapy regimens
- Another anti-neoplastic therapy administered after start of study treatment and prior to first efficacy assessment
- Study treatment received different from treatment assigned by randomization

10.1.4 Dose-determining analysis set

Not applicable.

[redacted]

10.1.5 Pharmacokinetic analysis set

The **Pharmacokinetic analysis set (PAS)** includes all patients who provide at least one evaluable PK concentration. For a concentration to be evaluable, patients are required to:

- Take a dose of asciminib prior to sampling,
- Take the same dose of asciminib for at least 3 consecutive days without dose interruption or dose modification prior to sampling,
- For post-dose samples, do not vomit within 4 hours after the dosing of asciminib (this is the current dose); for pre-dose samples do not vomit within 4 hours after the dosing of asciminib prior to sampling (this is the previous dose),
- Have the pre-dose sample collected before the next dose administration.

10.1.6 Other analysis set

For duration of MMR and time to MMR, the MMR Responder Set that will be used is a subset of FAS and includes patients who achieve MMR at any time.

For CCyR rates at and by scheduled time points, the CCyR Analysis Set that will be used is a subset of FAS and includes patients who are not in CCyR at baseline.

For duration of CCyR and time to CCyR, the Cytogenetic Responder Set that will be used is a subset of FAS and includes patients who do not have CCyR at baseline and achieve CCyR at any time on study treatment.

Patients who will receive at least one dose of asciminib after bosutinib failure will form the Switch Analysis Set which will be used for safety and exploratory efficacy endpoints defined on these patients.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the FAS or the Safety Set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, by treatment group.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The Safety set will be used for the analyses below.

Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in days to asciminib and bosutinib, as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and

[redacted]

the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics.

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized by treatment group and all dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

10.4 Primary objective

The primary objective of the study is to evaluate the efficacy of asciminib at the recommended dose in CML patients in chronic phase, previously treated with 2 or more tyrosine kinase inhibitors and to compare this efficacy profile in this population with that achieved by patients receiving bosutinib.

10.4.1 Variable

The primary efficacy variable of the study is the Major Molecular Response (MMR) rate at 24 weeks. A patient will be counted as having achieved MMR at 24 weeks if he meets the MMR criteria (BCR-ABL1 ratio $\leq$ 0.1%) at 24 weeks.

10.4.2 Statistical hypothesis, model, and method of analysis

The MMR rate at 24 weeks will be calculated based on the FAS and according to the Intention-ToTreat (ITT) principle. MMR rate and its 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. The confidence interval for the difference in MMR rate between treatment groups will be provided using the Wald method.

The null hypothesis is that there is no difference between the treatment groups with respect to MMR rate at 24 weeks. The Cochrane-Mantel-Haenszel chi-square test, stratified by the randomization stratification factor, i.e. major cytogenetic response status (PCyR or CCyR vs. others) at screening, will be used to compare MMR rate between the two treatment groups, at the two-sided 5% level of significance. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

10.4.3 Handling of missing values/censoring/discontinuations

Only patients with MMR at 24 week visit are considered responders. In other words, any patient who achieves MMR before 24 weeks, but is no longer in MMR at 24 weeks, will be considered as a non-responder in this primary analysis. Patients discontinuing the randomized treatment (having performed an EOT visit) prior to 24 weeks due to any reason will be considered as non-responders. One exception to the rule above is if the 24-week PCR evaluation is missing, but both a PCR evaluation at 16 weeks and a PCR evaluation at 36 weeks indicate MMR, the 24-week assessment is imputed as a ‘Response’. If PCR evaluations are performed at unscheduled visits closer to the Week 24 visit (before or after), these will be taken into account for the imputation.

[redacted]

10.4.4 Supportive and Sensitivity analyses

The analysis of the primary endpoint will also be repeated on the PPS if the PPS is different from the FAS.

Subgroup analyses and a logistic regression analysis will be employed. Refer to the exploratory objectives Section 10.6.1 for further details.

10.5 Secondary objectives

The secondary objectives in this study are as follows:

- To compare additional parameters of the efficacy of asciminib versus bosutinib, defined as:

Key secondary endpoints

- MMR rate at 96 weeks

Other efficacy endpoints

- Cytogenetic response (Complete, Partial, Major, Minor, Minimal, no response) rate at all scheduled data collection time points including, 24, 48 and 96 weeks.
- Cytogenetic response (Complete, Partial, Major, Minor, Minimal, no response) rate by all scheduled data collection time points including, 24, 48 and 96 weeks.
- MMR rate at all scheduled data collection time points (except 24 and 96 weeks which are already covered by primary and key secondary endpoints)
- MMR rate by all scheduled data collection time points including 24, 48 and 96 weeks.
- Time to MMR
- Duration of MMR
- Time to CCyR
- Duration of CCyR
- Time to treatment failure
- Progression free survival
- Overall survival
- To compare the safety and tolerability profile of asciminib versus bosutinib
- To characterize the PK of asciminib in the CML-CP population

10.5.1 Key secondary objective(s)

The key secondary endpoint to be evaluated is MMR rate at 96 weeks, which is defined as the proportion of patients with MMR at 96 weeks and derived in a similar fashion to MMR rate at 24 weeks.

[redacted]

10.5.1.1 Analysis for key secondary objectives

The null hypothesis is that there is no difference between the treatment groups with respect to MMR rate at 96 weeks. Formal statistical testing of the key secondary endpoint will be performed with $\alpha = 0.05$ (two-sided) only if the primary endpoint (i.e. MMR rate at 24 weeks) is significant by means of a gatekeeping procedure to control the overall alpha level. Otherwise, no statistical testing will be performed, and any analysis will be considered exploratory.

MMR rate at 96 weeks will be evaluated in a similar fashion to the primary analysis of MMR rate at 24 weeks. The rate and the associated 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. Confidence interval for the difference between treatment groups will be provided using the Wald method.

Statistical testing will be performed via CMH chi-square test stratified by the randomization strata. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

If the PCR evaluation at 96 weeks is missing, but a PCR evaluation both at 84 weeks and 108 weeks indicate MMR, the 96 week assessment is imputed as a "response", assuming that MMR is maintained between 84 and 108 weeks. If PCR evaluations are performed at unscheduled visits closer to the Week 96 visit (before or after), these will be taken into account for the imputation.

10.5.2 Other secondary efficacy objectives

Unless otherwise stated the FAS will be used for the analysis of all other secondary efficacy endpoints. The exceptions are using the Molecular Responder Set for duration of MMR and time to MMR, the CCyR Analysis Set for CCyR rates, and the Cytogenetic Responder Set for duration of CCyR and time to CCyR.

No statistical testing of non-key secondary efficacy endpoints will be performed, and any analysis will be considered exploratory.

Molecular Response

MMR rates at scheduled time points (except 24 and 96 weeks which have been specified as primary and key secondary endpoints) will be evaluated in a similar fashion to the primary analysis of MMR rate at 24 weeks. Patients discontinuing the randomized treatment prior to a specific time point due to any reason will be considered as non-responders for that time point.

MMR rates by scheduled time points are defined as the proportion of patients who achieve MMR at or before the specified visit, i.e. if a patient achieves an MMR but then loses it before or at the visit, he/she will still be classed as achieving MMR by that time point.

For each endpoint the rate and the associated 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. Confidence intervals for the differences in any response rates between treatment groups will be provided using the Wald method.

Statistical testing will be performed via CMH chi-square tests stratified by the randomization strata. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

[redacted]

Duration of MMR is defined in Section 7.2.1.1 as the time between the date of the first documented MMR and the earliest date of loss of MMR, progression to AP/BC, or CML-related death for patients in the Molecular Responder Set. The time will be censored at the last molecular assessment (PCR) date while on treatment for patients who have not experienced any of the above events.

Duration of MMR will be analyzed by K-M method and presented by K-M plots. The estimated rates of patients who are still responding at various time points will also be provided using K-M method.

The cumulative incidence of MMR will be graphically displayed by an increasing step function. This curve will increase each time (after randomization) at which a new responder is observed and thus will increase up to the best observed response rate (e.g. up to 50% if half of the patients in the analysis population are able to achieve response).

Time to MMR is defined in Section 7.2.1.1 and calculated as: date of first MMR - date of randomization +1, for patients in the Molecular Responder Set. Descriptive statistics (minimum, maximum, median, quartiles, mean, sd) of time to MMR will be provided for the two treatment groups separately.

Cytogenetic Response

Patients in FAS will be categorized with counts and percentages provided for cytogenetic response (Complete, Partial, Major, Minor, Minimal, No Response) at and by (i.e. best response up to a specified time point) scheduled time points. Shift tables will also be employed to examine the changes in cytogenetic response category from baseline.

Since there are expected to be only limited numbers who are actually in CCyR at baseline the analysis of CCyR rate at and by scheduled time points will only include patients who are not in CCyR at baseline, i.e. the CCyR Analysis Set.

CCyR rates at and by scheduled time points etc. and the associated 95% confidence intervals based on the Pearson-Clopper method will be presented by treatment group with the analysis of these endpoints only including patients who are not in CCyR at baseline.

Confidence intervals for the differences in any response rates between treatment groups will be provided using the Wald method.

Statistical testing will be performed via CMH chi-square tests stratified by the randomization strata. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

Time to CCyR is defined for patients in the Cytogenetic Responder Set as: date of first CCyR - date of randomization +1. Descriptive statistics (minimum, maximum, median, quartiles, mean, sd) of time to CCyR will be provided for the two treatment groups separately.

The cumulative incidence of CCyR will also be graphically displayed by an increasing step function. This curve will increase each time (after randomization) at which a new responder is observed and thus will increase up to the best observed response rate.

Duration of CCyR is defined as the time between date of first documented CCyR and the earliest date of loss of CCyR, progression to AP/BC, or CML-related death for patients in the

[redacted]

Cytogenetic Responder Set. The time will be censored at the last cytogenetic assessment date on treatment for patients for whom none of the above events is reported or last PCR evaluation on treatment indicating MMR.

Duration of CCyR response will be analyzed by K-M method and presented by K-M plots. The estimated rates of patients who are still responding at various time points will also be provided using K-M method.

Treatment failure, disease progression and survival

Time to treatment failure (TTF) is defined as the time from date of randomization to an event of treatment failure. The following events will constitute 'treatment failure', and are based on the ELN criteria (Baccarani et al 2013) defining failure of a second line treatment adapted to include discontinuation of randomized treatment as an event:

- No CHR or > 95% Ph+ metaphases at three months after randomization or thereafter
- BCR-ABL1 ratio > 10% IS and/or > 65% Ph+ metaphases at six months after randomization or thereafter
- BCR-ABL1 ratio > 10% IS and/or > 35% Ph+ metaphases at 12 months after randomization or thereafter
- Loss of CHR, CCyR or PCyR at any time after randomization
- Detection of new BCR-ABL1 mutations which potentially cause resistance to study treatment at any time after randomization
- Confirmed loss of MMR
- New clonal chromosome abnormalities in Ph+ cells: CCA/Ph+: at any time after randomization
- Discontinuation from randomized treatment for any reason

For patients who have not reached treatment failure, their TTFs will be censored at the time of last study assessment (PCR, cytogenetic, hematologic or extramedullary) before the cut-off date.

Progression-Free-Survival (PFS) is defined as the time from the date of randomization to the earliest occurrence of documented disease progression to AP/BC or the date of death from any cause (including progressions and deaths observed during the survival follow-up period) before the cut-off date.

The time will be censored at the date of last study assessment (PCR, cytogenetic, hematologic or extramedullary) or last post-treatment follow-up for patients without event.

Overall survival (OS) is defined as the time from the date of randomization to the date of death (including the survival follow-up period). Patients who are alive at the time of the analysis data cutoff date will be censored at the date of last contact before the cut-off date.

TTF, PFS and OS will be estimated and graphically displayed using the K-M approach on FAS. The estimated rates by K-M method at various time points will be provided and the endpoints will be compared between the two treatment groups using stratified log-rank test stratified by the randomization strata. The hazard ratio and 95% confidence intervals will be computed from a stratified Cox model.

[redacted]

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

The overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of subject's first informed consent to the day before first administration of study treatment
2. on-treatment period: from day of first administration of study treatment to 30 days after last actual administration of the same study treatment (including start and stop date)
3. post-treatment period: starting at day 31 after last administration of any study treatment

Summary tables for safety data will be presented for the on-treatment period. Comparative analysis will be performed only for the on-treatment period. Listings of safety data will include pre-treatment, on-treatment, and post-treatment periods, with a flag to indicate data collected before or after the on-treatment period.

The same analysis will be done for patients that switch to asciminib after treatment failure on bosutinib. However, safety events that initiated on or after start of asciminib during the switch treatment phase will be included.

10.5.3.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and serious adverse events (including those from the pre-treatment, on-treatment and post-treatment periods) will be listed and those collected before or after the on-treatment period will be flagged.

10.5.3.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

[redacted]

For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following listings and summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v4.03

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline in the on-treatment period.
- Shift tables using CTCAE grades to compare respective baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v4.03,

- Shift tables using the low/normal/high/ (low and high) classification to compare respective baseline to the worst on-treatment value.

10.5.3.4 Other safety data

ECG

ECGs (12-lead) including PR, QRS, QT, QTcF, and HR intervals will be obtained for each subject during the study. ECG data will be read and interpreted centrally.

Categorical analysis of QT/QTc interval data based on the number of patients meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these patients will be produced by treatment group.

Vital signs

Data on vital signs will be tabulated and listed, notable values will be flagged.

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

10.5.3.6 Tolerability

Tolerability of each study treatment will be assessed by summarizing the number of subjects with dose interruptions and dose reductions. Reasons for dose interruptions and dose reductions will be listed by subject and summarized.

10.5.4 Secondary PK objectives

The PK objective is to characterize the PK of asciminib in CML population.

Using PAS, summary statistics (n, mean, SD, coefficient of variation (CV) for mean, geometric mean, CV for geometric mean, median, minimum and maximum) will be presented for plasma concentration at each scheduled time point. The geometric mean with mean (SD) and individual plasma concentration versus time profiles of asciminib will be displayed graphically.

[redacted]

Using Safety set, concentration data will be listed. Concentration values below the limit of quantification (BLQ) will be set to zero by the Bioanalyst and displayed in listings as zero with a flag. BLQ values will be handled as zero in any calculations of summary statistics, but handled as missing for the calculation of the geometric means and CVs.

Pharmacokinetic parameters will be determined by non-compartmental method(s) using the pharmacokinetic profile of asciminib in patients with full PK sampling. PK parameters listed in Table 10-1 will be derived and reported, when feasible.

Population PK modeling may be performed and the results may be reported in a separate population PK report. Data from this study may be combined with data from other studies for this analysis.

Table 10-1 Non compartmental pharmacokinetic parameters in full PK group

AUC0-12h	The area under the plasma concentration-time curve from time zero to 12 h (mass x time x volume-1)[a]
Cmax	The maximum (peak) observed plasma drug concentration after dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma drug concentration after dose administration (time)
CL/F	The total body clearance of drug from the plasma after oral administration (volume x time-1)

10.6 Exploratory objectives

10.6.1 Exploratory efficacy objectives

- To evaluate the influence of factors such as major cytogenetic status at baseline, failure/intolerance to prior TKIs, line of therapy, gender, race and age on the effect of asciminib with respect to the primary efficacy endpoint.
- To characterize mutations in the BCR-ABL1 gene at Week 1 Day 1, upon confirmed loss of molecular response and/or at end of treatment and examine their association with molecular and cytogenetic response for asciminib vs. bosutinib.
- To assess the efficacy of asciminib when administered as treatment after bosutinib failure according to the 2013 ELN Guidelines.

10.6.1.1 Data analysis of exploratory efficacy objectives

Subgroup analyses will be performed to evaluate the influence of factors such as baseline major cytogenetic response status, baseline/Week 1 Day 1 BCR-ABL1 ATP-binding site mutation status (from local historical record and from Sanger Sequencing), failure/intolerance to prior TKIs, line of therapy, gender, race and age on the primary efficacy endpoint. In addition, a logistic regression analysis will incorporate the key baseline variables into the model to further evaluate the impact of these variables on the primary endpoint and to provide a treatment effect estimate which is adjusted for imbalances in the treatment groups. An adjusted odds ratio for the treatment effect with associated 95% confidence intervals will be presented. Mantel-Haenszel estimates of the common odds ratio and the corresponding 95% confidence interval will also be provided. The effect of asciminib when administered as treatment after bosutinib failure will be assessed using the Switch Analysis Set to estimate response rates (cytogenetic and molecular response) at all scheduled time points after switch, as well as time-to and duration

[redacted]

of response. The analysis of time-to-event endpoints will be conducted only if at least 5 events are observed.

10.6.2 Exploratory PK objectives

The potential relationship between asciminib exposure (e.g. trough concentration) and efficacy or safety endpoints may be assessed by graphic exploration and/or statistical modeling as appropriate. The details will be further specified in the SAP. Additional exposure-response analyses for ECG may be conducted and reported separately.

10.6.3 Exploratory biomarker objectives

The study is not powered to assess specific biomarker-related hypotheses, thus the statistical analyses of these data should be considered exploratory in nature. Analytical results from such analyses may be used to generate additional hypotheses that must then be verified with data derived from subsequent clinical trials. Furthermore, additional post hoc exploratory assessments may be performed.

While the goal of the biomarker analyses is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a sample collection, or not perform/ discontinue the analysis of blood and bone marrow (e.g. issues related to the quality and or quantity of samples, or issues related to the assay that preclude the analysis of samples). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed.

Unless otherwise specified, all statistical analyses of biomarker data will be performed on subjects with valid biomarker samples.

The exploratory biomarker objectives are:

- To characterize mutations in the BCR-ABL1 gene at Week 1 Day 1, upon confirmed loss of molecular response and/or at end of treatment and examine their association with molecular and cytogenetic response for asciminib vs. bosutinib
- [redacted]
- To assess clonal evolution of pre-existing mutations versus mutations acquired during treatment with asciminib vs. bosutinib

[redacted]

- [redacted]
- Explore the relationship between BCR-ABL1 mutations at baseline/Week 1 Day 1 and efficacy outcomes for the primary endpoint and key secondary endpoints. The association between loss of response and BCR-ABL1 mutations will also be explored descriptively.
- [redacted]

Additional exploratory biomarker analyses may be performed depending on the data. All patients with evaluable biomarker measurements in the FAS will be included in the analysis and will be reported in a separate biomarker report.

10.6.4 Exploratory Patient Reported Outcomes objectives

The exploratory patient reported outcomes objectives are:

- To compare the impact of treatment on health care resource utilization between treatment arms in all patients
- To compare the impact of treatment on patient reported outcomes (PRO) including CML-specific symptoms, patient quality of life, and impact on work productivity and activity impairment from baseline through end of treatment between treatment arms in all patients

10.6.4.1 Resource Utilization

Data relating to Resource Utilization from the FAS will be used for the purpose of economic evaluation. Descriptive statistics of the levels of resource utilization over time will be done for each treatment arm. The measures of healthcare Resource Utilization (RU) include: hospitalization (H), Emergency Room (ER) visit, general practitioner (GP) visits, specialist (Sp) visit and urgent care (UC) visit. Medical resource utilization (MRU) will be assessed as follows: frequency and duration of hospitalization from Baseline up to End of Treatment; frequency of emergency room visits from Baseline up to End of Treatment; frequency of additional outpatient office visits general practitioner, specialist, and urgent care visits from Baseline up to End of Treatment. Hospitalization visits will also record the number of days on ward and the type of ward (hospital unit) and the discharge status. At each RU collected, the reason for the visit, i.e. related to CML, AE related to CML therapy or other reason, will be collected, in order to quantify the impact of treatment on healthcare resources.

[redacted]

10.6.4.2 Patient Reported Outcomes

The MDASI CML, PGIC along with EQ-5D-5L will be used to compare data on the patient's disease-related symptoms and health-related quality of life from baseline to EOT between the treatment arms. The WPAI will be used to assess work productivity and activity impairment related to the patient's CML. All measures will assess differences between the treatment arms.

Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses. Missing data items in a scale will be handled according to the manual for each instrument. No imputation will be applied if the total or subscale scores are missing at a visit.

10.7 Interim analysis

No formal interim analysis is planned for this trial. As described in Section 10, three or four formal analyses are planned: the primary at week 24, another at the 96-week end of study treatment and a PFS/OS update at year 5.

- 24-week primary analysis: Formal testing of the primary endpoint with full alpha will be performed. Analyses of other efficacy endpoints at and by 24 weeks will also be performed.
- 96-week analysis: Formal statistical testing of the key secondary endpoint will be performed with $\alpha = 0.05$ (two-sided) only if the primary endpoint (i.e. MMR rate at 24 weeks) is significant. Otherwise, no statistical testing will be performed, and any analysis will be considered exploratory. Analyses of other efficacy endpoints (including MMR rate at 48 weeks) will also be performed.
- End of study treatment analysis (if required) similar to the 96-week analysis without formal statistical testing.
- 5-year PFS/OS update analysis: PFS and OS

In addition DMC safety analyses will be conducted as described in Section 8.6.

10.8 Sample size calculation

To test the null hypothesis that the response rate is equal in the two groups, based on two-sided 5% level of significance and with 90% power, 222 patients will be needed in total (i.e. 148 patients in the asciminib arm and 74 patients in the bosutinib arm based on 2:1 randomization allocation). This assumes that asciminib leads to a 20% improvement in the MMR rate at 24 weeks over bosutinib from 15% to 35% which corresponds to an odds ratio of 3.05.

The assumed bosutinib MMR rate of 15% at 24 weeks is based on previous trials evaluating bosutinib therapy (Khoury 2012, Gambacorti-Passerini 2014, García-Gutiérrez 2015).

No more than 66 patients (approximately 30% of the overall trial population) that are intolerant to their most recent TKI therapy with BCR-ABL1 < 1% will be recruited in order to ensure that the CML third line patient population is adequately represented.

[redacted]

10.9 Power for analysis of key secondary variables

If the primary analysis of MMR rate at 24 weeks is statistically significant, then the key secondary endpoint MMR rate at 96 weeks will be tested, with the overall alpha controlled at the 5% two-sided level. The testing will use a gatekeeping strategy. Full details of the testing strategy are provided in Section 10.5.1.

Table 10-2 below summarizes the treatment effects of the key secondary endpoint which can be detected with 80% and 90% power, based on the specified assumptions regarding the bosutinib effect. The calculations were made using the software package PASS (2008).

Table 10-2 Detectable effect sizes for key secondary endpoint

Endpoint	Anticipated effect with bosutinib	2-sided alpha	Power	Detectable effect size§
MMR rate at 96 weeks	30%*	0.05	90% 80%	≥ 23% ≥ 20%

*: Gambacorti-Passerini et al. 2014, Figure 1D.
§: Absolute difference from the anticipated effect with bosutinib.

For MMR rate at 96 weeks, if the anticipated effect with bosutinib is 30%, then the given sample size with 2-sided alpha=0.05 would allow to detect an absolute difference of at least 23% (i.e. MMR rate at 96 weeks with asciminib is at least 53%) for 90% power and of at least 20% (i.e. MMR rate at 96 weeks with asciminib is at least 50%) for 80% power.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

[redacted]

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Male subjects on asciminib treatment must be informed that if a female partner becomes pregnant while the male subject is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

Additional consent form

Not applicable.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.3.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to

[redacted]

present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study electronic case report form (eCRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

[redacted]

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

[redacted]

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[redacted]

14 Appendices

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited in Section 6.4 for patients on asciminib and Section 6.5 for patients on bosutinib.

The following lists are based on the internal [Pharmacokinetic Sciences memorandum on Drug-Drug Interaction] (release date: January 2018), which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (2017), and the University of Washington's Drug Interaction Database (2017). These lists are not comprehensive and are only meant to be used as a guide. Please contact the medical monitor with any questions. **If a medication appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.**

14.1 Appendix 1 List of concomitant medications for patients on asciminib

Table 14-1 Prohibited concomitant medications for asciminib arm

Category	Drug Names
Strong inhibitors of CYP3A	atazanavir/ritonavir[1], danoprevir/ritonavir[1], darunavir/ritonavir[1], elvitegravir/ritonavir[1], indinavir/ritonavir[1], lopinavir/ritonavir[1], saquinavir/ritonavir[1], tipranavir/ritonavir[1], ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[1], boceprevir, clarithromycin, cobicistat, conivaptan, grapefruit juice[2], idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, telaprevir, telithromycin, troleandomycin, voriconazole,
Strong inducers of CYP3A	carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort (*Hypericum perforatum*)[1]
UGT1A1/2B7 inducers	UGT1A1: carbamazepine, cigarette smoke, rifampicin, testosterone propiate, UGT2B7: Barbiturates
Torsade de pointe (TdP) TdP/QT risk : Known	amiodarone, anagrelide, arsenic trioxide, astemizole (off us mkt), azithromycin, bepridil (off us mkt), chloroquine, chlorpromazine, cilostazol, cisapride (off us mkt), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on us mkt), donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, grepafloxacin (off market worldwide), halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (off mkt worldwide), mesoridazine (off mkt worldwide), methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl, pentamidine, pimozide, probucol (off mkt worldwide), procainamide (oral off us mkt), propofol, quinidine, sevoflurane, sotalol, sparfloxacin (off us mkt), sulpiride (not on us mkt), terfenadine (off us mkt), thioridazine, vandetanib
TdP/QT risk: Possible	alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine, asenapine, bedaquiline, bortezomib, buprenorphine, capecitabine, ceritinib, clomipramine, clozapine, crizotinib, cyamemazine (cyamepromazine) (Only on Non US Market), dabrafenib, dasatinib, degarilix, delamanid (off US mkt), desipramine, dexmedetomidine, dolasetron, eribulin, ezogabine, famotidine, felbamate, fingolimod, foscarnet, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, lapatinib, lenvatinib, leuprolide, lithium, mifepristone, mirabegron, mirtazapine, moexipril/hctz, nicardipine, nilotinib, norfloxacin, nortriptyline, ofloxacin, olanzapine, osimertinib, oxytocin, paliperidone, panabinostat, pasireotide, pazopanib, perflutren lipid microspheres, pipamperone (not on us mkt), promethazine, quetiapine, ranolazine, rilpivirine, risperidone, roxithromycin (on non us mkt), saquinavir, sertindole (on non us mkt), sorafenib, sunitinib, tacrolimus, tamoxifen, telavancin, telithromycin, tetrabenazine

[redacted]

Category	Drug Names
	(orphan drug in us), tizanidine, tolterodine, toremifene, trimipramine, vardenafil, vemurafenib, venlafaxine, vorinostat, zotepine
TdP/QT risk: Conditional	amantadine, amisulpride, amitriptyline, atazanavir, chloral hydrate, diphenhydramine, doxepin, fluoxetine, furosemide (frusemide), galantamine, hydrochlorothiazide, hydroxyzine, hydroxychloroquine, indapamide, itraconazole, ivabradine (on non us mkt), ketoconazole, loperamide, metoclopramide, metronidazole, nelfinavir, pantoprazole, paroxetine, posaconazole, quinine sulfate, ritonavir, sertraline, solifenacin, telaprevir, torsemide, trazodone, voriconazole, ziprasidone
[1] Combination ritonavir-boosted regimens are listed here in the DDI memo as strong CYP3A inhibitors (to avoid potential confusion), even though some are considered moderate CYP3A inhibitors in the UW DDI Database. [2] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).	

Table 14-2 Concomitant medications to be used with caution in asciminib arm

Category	Drug Names
Narrow Therapeutic index substrates of CYP2C8	Paclitaxel
Narrow Therapeutic index substrates of CYP2C9	phenytoin, warfarin (also sensitive)
Narrow Therapeutic index substrates of CYP3A	alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus, terfanadine,
BCRP Inhibitors	abacavir, amprenavir, atorvastatin, ,curcumin[3], cyclosporine[3], daclatasvir, declatasvir[3], delavirdine, efavirenz, elbasvir, eltrombopag[3], elvitegravir[3], erlotinib, fluvastatin, fostamatinib, fumitremorgin, gefitinib, grazoprevir, lapatinib[3], ledipasvir[3], lopinavir, paritepravir[3], pitavastatin, rosuvastatin, simvastatin, sulfasalazine, tipranavir[3], velpatasvir, venetoclax
P-gp inhibitors	alogliptin, amiodarone[4], azithromycin[4], canaglifozin, captopril[4], carvedilol[4], clopidrogel, cremophor RH40, curcumin, diltiazem[4], dronedarone[4], elacridar[4], eliglustat, felodipine[4], fluvoxamine[4], fostamatinib, ginko[4,5], isavuconazole, ivacaftor, lopinavir,, milk thistle (silymarin, silibinin)[4,5], nifedipine[4], nitredipine[4],ombitasvir, paritaprevir, propafenone, quercetin,[4], ritonavir[4], sequinavir[4], schisandra chinesis extract[4,5], simepravir, St. John's wort extract (HYPERICUM PERFORATUM) [4,5],survorexant, talinolol[4], telaprevir[4], telmisartan[4], ticagrelor[4], tipranavir[4], tolvaptan[4], valspodar, vandetanib, verapamil[4], voclosporin, vorapaxar.
[3] Evidence of *in vivo* DDI [4] Dual P-gp and CYP3A4 inhibitor [5] Herbal product	

[redacted]

14.2 Appendix 2 List of concomitant medications for patients on bosutinib

Table 14-3 Prohibited concomitant medications for bosutinib arm

Category	Drug Names
Strong inhibitors of CYP3A	boceprevir, clarithromycin, cobicistat, conivaptan, grapefruit juice[2], idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, telaprevir, telithromycin, troleandomycin, voriconazole, atazanavir/ritonavir[1], danoprevir/ritonavir[1], darunavir/ritonavir[1], elvitegravir/ritonavir[1], indinavir/ritonavir[1], lopinavir/ritonavir[1], ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[1] , saquinavir/ritonavir[1], tipranavir/ritonavir[1]
Moderate inhibitors of CYP3A	aprepitant, amprenavir, atazanavir, cimetidine, ciprofloxacin, crizotinib, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, faldaprevir, fluconazole, grapefruit juice[2], imatinib, isavuconazole, netupitant, nilotinib, tofisopam, *Schisandra sphenanthera* (nan wu wei zi)[3], asafoetida resin (*Ferula asafoetida*)[3], verapamil
Strong inducers of CYP3A	carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort (*Hypericum perforatum*)[3]
Moderate inducers of CYP3A	bosentan, efavirenz, etravirine, modafinil, nafcillin, ritonavir/tipranavir, thioridazine, semagacestat[4], talviraline[4], lopinavir, lersivirine,
Proton pump inhibitors	dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole.

[1] Combination ritonavir-boosted regimens are listed here in the DDI memo as strong CYP3A inhibitors (to avoid potential confusion), even though some are considered moderate CYP3A inhibitors in the UW DDI Database.

[2] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

[3] Herbal product

[4] Dual P-gp and CYP3A4 inhibitor

Table 14-4 Concomitant medications to be used with caution in bosutinib arm

Category	Drug Names
Torsade de pointe (TdP) TdP/QT risk : Known	amiodarone, anagrelide, arsenic trioxide, astemizole (off us mkt), azithromycin, bepridil (off us mkt), chloroquine, chlorpromazine, cilostazol, cisapride (off us mkt), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on us mkt), donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, grepafloxacin (off market worldwide), halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (off mkt worldwide), mesoridazine (off mkt worldwide), methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl, pentamidine, pimozide, probucol (off mkt worldwide), procainamide (oral off us mkt), propofol, quinidine, sevoflurane, sotalol, sparfloxacin (off us mkt), sulpiride (not on us mkt), terfenadine (off us mkt), thioridazine, vandetanib
TdP/QT risk: Possible	alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine, asenapine, bedaquiline, bortezomib, buprenorphine, capecitabine, ceritinib, clomipramine, clozapine, crizotinib, cyamemazine (cyamepromazine) (Only on Non US Market), dabrafenib, dasatinib, degarilix, delamanid (off US mkt), desipramine, dexmedetomidine, dolasetron, eribulin, ezogabine, famotidine, felbamate, fingolimod, foscarnet, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, lapatinib, lenvatinib, leuprolide, lithium, mifepristone, mirabegron, mirtazapine, moexipril/hctz, nicardipine, nilotinib, norfloxacin, nortriptyline, ofloxacin, olanzapine, osimertinib, oxytocin, paliperidone, panabinostat, pasireotide, pazopanib, perflutren lipid microspheres, pipamperone (not on us mkt), promethazine, quetiapine, ranolazine, rilpivirine, risperidone, roxithromycin (on non us mkt), saquinavir, sertindole (on non us mkt), sorafenib, sunitinib, tacrolimus, tamoxifen, telavancin, telithromycin, tetrabenazine

[redacted]

Category	Drug Names
	(orphan drug in us), tizanidine, tolterodine, toremifene, trimipramine, vardenafil, vemurafenib, venlafaxine, vorinostat, zotepine
TdP/QT risk: Conditional	amantadine, amisulpride, amitriptyline, atazanavir, chloral hydrate, diphenhydramine, doxepin, fluoxetine, furosemide (frusemide), galantamine, hydrochlorothiazide, hydroxyzine, hydroxychloroquine, indapamide, itraconazole, ivabradine (on non us mkt), ketoconazole, loperamide, metoclopramide, metronidazole, nelfinavir, pantoprazole, paroxetine, posaconazole, quinine sulfate, ritonavir, sertraline, solifenacin, telaprevir, torsemide, trazodone, voriconazole, ziprasidone

[redacted]

Clinical Development

Asciminib/ABL001

A phase 3, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors

Protocol – Summary of changes

Amendment 3 (14-Dec-2018)

Amendment rationale

As of 21-Nov-2018, 137 patients were screened and 86 patients were randomized in the study, the study is currently ongoing.

The primary purpose of the amendment is:

Modification of the inclusion criterion of BCR-ABL1 transcript threshold required at study entry from a BCR-ABL1 ratio ≥ 1% IS to BCR-ABL1 ratio > 0.1% IS (i.e. not in MMR) for patients with intolerance to most recent TKI treatment. The threshold presented in this inclusion criteria affects only patients who are intolerant to prior treatment, since patients failing prior treatment must fulfill the criteria defined by ELN guidelines (Baccarani et al 2013). Although the number of treatment options is increasing, especially for patients with imatinib intolerance, alternatives for patients with resistance and/or intolerance to at least two previous TKIs are limited (NCCN 2018, ELN 2013). The reason of reducing the BCR-ABL1 ratio is that in routine clinical practice, physicians do not wait to observe increased BCR-ABL1 levels to switch treatment in patients with intolerance, which may increase the risk of disease progression, especially in patients with only limited further treatment options. This is in line with current CML treatment guidelines where the switch to an alternative therapy in intolerant patients is not linked to a BCR-ABL1 threshold (NCCN 2018, Baccarani et al 2013 and Hochhaus et al 2017).

Therefore, the threshold of ≥ 1% BCR-ABL1 in the current trial is reduced to BCR-ABL1 ratio > 0.1% IS for patients with intolerance to most recent TKI treatment. No more than 66 patients (approximately 30% of the overall trial population) that are intolerant to their most recent TKI therapy with BCR-ABL1 < 1% will be recruited in order to ensure that the CML third line patient population is adequately represented. As the primary endpoint is the rate of MMR at 24 weeks a baseline molecular response level > 0.1 % BCR-ABL1 is needed.

Patients experiencing documented treatment failure on bosutinib treatment will be allowed to switch to asciminib. Patients failing bosutinib treatment will have failed at least their third TKI treatment, with limited remaining treatment options. With this amendment patients who have failed bosutinib will be offered the possibility to continue in the study by receiving asciminib, if investigators consider that this treatment option is in the best interest of the patient. As of 15-Oct-2018, 4 patients could have potentially benefited from this option. Treatment failure during study treatment is assessed by measureable and pre-specified milestones defined by ELN criteria (Baccarani et al 2013), which are also used to define treatment failure as entry criteria for the study. Only documented treatment failure in the bosutinib arm will be considered for a treatment switch. For the purpose of the primary and secondary endpoint analyses, any patient meeting the ELN failure criteria while receiving study treatment, (either before or by the time of conducting the analysis and irrespective of treatment arm), will be considered as non-responders for the specific time point and for any subsequent time point. The switch to asciminib in case of bosutinib treatment failure is not expected to introduce bias as those patients will be regarded as non-responders irrespective of treatment switch and the disease burden will certainly not improve without further treatment. There is no option to switch patients failing on the asciminib treatment arm, as those patients can be offered approved

therapies outside of the context of the study. The efficacy data collected after the switch from patients switching to asciminib following bosutinib failure will be analyzed separately as exploratory endpoints and will not be included for primary and secondary study endpoints. In addition, safety data from patients receiving asciminib after bosutinib failure will be collected to further characterize asciminib's safety profile.

Potassium increase of up to 6.0 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits. Grade 2 increase of potassium is acceptable in case of normal creatinine clearance as this is not considered to be a risk factor for QTc prolongation. Total calcium (corrected for serum albumin) increase of up to 12.5 mg/dl or 3.1 mmol/L (Grade 2) is acceptable at study entry if associated with creatinine clearance within normal limits as this is not considered to be a risk factor for QTc prolongation.

A change to creatinine clearance instead of GFR is being made in relation to the magnesium inclusion requirement as GFR in this study is expressed by creatinine clearance.

Exclusion criteria #19 is being modified under this amendment in order to define the duration of the use of highly effective methods of contraception after the last dose of bosutinib under this study (one month after last dose of bosutinib). This is being done in order to align with the latest Bosulif® USPI.

Exclusion criteria #21 has also been removed under this amendment. In embryofetal development studies with asciminib, fetal malformations (cardiac malformations) and increased visceral and skeletal variants were observed in rats and increased incidence of resorptions indicative of embryo-fetal mortality and a low incidence of cardiac malformations indicative of dysmorphogenesis were observed in rabbits. Asciminib is not genotoxic. As published in the literature, small molecules can distribute to seminal fluid and the seminal accumulation suggested is semen/plasma ratios up to 11.3 (Klemmt and Scialli 2005). According to the FDA guidance, in general, there is increased concern for reproductive or developmental toxicity in humans for relative exposure ratios (animal: human) that are < 10 and decreased concern for exposure ratios > 25 (FDA Guidance for Industry 2011). The calculations for the asciminib safety margin were done based on Cmax (plasma) seen in patients at a dose of 200 mg BID (Cmax 6843 ng/ml). Safety margin calculation based on the embryo-fetal development study in rats was 768 and safety margin calculation based on the embryo-fetal development study in rabbits was 894. In conclusion, for asciminib, as outlined above, the safety margins are well above 25 and therefore no embryo- and fetotoxicity effects can be anticipated via seminal fluid. Removal of male contraception is in line with the Bosutinib USPI and SmPC.

In addition, patients can be re-screened up to three times for the study, instead of once. The patient population being investigated in this study is heavily pre-treated and patients might not have other treatment options outside the trial. There can be many intolerance-related temporary conditions resulting in ineligibility for the trial.

Recruitment period extension has been reflected in the VES table. Study length has changed with introduction of switch option for patients failing bosutinib treatment.

Patients enrolling in this trial will present a high disease burden after failure of previous therapies. Myelosuppression during TKI targeted treatment is a very common effect observed due to the suppression of the leukemic clone; this effect is also extended to hematopoiesis of

stem cells and progenitors (Steegmann et al 2016). For this reason, the recovery period for cytopenias has been extended from 28 to 42 days in order to allow for sufficient time to recover from suppression and to re-populate the bone marrow.

The biomarker sampling profile has been revised to remove the gene expression profile in leukemic stem cells in both blood and bone marrow due to technical limitations. In addition, there is currently no validated assay available.

A clarification has been made to how the tests for blood urea and Blood Urea Nitrogen (BUN) are noted. The text "blood urea, Blood Urea Nitrogen (BUN)" has been revised to “blood urea or Blood Urea Nitrogen (BUN)” in order to note that either test is permitted.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Change of the purpose of the study by decreasing the requirement of BCR-ABL1 ratio ≥ 1% IS to BCR-ABL1 ratio > 0.1% IS at the time of screening for patients with intolerance:
  - Protocol summary.
  - Section 2.1 Study rationale and purpose.
  - Section 4.1 Description of study.
  - Section 5.2 Inclusion criteria.
  - Section 10.5.2 Other secondary efficacy objectives.
- Change of the study design by introducing the switch to asciminib option for patients experiencing treatment failure on bosutinib treatment:
  - Protocol summary.
  - Section 2.2 Rationale for the study design.
  - Section 4.1 Description of study.
  - Figure 4-1 Schematic of Study Design.
  - Addition of Section 4.1.1 Study treatment switch from bosutinib to asciminib
  - Section 4.3 Definition of end of study.
  - Section 6.1.5 Treatment duration
  - Section 6.7.3.2 Study drug accountability.
  - Section 7 Visit schedule and assessments:
    - Addition of Table 7-2 Visit evaluation schedule (study treatment switch phase).
    - Addition of Section 7.1.2.2 Conditions to be fulfilled for asciminib switch.
    - Section 7.1.5 Visit windows.
    - Section 7.1.6 Discontinuation of study treatment.
    - Section 7.2.1.1 Molecular response.
    - Section 7.2.1.2 Bone marrow analysis and cytogenetics
    - Section 7.2.2.1 Physical examination.

    - Section 7.2.2.2 Vital signs.
    - Section 7.2.2.3 Height and weight.
    - Section 7.2.2.4 Performance status.
    - Section 7.2.2.5 Laboratory evaluations.
    - Section 7.2.2.6 Cardiac assessments.
    - Section 7.2.3 Pharmacokinetics.
    - Section 7.2.4 Biomarkers.
  - Section 10.1.6 Other analysis sets.
  - Section 10.5.3.1 Analysis set and grouping for the analysis
- Addition of new exploratory measure for patients that switch from bosutinib to asciminib:
  - Table 3-1 Objectives and related endpoints.
  - Section 10.1.6 Other analysis sets.
  - Section 10.6 Exploratory objectives:
    - Section 10.6.1 Exploratory efficacy objectives.
    - Section 10.6.1.1 Data analysis of exploratory efficacy objectives.
- Reference for concomitant medications with a "known risk of TdP" has been updated to wwwcrediblemeds.org/
  - Protocol summary
  - Section 5.3 Exclusion criteria
  - Section 6.3.2 Dose adjustments for QTcF prolongation
  - Section 6.4.3 Prohibited concomitant therapy
- [redacted]
- Section 5.2 Inclusion criteria and protocol summary: updated inclusion criteria to reflect the changes below:
  - Inclusion Criteria #3: As referenced above, the requirement of BCR-ABL1 ratio ≥ 1% IS has been decreased to BCR-ABL1 ratio > 0.1% IS at the time of screening for patients intolerant to previous TKI.
  - Inclusion Criteria #10: Potassium increase of up to 6.0 mmol/L is accepted at study entry if associated with creatine clearance within normal limits. Calcium increase of up to 12.5 mg/dl or 3.1 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits. GFR replaced by Creatinine clearance (calculated using Cockcroft-Gault formula) in order to maintain consistency throughout the protocol as creatinine clearance is already calculated based on inclusion criteria #7.
  - Inclusion Criteria #11: As study eligibility is assessed during screening with BCR-ABL1 PCR quantification via international scale this requirement was added as

clarification. Measurement according to international scale is only possible for typical BCR-ABL1 transcripts.

- Section 5.3 Exclusion Criteria and Protocol summary: updated exclusion criteria to reflect the following changes:
  - Exclusion Criteria #14: Removal of P-gp as a moderate or strong inhibitor of CYP3A as P-gp inhibitors are no longer prohibited per updated USPI, and SmPC
  - Exclusion Criteria #19: Duration of the use of highly effective methods of contraception after the last dose of bosutinib has been defined to align with the latest bosutinib USPI.
  - Exclusion Criteria #21 Removal of this criteria in order to align with updated pre-clinical data.
- Section 6.3.1 Dose modification and dose delay: The recovery period for cytopenias has been extended from 28 to 42 days in order to allow for sufficient time to recover from suppression and to re-populate the bone marrow.
- Table 7-1 Visit evaluation schedule: updates due to inadvertent omissions in previous protocols and to reflect extension of study treatment period
  - ECOG Performance status: X has been replaced by “If needed” under Week 6, Week 10 and Week 14.
  - Vital signs: added “If needed” under Week 6, Week 10 and Week 14.
  - Visit name: “W108, W120, W132, W144, W156” has been changed to “Every 12 weeks up to end of study treatment” to align with new extended recruitment timelines.
- Section 7.1.2 Change of patient re-screening allowance from once to up to three times.
- Section 7.1.2.2 Addition of new section with screening eligibility criteria for patients switching from bosutinib to asciminib.
- Section 7.1.4 Change of treatment duration for patients including those patients that switch to asciminib after failure on bosutinib. Patients can remain on asciminib treatment for up to 96 weeks after the last patient received the first dose in the study or up to 48 weeks after the last patient has switched to asciminib whichever is longer.
- Section 7.1.6 Discontinuation of study treatment: updated to specify that the safety follow-up visit can be conducted by telephone and replacement of “after randomization” by “after initiation of therapy” in the event that constitutes a treatment failure.
- Section 7.2.2.5.3 Pregnancy and assessments of fertility: Change in requirement for reporting pregnancies under this study. Pregnancies diagnosed in female partners of male participants are no longer required to be reported to CMO&PS. Contraception use by sexually active males while on study treatment is no longer required.
- Table 7-5 Central clinical laboratory parameters collection plan: Clarification on blood urea and Blood Urea Nitrogen (BUN). The text "blood urea, Blood Urea Nitrogen (BUN)" has been revised to “blood urea or Blood Urea Nitrogen (BUN)”.
- Section 8.4 Pregnancies: removal of male contraception requirement due to new information of asciminib embryo and fetotoxicity.
- Section 10.4.3 Handling of missing values/censoring/discontinuations: imputation rules updated to take in account unscheduled visits close to visit Week 24.

- Section 10.5.1.1. Analysis for key secondary endpoints: imputation rules updated to take in account unscheduled visits close to visit Week 96.
- Section 14 Appendices: updates to reflect that P-gp inhibitors are no longer prohibited
  - Section 14.2 Appendix List of concomitant medications for patients on bosutinib:
    - Removal of P-gp inhibitors from Table 14-3 Prohibited concomitant medications for bosutinib arm.
    - Addition of new medications to Category Torsade de pointe (TdP) TdP/QT risk: Known.
    - Addition of new category, TdP/QT risk: Possible.
    - Addition of new category, TdP/QT risk: Conditional.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 2 (13-Jul-2018)

Amendment rationale

As of 29-Jun-2018, this study has been submitted in 25 and approved in 24 countries. Eighty five (85) sites were initiated, 67 patients were screened and 38 patients were randomized in the study.

The primary purposes of the amendment are:

The frequency of bone marrow aspirate (BMA) to perform cytogenetic analysis has been decreased in accordance with treatment guidelines (European Leukemia Network (ELN) Guidelines (Baccarani et al 2013), National Comprehensive Cancer Network (NCCN) (Clinical Practice Guidelines in Oncology-Chronic Myeloid Leukemia v4.2018). Initially BMAs were foreseen at screening, every 24 weeks thereafter and at end of treatment. With the protocol amendment BMA is no longer needed for patients that have achieved MMR during study, however BMA assessment is requested at the time of end of treatment for biomarker analysis.

Toxicity studies performed in rats, dogs and cynomolgus monkeys identified the pancreas as potential target tissues. Therefore the assessment for laboratory parameters that are associated with pancreatitis were part of the inclusion criteria (amylase, lipase). Serum lipase is the preferred test due to its improved sensitivity, and a threshold concentration of 2-3 x ULN is recommended for the diagnosis of pancreatitis. There are a number of other conditions that can elevate lipase, including TKI pretreatment, thus the screening threshold for lipase is increased from ≤ ULN to ≤ 1.5 x ULN (CTCAE v4.03 grade 1), as patients with history of acute pancreatitis within 1 year of study and history of chronic pancreatitis are excluded. Amylase is not a specific marker for pancreatitis, as up to 60% of total serum amylase originates from non-pancreatic sources. Its short half-life reduces its value as a diagnostic test in the early clinical course. Lipase has replaced amylase as the biochemical test of choice for acute pancreatitis due to its higher specificity (Basnayake 2015), therefore the requirement of amylase ≤ ULN at screening has been removed.

Assessments for visits at weeks 6, 10 and 14 will be limited to the monitoring of the bone marrow function to allow for adjustments of study treatment. Assessments will comprise a complete blood count to detect neutropenia and thrombocytopenia which are among the most frequent adverse reactions [Asciminib Investigator's Brochure, Bosutinib label]. The physical examination must be done at site only in case of previous or newly occurring adverse events.

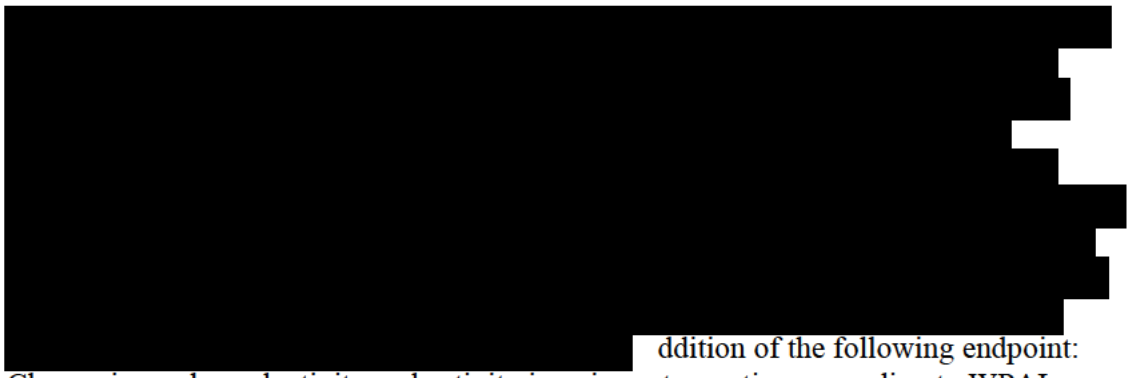
The concomitant medication section has been updated to reflect the most recent clinical updates on asciminib as well to align with the Bosutinib label.

In addition some minor inconsistencies (discrepancies between sections, typos) have been corrected.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- ABL001 has been replaced by International Nonproprietary Name (INN) asciminib throughout the protocol amendment.

- Protocol Summary and Section 5.2 Inclusion criteria:
  - Inclusion criterion 5: rewording of the reference to previous TKI therapy for more clarity.
  - Inclusion criterion 7: Criteria for amylase removed. Threshold for lipase increased to CTCAEv4.03 grade 1.
  - Inclusion criterion 10: grade 1 increase of magnesium is acceptable in case of normal Glomerular Filtration Rate (GFR) as this is not considered to be a risk factor for QTc prolongation.
- Protocol Summary and Section 5.3 Exclusion criteria:
  - Exclusion criterion 5: adapting the exclusion criteria concerning QT prolonging agents for clarification regarding known, possible or conditional risk for TdP, and adding the external web link to qtdrugs.org.
  - Exclusion criterion 8: deleted to avoid redundancy with inclusion and exclusion criteria 7.
  - Exclusion criterion 14: removal of substrates of CYP3A4/5, CYP2C8, or CYP2C9 with narrow therapeutic index based on most updated PBPK modeling predicting a negligible risk for sensitive CYP3A4/5, CYP2C8, or CYP2C9 substrates. These substrates will be moved under requiring caution and/or action section.
  - Exclusion criteria 19: changed from tubal ligation to bilateral tubal ligation,
  - Exclusion criterion 20: definition of menopausal women should be part of exclusion criterion 19.
- Section 1.2.1 Overview of asciminib (ABL001): updated.
- Section 1.2.1.1 Non-clinical experience/ Non-clinical pharmacokinetics and metabolism:
  - Rephrased to add more clarity on interspecies differences observed and recommendation about sunlight protection.
  - Updated with current available information.
- Section 1.2.1.2 Clinical experience: updated with current available information.
- Section 2.2.1 Rational for biomarker assessment: harmonization of time points for BCR-ABL1 gene mutation analysis.
- 
  ddition of the following endpoint: Change in work productivity and activity impairment over time according to WPAI.
- Section 4.3 Definition of end of study: rephrased to add more clarity.
- Section 6.1.1 Dosing regimen: precision on patient fasted state for asciminib dosing.

- Section 6.3.1 Dose modification and dose delay: clarification made on treatment discontinuation.
- Table 6-2 Criteria for dose reduction/interruption and re-initiation of asciminib and bosutinib treatment for adverse drug reactions:
  - Gastro intestinal/ Pancreatitis/Grade 2: precisions provided and treatment delay changed from 7 to 21 days to give investigators sufficient time for re-assessment.
  - Removal of "other adverse event" section which was redundant with the section "non-hematological adverse event reaction except where further specified in individual section".
  - Mandatory instructions for grade 3 and 4 "Non-hematological adverse event reaction except where further specified in individual section" for bosutinib have been aligned with those of asciminib: dose hold until resolved to ≤ grade 1, to handle the patients identically independent of the treatment assigned.
- Section 6.3.2 Dose adjustments for QTcF prolongation: adapting the dose adjustment concerning QT prolonging agents to the classification known, possible or conditional risk for TdP, and adding the external web link to qtdrugs.org.
- Section 6.4.2 Permitted concomitant therapy requiring caution and/or action: updated with the most clinical data available.
- Section 6.4.3 Prohibited concomitant therapy (asciminib):
  - Section on other anticancer agent added,
  - Sections on strong CYP3A4/5 inhibitors and P-gp inhibitors: prohibition on P-gp inhibitors has been removed and moved under requiring caution and/or action section based on CABL001A2102 ADME study,
  - Section on strong CYP3A4/5, UGT1A/2B inducers updated to provide instructions on action to be taken in case these inducers are taken,
  - Section on NTI substrates of CYP3A4/5, CYP2C8 and CYP2C9 removed based on a most updated PBPK modeling predicting a negligible risk for sensitive CYP3A4/5, CYP2C8, or CYP2C9 substrates and moved under requiring caution and/or action section,
  - Section on QT prolonging agents updated to change agents known to prolong QT interval to agents with "known", "possible" or "conditional" risk of Torsades de Pointes.
- Section 6.5.1 Permitted concomitant therapy requiring caution (bosutinib): has been updated to reflect the bosutinib label information regarding the use of QT prolonging agents.
- Section 6.5.2 Prohibited concomitant therapy (bosutinib):
  - Section on other anticancer agent added,
  - Concomitant use with CYP3A4/5 inhibitors/inducers: further clarifications on necessary actions.
- Table 7-1 Visit evaluation schedule:
  - Exploratory BCR-ABL1 mutation analysis (Sanger Sequencing) for patients with mutations at Week 1 Day 1: rephrased to indicate that this assessment will be performed without any dedicated blood collection.

  - [redacted]
  - Removal of PGIC questionnaire at screening: the question should only be completed for patients on treatment.
  - Week 6, 10 and 14: physical examination and extramedullary involvement to be performed only if new or ongoing adverse event since last visit. Chemistry and coagulation testings removed.
- Section 7.1.2 Screening, section 7.2.1.2 Bone marrow analysis and cytogenetics and Table 7-1 Visit evaluation schedule: timeframe for performing bone marrow aspirate and biopsy changed from 42 to 56 days. Historical bone marrow assessments performed before main informed consent form signature allowed if within 56 days of Week 1 Day 1.
- Section 7.1.2.2 Information to be collected on screening failures: correction of screening failure definition.
- Section 7.1.4 Treatment period: treatment failure added as a reason for stopping study treatment.
- Section 7.1.5 Visit windows: correction of the start of visit scheduled every two weeks.
- Section 7.1.6 Discontinuation of study treatment:
  - Has been made mandatory in case of pregnancy.
  - Confirmed loss of MMR in 2 consecutives tests rephrased for consistency with the efficacy assessments.
  - Ineligibility of patient due to detection of T315I or V299L mutations at any time has been added under the section describing the cases when a patient MUST be discontinued to remove any ambiguity.
- Section 7.1.7 Withdrawal of consent and Glossary of terms: these sections were added/updated to incorporate and reflect the European Economic Area (EEA) General Data Protection Regulation (GDPR) requirements.
- Section 7.2.1.1 Molecular response: definition of loss of MMR rephrased and harmonization of time points for BCR-ABL1 gene mutation analysis.
- Table 7.2 Blood samples (efficacy primary endpoint): updated to reflect:
  - [redacted]
  - Exploratory BCR-ABL1 mutation analysis (Sanger Sequencing) for patients with mutations at Week 1 Day 1 will be performed without any dedicated blood collection.
- Section 7.2.1.2 Bone marrow analysis and cytogenetics: bone marrow aspirate for cytogenetic analysis at week 24, 48, 72 and 96 has been limited to patients who have not achieved MMR.
- Section 7.2.2.1 Physical examination: week 6, 10 and 14 assessments must be performed only if new or ongoing adverse event since last visit.
- Section 7.2.2.3 Height and weight and Table 7-1 Visit evaluation schedule: weight to be collected at Week 1 Day 1 and thereafter every 12 weeks.

- Section 7.2.2.5 Laboratory evaluations: was updated to allow on exceptional basis local laboratory evaluations.
- Section 7.2.2.5.1 Hematology: the week 6, 10 and 14 assessments can be performed at site or at any peripheral local laboratory.
- Table 7-4 Central clinical laboratory parameters collection plan and Section 7.2.2.5.2 Clinical chemistry: clarification added for some of the parameters. Parameter naming clarified and total calcium (corrected for albumin) added.
- Table 7-5 Central ECG collection (all patients): clarification for ECG on Week 2 Day 1 for patients treated with bosutinib.
- Section 7.2.4.2 Biomarker assessments in blood samples:
  - Characterization of low level mutations in BCR-ABL1: clarification of time points for Sanger mutation testing.
  - [redacted]
- Table 7-9 Biomarker sample collection plan:
  - Bone marrow samples (exploratory): clarifications added.
  - [redacted].
  - Addition of one time point collection for low level mutation analysis to be consistent with text in Section 7.2.4.2 Biomarker assessment in blood sample.
- Section 7.2.2.5.3 updated to reflect the change of name of the Novartis Drug Safety and Epidemiology (DS&E) department to the present name, Chief Medical Office and Patient Safety (CMO&PS).
- Section 7.2.2.6.1 Electrocardiogram (ECG): additional instruction given if ECG and blood samples for PK scheduled at the same time point.
- Section 7.2.5 Resource utilization and Section 10.6.4.1 Resource Utilization: precision of the reasons for resource utilization.
- Section 7.2.6 Patient reported outcome: precision that completion of questionnaires is mandatory.
- Section 8.4 Pregnancies: updated to reflect the change of name of the Novartis Drug Safety and Epidemiology (DS&E) department to the present name, Chief Medical Office and Patient Safety (CMO&PS) and the change in collection of pregnancy outcomes from "must" to "should".
- Section 10 Statistical methods and data analysis: precisions provided regarding the cut-off dates for the primary and end of study treatment phase analysis.
- Section 10.1.5 Pharmacokinetic analysis set: precision provided on the post and pre-dose samples and vomiting.
- Section 10.1.6 Other analysis sets: precision of MMR and CCyR responder sets.
- Section 10.5.1.1 Analysis of key secondary objectives: adding an imputation rule for the secondary objective at 96 weeks and clarification concerning the analysis of the key secondary endpoint at week 96 if statistical significance is not reached for primary endpoint at week 24.

- Section 10.5.2 Other secondary efficacy objectives: update of descriptive statistics definition and removal of presentation of p value as no formal statistical testing will be performed.
- Section 10.6.1 Exploratory efficacy objectives and Section 10.6.3 Exploratory biomarker objectives:
  - Correction of time points for BCR-ABL1 mutation characterization (baseline corrected to Week 1 Day 1, adding "upon confirmed loss of MMR, and changed "and" to "and/or" End of treatment).
  - [redacted].
- Section 10.6.4.1 Resource utilization: correction on duration of resource utilization reporting.
- Section 10.7 Interim analysis: clarification concerning the analysis of the key secondary endpoint at week 96 if statistical significance is not reached for primary endpoint at week 24.
- Section 14 Appendices: the lists of concomitant medications for patients on asciminib and bosutinib have been updated based on the internal Pharmacokinetic Sciences memorandum on Drug-Drug Interaction (release date: January 2018).
- Some minor inconsistencies (discrepancies between sections, typos) have been corrected.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1 (10-Apr-2017)

Amendment rationale

This study is currently in the protocol submission phase. The protocol was submitted to the FDA only. The submissions to the other HA and IRB/EC will be performed once the amended protocol is available. As of 30 Mar 2017, no sites were initiated nor any patients screened for this study.

The primary purpose of this amendment is:

Patients with a mutation V299L are excluded from the study, due to the known inactivity of the comparator drug bosutinib. The designation of the mutation was inadvertently identified incorrectly throughout the protocol as V229L instead of V299L. The purpose of this amendment is to correctly identify the exclusionary mutation as "V299L" throughout the document.

In addition some inconsistencies that were discovered after the finalization of the initial protocol are corrected.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Protocol summary: The wrongly designated mutation V229L was corrected to V299L
- Protocol summary: The missing exclusion criteria number 18 "Pregnant or nursing (lactating) women" was added, to be consistent with Section 5.3.
- Section 1.2.2- Overview of bosutinib: The wrongly designated mutation V229L was corrected to V299L
- Section 2.5- Rationale for choice of comparators drug bosutinib: The wrongly designated mutation V229L was corrected to V299L
- [redacted]
- Section 5.1- Patient population: The wrongly designated mutation V229L was corrected to V299L
- Section 5.3- Exclusion criteria: The wrongly designated mutation V229L was corrected to V299L
- Section 6.4.4- Other concomitant medications: The duration of contraception was corrected to "3 days" after treatment discontinuation. Highly effective contraception needs to be continued until 3 days post-treatment discontinuation.
- Table 7-1-Visit evaluation schedule: X for weight removed from Visit Week 1 Day 1, to be consistent with Section 7.2.2.3.
- Table 7-1-Visit evaluation schedule: X for antineoplastic therapies since discontinuation of study treatment added to survival follow-up phase to be consistent with Section 7.1.6.

- Section 7.1.6- Discontinuation of study treatment: The criteria for study treatment discontinuation "documented lack of efficacy, disease progression" was removed. All patients (excluding patients that died, withdrew consent or are lost to follow-up), are followed up for survival after the treatment phase.
- Section 7.1.6- Discontinuation of study treatment: clarification added to distinguish between discontinuation of study treatment versus discontinuation of study.
- Section 7.2.2.1- Physical examination: clarification of methodology to assess extramedullary involvement.
- [redacted]
- Section 7.2.6- Patient reported outcomes: The statement "The original questionnaire will be kept with the patient's file as the source document." was removed. Questionnaires will be completed electronically; no paper copies will be kept in the source documents.
- Section 10.1.5- Pharmacokinetic analysis set: The number of consecutive days required for PK concentration evaluability was corrected to "3" days. ABL001 should be taken at least 3 consecutive days without interruption or dose modification prior to full PK day.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

2. Statistical Analysis Plan

NOVARTIS

Clinical Development

ABL001/asciminib

CABL001A2301

A phase 3, multi-center, open-label, randomized study of oral ABL001 versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors

Statistical Analysis Plan (SAP)

Author: Statistician, [redacted]

Document type: SAP Documentation

Document status: Final

Release date: 25-Aug-2017

Number of pages: 53

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
25-Aug-2017	Prior to DB lock for primary analysis	Creation of final version	N/A - First version	NA

Table of contents

List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AP	Accelerated phase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic classification
AUC	Area under the curve
BC	Blast crisis
bid	bis in diem/twice a day
CCyR	Complete cytogenetic response
CHR	Complete hematologic response
CMH	Cochrane-Mantel-Haenszel
CML	Chronic myelogenous leukemia
CML-CP	Chronic myelogenous leukemia in chronic phase
CRO	Contract research organization
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
DAR	Dosage administration record
DI	Dose intensity
DMC	Data monitoring committee
DRL	Drug reference listing
DSUR	Development safety update report
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End of treatment
ER	Emergency room
FAS	Full analysis set
GP	General practitioner
H	Hospitalization
HCRU	Health care resource utilization
HLT	High level term
HLGT	High level group term
IRT	Interactive response technology
IS	International scale
LLOQ	Lower limit of quantitation
LPFT	Last patient first treatment
LSC	Leukemic stem cell
LVEF	Left ventricular ejection fraction
MCyR	Major cytogenetic response

mCyR	Minor cytogenetic response
MedDRA	Medical dictionary for regulatory activities
MMR	Major molecular response
NCI	National Cancer Institute
NGS	Next generation sequencing
NMQ	Novartis MedDRA Query
OS	Overall survival
PAS	Pharmacokinetic analysis set
PCR	Polymerase chain reaction
PCyR	Partial cytogenetic response
PD	Pharmacodynamic
PDI	Planned dose intensity
PFS	Progression-free rurvival
Ph+	Philadelphia chromosome positive
PK	Pharmacokinetics
PPS	Per-protocol set
PRO	Patient-reported outcomes
PSUR	Periodic safety update report
PT	Preferred term
qd	Qua'que di'e / once a day
RDI	Relative dose intensity
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SMQ	Standardized MedDRA query
SOC	System organ class
Sp	Specialist
TBL	Total bilirubin
TKI	Tyrosine kinase inhibitor
TTF	Time to treatment failure
UC	Urgent care
ULN	Upper limit of norm
VAS	Visual analogue scale
W1D1	Week 1 Day 1
WBC	White blood cells
WHO-DD	World Health Organization Drug Dictionary

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses of primary objective, secondary objectives and selected exploratory objectives for the clinical study reports (CSR) of study CABL001A2301, a phase 3, multi-center, open-label, randomized study of oral ABL001 versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors.

The content of this SAP is based on protocol CABL001A2301 version 01. All decisions regarding safety monitoring analysis for the data monitoring committee, 24-week primary analysis, 96-week end of study treatment analysis, 5-year progression-free survival (PFS)/overall survival (OS) update analysis, development safety update report (DSUR)/periodic safety update report (PSUR), and postings for ClinTrial.gov and EudraCT, as defined in this SAP document, have been made prior to the first database lock of the study data for the primary analysis.

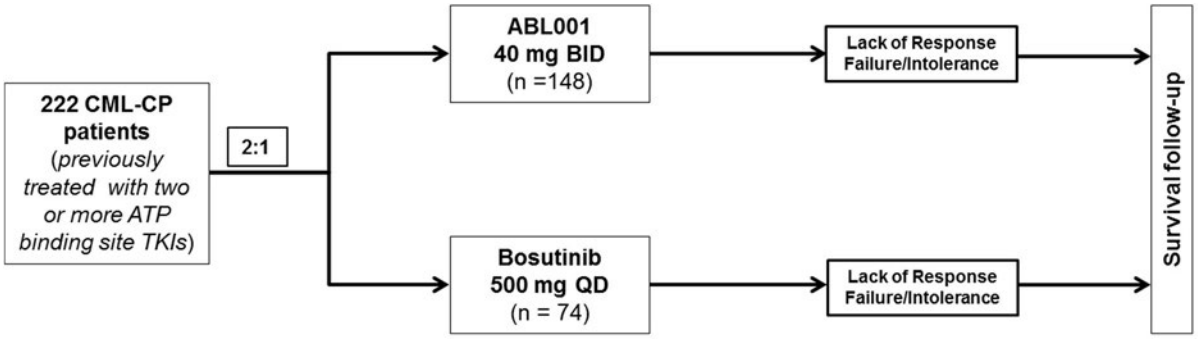
1.1 Study design

This is a randomized, Phase III , open-label, active-controlled, multi-center study comparing safety and efficacy of ABL001 to bosutinib in patients with CML-CP, previously treated with 2 or more tyrosine kinase inhibitors (Figure 1-1). Approximately 220 patients will be randomized to one of the following treatment arms in 2:1 ratio:

- ABL001
- Bosutinib

Randomization will be stratified by the following factor: cytogenetic response status (with or without major cytogenetic response).

Figure 1-1 Schematic of Study Design



Patients will be treated for up to 96 weeks after the last patient received the first study dose (LPFT), if they do not discontinue study treatment earlier. After the study treatment period (i.e. LPFT + 96 weeks), the assigned study treatment will be made available to patients who in the opinion of the investigators are still deriving clinical benefit. This may be outside of this study through alternative options including, but not limited to, an expanded

access/compassionate use/managed access program or access to commercial supplies in applicable countries.

Major Molecular Response (MMR) rate at 24 weeks is the primary endpoint in this study. MMR rate at 96 weeks is the key secondary endpoint.

The primary analysis will be performed after all patients have been followed for at least 24 weeks or have discontinued study earlier. The end of study treatment analysis will be performed after all patients have been followed for at least 96 weeks or have discontinued study earlier. The PFS/OS update analysis will be performed about 5 years after the date the last patient received the first study dose.

No formal interim efficacy analysis is planned in this study. A data monitoring committee (DMC) will monitor unblinded safety data approximately 6 months after the first randomized patient has started study treatment. Subsequent reviews will be conducted approximately every 6 months on an as and when needed basis thereafter (ie. if significant safety findings are noted) until the primary analysis.

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary	
To compare the MMR rate at 24 weeks of ABL001 versus bosutinib	Major Molecular Response (MMR) rate at 24 weeks
Key secondary	
To compare additional parameters of the efficacy of ABL001 versus bosutinib	MMR rate at 96 weeks
Other secondary	
To compare additional parameters of the efficacy of ABL001 versus bosutinib	• Cytogenetic response rate (Complete, Partial, Major, Minor, Minimal, no response) at and by all scheduled data collection time points including 24, 48 and 96 weeks • MMR rate at all scheduled data collection time points (except 24 and 96 weeks which are already covered by primary and key secondary endpoints) • MMR rate by all scheduled data collection time points including 24, 48 and 96 weeks • Time to MMR • Duration of MMR • Time to CCyR • Duration of CCyR • Time to treatment failure • Progression free survival • Overall survival
To compare the safety and tolerability profile of ABL001 versus bosutinib	Type, frequency and severity of adverse events, Changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG and other safety data (vital signs, physical examination)
To characterize the PK of ABL001 in the CML-CP population	Trough plasma concentrations, PK parameters in full PK group: Cmax, Tmax, AUC0-12h, CL/F

Objective	Endpoint
Exploratory	
To evaluate the influence of factors such as cytogenetic response at baseline, failure/intolerance to prior TKIs, line of therapy, gender, race and age on the effect of ABL001 with respect to the primary efficacy endpoint	Major Molecular Response (MMR) rate at 24 weeks
To explore the exposure-response relationships of ABL001; evaluate the effect of population covariates	Exposure-safety, exposure-efficacy, and exposure-biomarker analyses
To characterize mutations in the BCR-ABL1 gene at baseline and at end of treatment and examine their association with molecular and cytogenetic response for ABL001 vs bosutinib	BCR-ABL1 gene mutations at baseline and at end of treatment as determined by Sanger Sequencing
To correlate gene expression profiles in leukemic stem cell (LSC)-enriched blood and bone marrow with response to ABL001 vs. bosutinib	Gene expression profile at baseline and changes to gene expression at end of treatment
To characterize the effect of ABL001 vs. bosutinib treatment on CML LSC and normal progenitor cells (e.g. growth and differentiation) and their bone marrow microenvironment niches	Assess Week 1 Day1 pre-dose and at EOT correlation of molecular and cytogenetic response by flow cytometry analysis of: 1) LSCs; 2) T-cell maturation; 3) T-cell activation and differentiation; 4) myeloid derived suppressor cells in blood and bone marrow aspirates.
	Bone marrow biopsies characterization for adaptive immune response by IHC (Immunohistochemistry) for PD-L1, CD8
To assess clonal evolution during treatment with ABL001 vs. bosutinib	Low level BCR-ABL1 mutation profiles assessed by mass spectrometry at baseline and at EOT.
	Clonal evolution of several genes implicated in CML assessed by Next Generation Sequencing (NGS) methods
To evaluate soluble factors that correlate with response to ABL001 vs. bosutinib treatment in terms of tumor immunogenicity status	Baseline and changes from baseline of cytokine expression in plasma
To compare the impact of treatment on patient reported outcomes (PRO) including CML-specific symptoms, patient quality of life, and impact on work productivity and activity impairment from baseline and EOT between treatment arms in all patients	Change in symptom burden and interference from baseline over time according to the MDASI-CML PRO instrument
	Change in patient's impression of CML symptoms according to PGIC
	Change in health utility from baseline over time according to EQ-5D-5L
To compare the impact of treatment on health care resource utilization between treatment arms in all patients	Health care resource burden over time

2 Statistical methods

2.1 Data analysis general information

The planned analyses will be performed by Novartis and/or a designated CRO. SAS version 9.4 or later will be used to perform all data analyses and to generate tables, figures and listings.

There is no planned interim efficacy analysis. Prior to the database lock for the primary analysis, tables and figures aggregated by treatment arm for safety data review by the data

monitoring committee or for other reporting activities will be produced by an independent statistician and independent statistical programmers.

For between-treatment comparisons of efficacy endpoints, randomization stratification factor, i.e. cytogenetic response status (MCyR vs no MCyR) at screening, will be included in respective stratified statistical tests.

Data included in the analyses

The analysis data cut-off dates for the planned analyses are:

- Primary analysis: After all randomized patients have been on study treatment for 24 weeks or discontinued earlier, i.e., LPFT + 24 weeks.
- End of study treatment analysis: 30 days after all patients have been on treatment for at least 96 weeks or discontinued earlier, i.e., LPFT + 96 weeks + 30 days. (Note: After the study treatment period, the assigned study treatment will be made available, may be outside of this study, to patients who in the opinion of the investigators are still deriving clinical benefit.)
- PFS/OS update analysis: 5 years from the date when the last patient received the first study dose.

All statistical analyses will be performed using all data collected in the database up to the respective data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the respective cut-off date and end date after the respective cut-off date will be reported as ongoing. The same rule will be applied to events starting before or on the respective cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by treatment group; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment group. For pharmacokinetics (PK) concentration and parameters descriptive statistics also include coefficient of variation (CV)%, geo-mean and geo-CV%.

2.1.1 General definitions

Investigational drug and study treatment

Investigational drug, will refer to the ABL001 only. Whereas, ***study treatment*** will refer to ABL001 or control treatment, i.e. bosutinib.

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a non-zero dose of study treatment was administered as per the Dosage Administration Record (DAR) electronic case report form (eCRF). The date of first administration of study treatment will also be referred as ***start of study treatment***.

The date of first administration of study treatment is the same as the date of first administration of investigational drug or control drug.

Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a non-zero dose of study treatment was administered as per DAR eCRF.

The date of last administration of study treatment is the same as the date of last administration of investigational drug or control drug.

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date, etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date, etc.) − reference start date if event precedes the reference start date.

The reference start date for safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, PK, etc.) is the start of study treatment.

The reference start date for all other, non-safety assessments (e.g. molecular response, survival time, disease progression, ECOG performance status, patient reported outcomes (PRO), etc.) is the date of randomization.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 (=365.25/12) days. If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

A week length is defined as 7 days. If duration is reported in weeks, duration in days will be divided by 7.

Baseline

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as "baseline" value or "baseline" assessment. In the context of baseline definition, the efficacy evaluations also include PRO and performance status.

For safety evaluations, the last available assessment on or before the date of start of study treatment is taken as ''baseline" assessment.

For pre-dose electrocardiogram (ECG), the last available assessment before the treatment start date/time is used for baseline.

For ECGs, where study requires multiple replicates per time point, the average of theses measurements would be calculated for baseline (if not already available in the database).

In rare cases where multiple laboratory measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline.

If patients have no value as defined above, the baseline result will be missing.

On-treatment assessment/event and observation periods

For adverse event reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of patient's informed consent to the day before first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date). Note: Patients will be treated for up to LPFT + 96 weeks. This will be the last actual administration of study treatment for each patient if the patient has not discontinued study treatment earlier. After this period, the assigned study treatment will be made available, may be outside of this study, to patients who in the opinion of the investigators are still deriving clinical benefit.
3. ***post-treatment period***: starting at day 31 after last administration of study treatment.

If dates are incomplete in a way that clear assignment to pre-, on-, or post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period

(***treatment-emergent*** AEs). In addition, a separate summary for death including on-treatment and post-treatment deaths will be provided.

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Windows for multiple assessments

In order to summarize molecular response, cytogenetic response, ECG, left ventricular ejection fraction (LVEF), and PK collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the average of the 2 assessments will be used. If multiple assessments on the same date, then the the average will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Table 2-1 Time windows for molecular response

Assessment	Target day of assessment	Time Interval
Baseline	≤ 1	≤ Day 1#
Week 4	22-28	Day 2 to day 38
Week k (k=8, 12)	From d=(k-1)×7+1 to d+6	Day d-11 to day d+16
Week 16	106-112	Day 95 to day 136
Week 24	162-168	Day 137 to day 207
Week k (k=36, 48, …)	From d=(k-1)×7+1 to d+6	Day d-39 to day d+44

Day 1 = Date of randomization

Figure 2-1 Illustrating diagram for time windows for molecular response

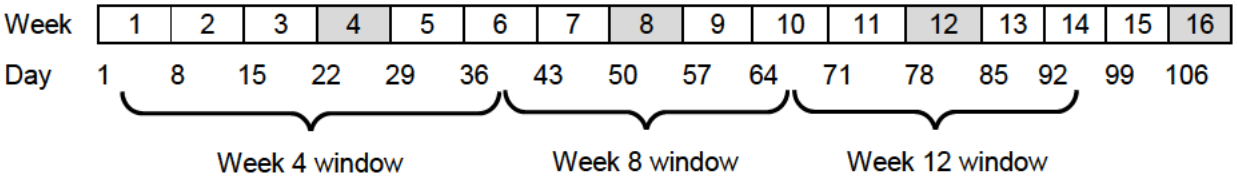


Table 2-2 Time windows for cytogenetic response

Assessment	Target day of assessment	Time Interval
Baseline	≤ 1	≤ Day 1#
Week 12*	78-84	Day 2 to day 122
Week 24	162-168	Day 123 to day 248
Week 48	330-336	Day 249 to day 416
Week 72	498-504	Day 417 to day 584
Week 96	666-672	Day 585 to day 700

Day 1 = Date of randomization
* Optional for patients in bosutinib arm to allow potential intra-patient dose escalation

Table 2-3 Time windows for ECG assessments

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1#
Week 2 Day 1	8	Day 2 to day 14
Week 4	22-28	Day 15 to day 52
Week 12	78-84	Day 53 to day 122
Week 24	162-168	Day 123 to day 329
Week 96	666-672	Day 330 to day 700

Day 1 = Date of first administration of study treatment

Table 2-4 Time windows for LVEF

Assessment	Target day of assessment	Time Interval
Baseline	≤ 1	≤ Day 1#
Week 20	134-140	Day 2 to day 168

Day 1 = Date of first administration of study treatment

Table 2-5 Time windows for pharmacokinetic assessments

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1#
Week 2 Day 1	8	Day 2 to day 14
Week 4	22-28	Day 15 to day 52
Week 12	78-84	Day 53 to day 122
Week 24	162-168	Day 123 to day 329
Week 96	666-672	Day 330 to day 700

Day 1 = Date of first administration of study treatment

For PRO data time windows will be defined for descriptive summary by visit and longitudinal data analysis. If more than one assessment is available in the same time window, the assessment closest to the planned date will be considered. If two assessments are obtained with the same time difference compared to the scheduled visit day, the assessment obtained prior to visit will be considered.

Table 2-6 Time windows for PRO: MDASI-CML, EQ-5D-5L, PGIC

Assessment	Target day of assessment	Time Interval
Baseline	≤ 1	≤ Day 1#
Week 4	22-28	Day 2 to day 38
Week 8	50-56	Day 39 to day 66
Week 12	78-84	Day 67 to day 94
Week 16	106-112	Day 95 to day 136
Week 24	162-168	Day 137 to day 206
Week 36	246-252	Day 207 to day 290
Week 48	330-336	Day 291 to day 500
Week 96	666-672	Day 501 to day 700

Day 1 = Date of randomization

Table 2-7 Time windows for PRO: WPAI-CML

Assessment	Target day of assessment	Time Interval
Baseline	≤ 1	≤ Day 1#
Week 4	22-28	Day 2 to day 52
Week 12	78-84	Day 53 to day 122
Week 24	162-168	Day 123 to day 248
Week 48	330-336	Day 249 to day 500
Week 96	666-672	Day 501 to day 700

Day 1 = Date of randomization

Last contact date

The last contact date will be derived for patients not known to have died at the respective analysis data cut-off date using the last complete date among the following:

Table 2-8 Last contact date data sources

Source data	Conditions
Date of randomization	No condition
Last contact date/last date patient was known to be alive from Survival Follow-up page	Patient status is reported to be alive, lost to follow-up or unknown
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term
Start/End dates from drug administration record	Non-missing dose. Doses of 0 are allowed
End of treatment date from end of treatment page	No condition
Any specific efficacy (molecular or cytogenetic) assessment date if available	Evaluation is marked as 'done'
Laboratory/PK collection dates	Sample collection marked as 'done'
Vital signs date	At least one non-missing parameter value
Performance status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the respective data cut-off date. The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post the cut-off date will be used. Completely imputed dates (e.g. the analysis data cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date.

The last contact date will be used for censoring of patients in the analysis of overall survival.

2.2 Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment and stratum they have been assigned to during the randomization procedure.

Per Protocol Set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the clinical study protocol (CSP). The PPS will be used for sensitivity analyses on the primary endpoint only.

The following list of protocol deviations will lead to exclusion of the patient from the PPS:

- Type of indication different from those required by the CSP, e.g., not CML-CP, BCR-ABL ratio <1% International Scale (IS), with T315I or V299L mutation (INCL03, INCL04, INCL05, EXCL01)
- If prior therapy does not match with CSP requirements in terms of number and types of previous therapy regimens (INCL06)
- Study treatment received different from treatment assigned by randomization (TRT08)

Safety Set

The **Safety Set** includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment actually received.

The actual treatment received corresponds to:

- the randomized treatment if patients took at least one dose of that treatment;
- the first treatment received if the randomized treatment was never received.

Pharmacokinetic Analysis Set

The **Pharmacokinetic Analysis Set (PAS)** includes all patients who provide at least one evaluable PK concentration. For a concentration to be evaluable, patients are required to:

- Take a dose of ABL001 prior to sampling
- Take the same dose of ABL001 for at least 3 consecutive days without dose interruption or dose modification prior to sampling
- For pre-dose samples, do not vomit within 4 hours after the dosing of ABL001 prior to sampling (this is the previous dose); for post-dose samples, do not vomit within 4 hours after the dosing of ABL001 (this is the current dose)
- Have the pre-dose sample collected before the next dose administration

Other analysis sets

- For duration of MMR and time to MMR, the **MMR Responder Set** will be used that is a subset of FAS and includes patients who achieve MMR at any time on study treatment.
- For CCyR rates at and by scheduled time points, the **CCyR Analysis Set** will be used that is a subset of FAS and includes patients who are not in CCyR at baseline.
- For duration of CCyR and time to CCyR, the **Cytogenetic Responder Set** will be use that is a subset of FAS and includes patients who do not have CCyR at baseline and achieve CCyR at any time on study treatment.

Patient Classification

Patients may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific subject classification rules defined in Table 2-9.

Table 2-9 Subject classification based on protocol deviations and non protocol deviation criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written inform consent	Not applicable
Safety set	No written inform consent	No dose of study medication
Per-protocol set	See definition of PPS	Another anti-neoplastic therapy administered after start of study treatment
PK analysis set	No written inform consent	See definition of PAS
MMR Responder Set	Not applicable	See definition of MMR Responder Set
CCyR Analysis Set	Not applicable	See definition of CCyR Analysis Set
Cytogenetic Responder Set	Not applicable	See definition of Cytogenetic Responder Set

Withdrawal of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the eCRF.

2.2.1 Subgroup of interest

Subgroup analyses will use the same method as for the analysis in the respective overall analysis set.

The objective for carrying out these subgroup analyses is to identify potential issues that may be limited to a subgroup of patients, or that are more commonly observed in a subgroup of patients.

Summary tables and figures will be generated only if at least 15 patients are present in each subgroup.

Efficacy

The primary efficacy endpoint will be summarized by the following subgroups to examine the homogeneity of treatment effect provided that the primary efficacy analysis based on the FAS is statistically significant:

- Stratification factor (based on randomization data from Interactive Response Technology [IRT]): "Major Cytogenetic Response" or "No Major Cytogenetic Response"
- Sex: Female or male
- Race: Asian, Caucasian, or others
- Age category (< 65 years, ≥ 65 years)
- Reason for discontinuation of the last prior Tyrosine Kinase Inhibitor (TKI): Failure (i.e. disease progression, lack of efficacy) or intolerance (i.e. adverse event, lack of tolerability).
  Note: Only one reason for discontinuation is allowed for each prior therapy.
- Number of prior TKI therapies: 2 or ≥3
- Historical BCR-ABL1 mutation by local lab: With or without mutation
- Baseline BCR-ABL1 mutation by Sanger Sequencing at central lab: Wild type or mutant

No formal statistical test of hypotheses will be performed for the subgroups, only point estimate of the treatment effect and 95%-confidence intervals will be provided (see Section 2.14 for further analysis details). The objective of the efficacy subgroup analysis is to demonstrate homogeneity of treatment effect in the above subgroups.

Safety

Subgroup analyses for selected safety endpoints will be defined when required.

Japan-specific subgroup analyses

Two subgroups will be formed based on geographic region: Japan or other region (this is not based on ethinicity). These subgroup analyses will be only used for submission to Japan health authority.

Summary tables and figures will be presented for the two subgroups for the following outcome measures:

- Baseline characteristics: Tables of demographics, diagnosis and extent of cancer, extramedullary involvement, bone marrow analysis, patient disposition, analysis sets
- Exposure: Tables of duration of exposure, dose received
- Tables of concomitant medications as well as surgical and medical procedures
- PK (only in ABL001 arm): Table and figure of ABL001 concentration by time, figure of average trough ABL001 concentration from week 2, 4, 12 and 24 vs. BCR-ABL ratio IS (%) at 24 weeks
- AEs: Tables of all AEs, treatment-related AEs, AEs requiring dose adjustment or interruption, AEs requiring additional therapies, serious adverse events (SAEs), adverse events of special interest (AESIs)
- ECG: Tables of Notable ECG values, change from baseline in ECG parameters values
- Lab: Hematology shift table, biochemistry shift table
- Efficacy: Tables of molecular response categories at and by each time point, MMR rate at and by each time point, time to MMR, duration of MMR, cytogenetic response categories at and by each time point, time to CCyR, duration of CCyR, TTF, PFS, OS. Figures of cumulative incidence of MMR and of CCyR.

2.3 Patient disposition, demographics and other baseline characteristics

The FAS will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries will be reported by treatment arm and for all patients, and listings will be reported by treatment arm to assess baseline comparability. No inferential statistics will be provided.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by treatment arm. Categorical data (e.g. age groups: 18 - <65, 65 - <85, and ≥ 85 years, sex, race, ethnicity, ECOG performance status) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height, body mass index) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum), where BMI (kg/m^2) will be calculated as weight[kg] / (height[m]^2) using weight at screening.

In addition, a summary table by sex, age group (18 - <65, 65 - <85, and ≥ 85 years) and treatment group and another summary table by race and treatment group will be generated using the safety set for DSUR/PSUR.

Baseline stratification factors

The number (%) of patients in each stratum ("Major Cytogenetic Response" or "No Major Cytogenetic Response") based on data obtained from the IRT system will be summarized

overall and by treatment arm for the FAS. Discordances between the stratum recorded in IRT at the time of randomization and the actual stratum recorded in the clinical database through the data collected on eCRF will be cross-tabulated and listed.

Diagnosis and extent of cancer

All diagnosis and extent of cancer data will be summarized and listed by treatment arm. One summary table will include time (years) since initial diagnosis (descriptive statistics with N, mean, median, standard deviation, minimum and maximum) and historical mutation (frequency counts and percentages). Another table will include extramedullary involvement (frequency counts and percentages).

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on eCRF will be summarized and listed by treatment arm. The summary will be presented by primary system organ class (SOC), preferred term (PT) and treatment arm. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

In addition, separate listings will be produced for medical history possibly contributing to liver dysfunction, and medical history of protocol solicited cardiovascular events.

Other

All data collected at baseline, including child bearing potential as well as informed consent for additional research on study data and biological samples, will be listed.

2.3.1 Patient disposition

Enrollment by country and center will be summarized for all screened patients and also by treatment arm using the FAS. The number (%) of randomized patients included in the FAS will be presented overall and by treatment group. The number (%) of screened and not-randomized patients and the reasons for screening failure will also be displayed. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment group.

The following summaries will be provided (with % based on the total number of FAS patients):

- Number (%) of patients who were randomized (based on data from IRT system)
- Number (%) of patients who were randomized but not treated (based on DAR eCRF page not completed for any study treatment component)
- Primary reason for not being treated (based on “End of Screening Phase” and “Withdrawl of Informed Consent(s)” eCRF pages)
- Number (%) of patients who were treated (based on DAR eCRF pages of each study treatment completed with non-zero dose administered)

- Number (%) of patients who are still on-treatment (based on the "End of Treatment Disposition" page not completed);
- Number (%) of patients who discontinued the study treatment phase (based on the "End of Treatment Disposition" page)
- Primary reason for study treatment phase discontinuation (based on the "End of Treatment Disposition" page)
- Number (%) of patients who have entered the survival follow-up (based on the "End of Treatment Disposition" page);

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the Study Specification Document) overall and by treatment group for the FAS. All protocol deviations will be listed.

Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized by treatment group and stratum. Reasons leading to exclusion from analysis sets will be listed by treatment group and stratum as well as tabulated overall and by treatment group.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment arm. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of subjects in each interval. The number (%) of subjects who have dose reductions or interruptions, and the reasons, will be summarized by treatment group.

Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study treatment.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to the investigational drug or control:

Duration of exposure to study treatment (days) = (date of last administration of study treatment) – (date of first administration of study treatment) + 1.

The date of last administration of study treatment is defined in Section 2.1.1.

Summary of duration of exposure of study treatment will include categorical summaries based on intervals (<24 weeks, ≥24 weeks, ≥48 weeks, ≥96 weeks) and continuous summaries (i.e. mean, standard deviation etc.).

Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure.

The **planned cumulative dose** for a study treatment refers to the total planned dose as per the protocol up to the last date of study treatment administration. The calculations for the two study treatments are:

- ABL001: 40 mg/administration × 2 (administration/day) × duration of exposure (day)
- Bosutinib: 500 mg/day × duration of exposure prior to dose escalation (day)
  + 600 mg/day × duration of exposure since dose escalation (day),
  where the starting day of dose escalation is identified as the first record in the DAR eCRF with dose increased and reason "As per protocol".

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the DAR eCRF. It is the sum of the non-zero total daily doses recorded over the dosing period. For patients who did not take any drug the actual cumulative dose is by definition equal to zero. The actual cumulative dose will be summarized for each of the study treatment.

Dose intensity and relative dose intensity

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (mg/day) = Actual cumulative dose (mg) / Duration of exposure to study treatment (day).

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as:

PDI (mg/day) = Planned cumulative dose (mg) / Duration of exposure (day).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg/day) / PDI (mg/day).

DI and RDI will be summarized separately for the two study treatments.

Dose changes, interruptions or permanent discontinuations

The number of subjects who have dose increase (allowed for bosutinib starting week 8, see protocol Section 6.2), dose reductions, dose interruptions or permanent discontinuations, and the reasons, will be summarized separately for the two study treatments.

'Dose Changed', 'Dose Interrupted' and 'Dose Permanently Discontinued' fields from the DAR eCRF pages will be used to determine the dose changes, dose interruptions, and permanent discontinuations, respectively.

The corresponding fields 'Reason for Dose Change/Dose Interrupted' and 'Reason for Permanent Discontinuation' will be used to summarize the reasons.

A dose change occurs when total daily dose is different from the most recently planned dose. For patients in ABL001 arm, there is only one planned dose, i.e. 80 mg/day. For patients in bosutinib arm, the initial planned dose is 500 mg/day and could be changed to 600 mg/day in week 8 or later.

For the purpose of summarizing interruptions and reasons, multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in the mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Reduction: A dose change where the actual total daily dose is lower than the most recently planned dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the eCRF, while number of reductions will be derived programmatically based on the change and the direction of the change.

Increase: A dose change where the actual total daily dose is greater than the most recently planned dose. Therefore any dose change to correct a dosing error will not be considered a dose increase. Only dose change is collected in the eCRF, while number of increase will be derived programmatically based on the change and the direction of the change.

2.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

The number and percentage of patients who received any prior anti-neoplastic medications will be summarized by treatment arm for setting (e.g. adjuvant, metastatic, etc.) and also for the lowest anatomical therapeutic classification (ATC) class and preferred term. Summaries will include total number of regimens. A listing will also be produced.

Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD). Details regarding WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by ATC class, preferred term, overall and by treatment group by means of frequency counts and percentages using FAS.

Anti-neoplastic medications will be coded using the WHO-DD. Details regarding WHO-DD version will be included in the footnote in the tables/listings.

Concomitant therapies

Concomitant therapies are defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapies include medications (other than study drugs) and medical

procedures starting on or after the start date of study treatment, or starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO ATC classification system and summarized by the lowest ATC class and PT using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and PT. These summaries will include:

1. Therapies starting on or after the start of study treatment but no later than 30 days after last dose of study treatment and
2. Therapies starting prior to start of study treatment and continuing after the start of study treatment.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

2.5 Analysis of the primary objective

The primary objective of the study is to evaluate the efficacy of ABL001 at the recommended dose in CML patients in chronic phase, previously treated with 2 or more tyrosine kinase inhibitors and to compare this efficacy profile in this population with that achieved by patients receiving bosutinib.

2.5.1 Primary endpoint

The primary efficacy variable of the study is the Major Molecular Response (MMR) rate at 24 weeks. A patient will be counted as having achieved MMR at 24 weeks if he/she meets the MMR criterion (BCR-ABL ratio $\leq$ 0.1%) at 24 weeks. Details of derivation of Polymerase Chain Reaction (PCR) results and calculation of BCR-ABL ratio are presented in Section 5.4.

Further categories of molecular response are defined below:

- 1% < BCR-ABL ratio $\leq$ 10%
- 0.1% < BCR-ABL ratio $\leq$ 1%
- 0.01% < BCR-ABL ratio $\leq$ 0.1%
- 0.0032% < BCR-ABL ratio $\leq$ 0.01%
- BCR-ABL ratio $\leq$ 0.0032%

2.5.2 Statistical hypothesis, model, and method of analysis

The MMR rate at 24 weeks will be calculated based on the FAS and according to the Intent To Treat (ITT) principle. MMR rate and its 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group.

The null hypothesis is that there is no difference between the treatment groups with respect to MMR rate at 24 weeks. The Cochrane-Mantel-Haenszel (CMH) chi-square test, stratified by

the randomization stratification factor, i.e. cytogenetic response status (MCyR vs no MCyR) at screening, will be used to compare MMR rate between the two treatment groups, at the two-sided 5% level of significance. The 95% confidence interval for the difference in MMR rate between treatment groups will be provided using the Wald method. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be presented.

2.5.3 Handling of missing values/censoring/discontinuations

Only patients with MMR at 24 weeks are considered responders. In other words, any patient who achieves MMR before 24 weeks, but is no longer in MMR at 24 weeks, will be considered as a non-responder in this primary analysis. Patients discontinuing the randomized treatment prior to 24 weeks due to any reason will be considered as non-responders.

One exception to the rule above is if the 24-week PCR evaluation is missing, but both a PCR evaluation at 16 weeks and a PCR evaluation at 36 weeks indicate MMR, the 24-week assessment is imputed as a 'Response', assuming that MMR is maintained between 16 and 36 weeks.

2.5.4 Supportive analyses

The CMH chi-square test of MMR rate at 24 weeks, stratified by the randomization stratification factor (MCyR vs no MCyR at screening), will be repeated using the PPS, if the PPS is different from the FAS.

Additional exploratory logistic regression and subgroup analyses are described in Section 2.14.

2.6 Analysis of the key secondary objective

The key secondary objective of the study is to compare additional parameters of the efficacy of ABL001 versus bosutinib.

2.6.1 Key secondary endpoint

The key secondary endpoint is MMR rate at 96 weeks, which is defined as the proportion of patients with MMR at 96 weeks and derived in a similar fashion to MMR rate at 24 weeks.

2.6.2 Statistical hypothesis, model, and method of analysis

The null hypothesis is that there is no difference between the treatment groups with respect to MMR rate at 96 weeks. Following a gatekeeping procedure to control the overall alpha level, only if the primary endpoint is significant, formal statistical testing of the key secondary endpoint with two-sided 5% level of significance will be performed using the CMH chi-square test, stratified by the randomization stratification factor, i.e. cytogenetic response status (MCyR vs no MCyR) at screening.

MMR rate and its 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. The 95% confidence interval for the difference in MMR rate between treatment groups will be provided using the Wald method. The Mantel-Haenszel

estimate of the common risk difference and the corresponding 95% confidence interval will also be presented.

2.6.3 Handling of missing values/censoring/discontinuations

Only patients with MMR at 96 weeks are considered responders. In other words, any patient who achieves MMR before 96 weeks, but is no longer in MMR at 96 weeks, will be considered as a non-responder. Patients discontinuing the randomized treatment prior to 96 weeks due to any reason will be considered as non-responders.

2.7 Analysis of secondary efficacy objective(s)

The other secondary efficacy objective is to compare additional parameters (defined below) of the efficacy of ABL001 versus bosutinib.

2.7.1 Secondary endpoints

2.7.1.1 Molecular response

MMR rates at all scheduled data collection time points, except for 24 weeks and 96 weeks which are already covered by primary and key secondary endpoints. In addition to baseline assessment, the time points include week 4, 8, 12, 16, 36, 48, 60, 72, 84, 108, 120, 132, 144, 156, 168, and end of treatment.

MMR rates by all scheduled data collection time points, i.e., week 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156 and 168, and end of treatment. These are cumulative MMR rates by time points and are defined as the proportion of patients who achieve MMR at or before specified visits, i.e. if a patient achieves an MMR but then loses it before or at a specific visit, he/she will still be classed as achieving MMR by that specific time point.

Time to MMR is defined for patients in the Molecular Responder Set as: date of first MMR - date of randomization + 1.

Duration of MMR is defined for patients in the Molecular Responder Set as the time between the date of the first documented MMR and the end date of MMR, i.e. the earliest date of loss of MMR, progression to accelerated phase (AP)/blast crisis (BC), or CML-related death.

Loss of MMR is defined as confirmed loss of a greater than or equal to 3.0 log reduction in BCR-ABL transcript levels compared to the standardized baseline value (= confirmed loss of a less than or equal to 0.1% BCR-ABL/ABL by international scale) in association with a $\geq$ 5-fold rise in BCR-ABL from the lowest value achieved on study treatment confirmed by a duplicate analysis of the same sample. This result has to be confirmed by a subsequent sample within 4-6 weeks unless it is associated with confirmed loss of complete hematologic response (CHR) or loss of CCyR or progression to AP/BC or CML-related death.

For patients for whom none of the events above is reported, the duration will be censored (see Section 2.7.3). The duration of MMR is calculated as: end date or censoring date of MMR - date of first MMR + 1.

2.7.1.2 Cytogenetic response

At each assessment time point the cytogenetic response status of each patient is classified as complete, partial, major, minor, minimal response and none:

- Complete response (CCyR): 0% Philadelphia chromosome positive (Ph+) metaphases
- Partial response (PCyR): >0 to 35% Ph+ metaphases
- Major response (MCyR = CCyR + PCyR): 0 to 35% Ph+ metaphases
- Minor response (mCyR): >35 to 65% Ph+ metaphases
- Minimal response: >65 to 95% Ph+ metaphases
- None: >95 to 100% Ph+ metaphases.

CCyR rates at all scheduled data collection time points, i.e., week 24, 48, 72 and 96, and end of treatment. Such rates are defined as the proportion of patients in CCyR at the respective time points among patients in the CCyR Analysis Set, which excludes patients who are in CCyR at baseline.

CCyR rates by all scheduled data collection time points, i.e., week 24, 48, 72 and 96, and end of treatment. Such rates are defined as the proportion of patients who achieve CCyR at or before the respective time points among patients in the CCyR Analysis Set.

Time to CCyR is defined for patients in the Cytogenetic Responder Set as: date of first documented CCyR - date of randomization + 1.

Duration of CCyR is defined for patients in the Cytogenetic Responder Set as the time between date of first documented CCyR and the end date of CCyR, i.e. the earliest date of loss of CCyR, progression to AP/BC, or CML-related death. For patients for whom none of the events above is reported or the last PCR evaluation on treatment indicating MMR, the duration will be censored (see Section 2.7.3). The duration of CCyR is calculated as: end date or censoring date of CCyR - date of first CCyR + 1.

2.7.1.3 Other secondary efficacy endpoints

Time to treatment failure (TTF) is defined for patients in FAS as the time from date of randomization to an event of treatment failure. The following events will constitute 'treatment failure', and are based on the ELN criteria [Baccarani et al. 2013] defining failure of a second line treatment adapted to include discontinuation of randomized treatment as an event:

- No CHR or > 95% Ph+ metaphases at three months after randomization or thereafter
- BCR-ABL ratio > 10% IS and/or > 65% Ph+ metaphases at six months after randomization or thereafter
- BCR-ABL ratio > 10% IS and/or > 35% Ph+ metaphases at 12 months after randomization or thereafter
- Loss of CHR, CCyR or PCyR at any time after randomization
- Detection of new BCR-ABL1 mutations at any time after randomization
- Confirmed loss of MMR in 2 consecutive tests, of which one must have a BCR-ABL ratio ≥ 1% IS 6 months after randomization

- New clonal chromosome abnormalities in Ph+ cells: CCA/Ph+: at any time after randomization
- Discontinuation from randomized treatment for any reason

TTF is calculated as: date of treatment failure or censoring date (see Section 2.7.3) - date of randomization + 1.

Progression-Free-Survival (PFS) is defined for patients in FAS as the time from the date of randomization to the earliest occurrence of documented disease progression to AP/BC or the date of death from any cause (including progressions and deaths observed during the survival follow-up period). PFS is calculated as: date of disease progression/death or censoring date (see Section 2.7.3) - date of randomization + 1.

Overall survival (OS) is defined for patients in FAS as the time from the date of randomization to the date of death (including the survival follow-up period). OS is calculated as: date of death or censoring date (see Section 2.7.3) - date of randomization + 1.

2.7.2 Statistical hypothesis, model, and method of analysis

No confirmatory statistical testing of non-key secondary efficacy endpoints will be performed, however, nominal p-values will be presented for exploratory purposes (as specified in protocol Section 10.5.2).

MMR rates at and by time points

The FAS will be used for these endpoints. For each time point the MMR rate and the associated 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. The respective null hypothesis of each MMR rate is that there is no difference between treatment groups. Statistical testing will be performed via CMH chi-square tests stratified by the randomization strata, i.e. MCyR vs no MCyR at screening. A 95% confidence interval for the difference in each MMR rate between treatment groups will be provided using the Wald method. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

The cumulative incidence of MMR by treatment group will be graphically displayed by an increasing step function. Each curve will increase each time (after randomization) at which a new responder is observed and thus will increase up to the best observed response rate (e.g. up to 50% if half of the patients in the analysis population are able to achieve MMR).

Molecular response at and by time points

Frequency and percentage of all molecular response categories (defined in Section 2.5.1) by treatment arm using FAS will be presented for each time point.

For the by-time-points summary, the within-patient best molecular response category up to the specific time points is used to calculate the frequency and percentage.

Time to MMR

The MMR Responder Set will be used. Descriptive statistics (minimum, maximum, median, quartiles, mean, sd) of time to MMR will be provided for the two treatment groups separately.

Duration of MMR

The MMR Responder Set will be used. The survival distribution of duration of MMR will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals [Brookmeyer and Crowley 1982] of the medians, along with the proportion of patients who are still in MMR at 24, 48, 72 and 96 weeks and the associated 95% confidence intervals, will be presented for each treatment group.

CCyR rates at and by time points

The CCyR Analysis Set will be used for these endpoints.

For each time point the CCyR rate and the associated 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. The respective null hypothesis of each CCyR rate is that there is no difference between treatment groups. Statistical testing will be performed via CMH chi-square tests stratified by the randomization strata, i.e. MCyR vs no MCyR at screening. A 95% confidence interval for the difference in each CCyR rate between treatment groups will be provided using the Wald method. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

The cumulative incidence of CCyR by treatment group will be graphically displayed by an increasing step function. Each curve will increase each time (after randomization) at which a new responder is observed and thus will increase up to the best observed response rate (e.g. up to 50% if half of the patients in the analysis population are able to achieve CCyR).

Cytogenetic response at and by time points

Frequency and percentage of all cytogenetic response categories (defined in Section 2.7.1.2) by treatment arm using FAS will be presented for each time point. A shift table comparing baseline and best post-baseline cytogenetic response categories by treatment will also be presented. All assessments of cytogenetic response categories will also be listed by treatment arm.

For the by-time-points summary, the within-patient best cytogenetic response category up to the specific time points is used to calculate the frequency and percentage.

Assessments of bone marrow aspirate at different time points will also be summarized.

Time to CCyR

The Cytogenetic Responder Set will be used. Descriptive statistics (minimum, maximum, median, quartiles, mean, sd) of time to CCyR will be provided for the two treatment groups separately.

Duration of CCyR

The Cytogenetic Responder Set will be used. The survival distribution of duration of CCyR will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals [Brookmeyer and Crowley 1982] of the medians, along with the

proportion of patients who are still in CCyR at 24, 48, 72 and 96 weeks and the associated 95% confidence intervals, will be presented for each treatment group.

TTF, PFS and OS

For each endpoint the respective null hypothesis is that there is no difference between treatment groups. Distribution of each endpoint will be compared between two treatments using a stratified log-rank test at an overall two-sided 5% level of significance. The stratification will be based on the randomization stratification factor, i.e. cytogenetic response status (MCyR vs no MCyR) at screening.

For each endpoint the survival distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals [Brookmeyer and Crowley 1982] of the medians, along with the proportion of patients who have not experienced the respective events at 1, 3 and 5 years and the associated 95% confidence intervals, will be presented for each treatment group. The hazard ratio will be calculated, along with its 95% confidence interval, using a stratified Cox model.

2.7.3 Handling of missing values/censoring/discontinuations

MMR rates at specific time points: Patients discontinuing the randomized treatment prior to a specific time point due to any reason will be considered as non-responders for that time point.

Molecular response at specific time points: The category "Missing" will be assigned to

- Ongoing cases, i.e. patients who have not discontinued study treatment and have not been treated sufficiently long for a specific time point
- Discontinued due to progressive disease/death prior to a specific time point
- Discontinued due to other reasons prior to a specific time point

Duration of MMR: For patients who have not experienced any event (loss of MMR, progression to AP/BC, or CML-related death) the duration will be censored at the last molecular assessment (PCR) date on treatment.

CCyR rates at specific time points: Patients discontinuing the randomized treatment prior to a specific time point due to any reason will be considered as non-responders for that time point.

For the primary analysis and the end of study treatment analysis, the cytogentic response of patients who have not discontinued study treatment and have not been treated sufficiently long for a specific time point will be classified as "Missing".

Cytogenetic response at specific time points: The category "Missing" will be assigned to

- Ongoing cases, i.e. patients who have not discontinued study treatment and have not been treated sufficiently long for a specific time point
- Discontinued due to progressive disease/death prior to a specific time point
- Discontinued due to other reasons prior to a specific time point

Duration of CCyR: For patients who have not experienced any event (loss of CCyR, progression to AP/BC, or CML-related death) the duration will be censored at the last cytogenetic assessment date on treatment or the last PCR evaluation on treatment indicating MMR.

TTF: For patients who have not reached treatment failure, their TTFs will be censored at the time of last study assessment (PCR, cytogenetic, hematologic or extramedullary) before the cut-off date.

PFS: For patients who have not experienced an event (disease progression to AP/BC or death from any cause), their PFS times will be censored at the date of last study assessment (PCR, cytogenetic, hematologic or extramedullary) before the cut-off date.

OS: Patients who are alive at the time of the analysis data cutoff date will be censored at the date of last contact (see Section 2.1.1) before the cut-off date.

2.8 Safety analyses

All safety analyses will be based on the safety set. All listings and tables will be presented by treatment group.

2.8.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on treatment period. All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome, etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sorting order for the preferred term will be based on their frequency in the ABL001 arm.

The following adverse event summaries will be produced by treatment arm: overview of adverse events and deaths, AEs by SOC and PT, summarized by relationship, seriousness, leading to treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy, and leading to fatal outcome. For posting to ClinTrial.gov and EudraCT, a summary table of on-treatment deaths and serious AEs and another summary table of non serious AEs by treatment, both including occurrences (an occurrence is defined as >1 day between start and prior end date of record of same preferred term) and sorted by SOC and PT, will be presented as well.

2.8.1.1 Adverse events of special interest / grouping of AEs

Data analysis of AESIs

An adverse event of special interest (AESI) is a grouping of adverse events that are of scientific and medical concern specific to compound ABL001. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HLGTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. The latest approved version of CRS prior to the respective database lock will be used.

For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized.

Summaries of these AESIs will be provided by treatment arm (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, hospitalization, death, etc.). If sufficient number of events occurred, analysis of time to first occurrence will be applied.

A listing of all grouping levels down to the MedDRA PTs used to define each AESI will be generated.

2.8.2 Deaths

Separate summaries for on-treatment and all deaths *(including post-treatment deaths)* will be produced by treatment arm, system organ class and preferred term.

All deaths will be listed, where post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

2.8.3 Laboratory data

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. Details of CTCAE grading and imputation rules are presented in Appendix 5.3.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

On analyzing laboratory data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date.

The following summaries will be produced separately for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline in the on-treatment period.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

The following listings will be produced separately for hematology and biochemistry for the laboratory data:

- Listings of all laboratory data, with CTCAE grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTCAE grade 3 or 4 laboratory toxicities

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized:

The following summaries will be produced:

- ALT or AST > 3x upper limit of norm (ULN)
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

12-lead ECGs including PR, QRS, QT, QTcF and RR intervals will be obtained centrally for each subject during the study. ECG data will be read and interpreted centrally.

The echocardiogram will be performed and evaluated locally to assess the left ventricular ejection fraction (LVEF).

Data handling

The average of the triplicate ECG parameters at each time point will be used in the analyses.

Data analysis

The number and percentage of subjects with notable ECG values will be presented by treatment arm. Notable values are defined below:

- QT, QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

A listing of all ECG assessments will be produced by treatment arm and notable values will be flagged. A separate listing of only the subjects with notable ECG values will also be produced. In each listing the assessments collected during the post-treatment period will be flagged.

Change from baseline ECG parameters by timepoint will also be summarized by treatment.

A listing of all LVEF assessments will be produced by treatment arm. In the listing, the assessments collected outside of on-treatment period will be flagged. A summary table by treatment arm with descriptive statistics for LVEF at different timepoints (baseline, week 20) and for change from baseline will be presented. A shift table for LVEF categories (≤40%, 41-49%, ≥50%) at baseline versus worst value on treatment will also be presented.

2.8.4.2 Cardiovascular risk factor assessment

Prior to randomization and at the end of treatment, for each patient information of the following risk factors is collected: heavy smoking, low physical activity, unhealthy diet, and other. A listing by treatment arm will be presented.

Family medical history of each patient for ischemic heart disease, cardiac arrhythmia, sudden death, high cholesterol, diabetes mellitus, heart defects (congenital heart disease), and heart failure is also collected prior to randomization and at the end of treatment. A listing by treatment arm will be presented.

2.8.4.3 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

The number and percentage of subjects with notable vital sign values (high/low) in systolic blood pressure, diastolic blood pressure, pulse rate, weight and temperature will be presented by treatment arm.

A listing of all vital sign assessments will be produced by treatment arm and notable values will be flagged. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.8.4.4 Liver events

There are separate eCRF pages to collect acetaminophen/paracetamol, autoimmune, drug use 6 months prior to liver event, immunoglobulin, liver function tests, pathology, related imaging, viral serology and potential impact of alcohol use, and an overview eCRF page. Data on the overview eCRF page will be listed by treatment arm. Assessments collected during the post-treatment period will be flagged.

2.8.4.5 Pulmonary function tests

Data of pulmonary function tests will be listed by treatment arm. Assessments collected during the post-treatment period will be flagged.

2.8.5 Additional Analyses

Not applicable.

2.9 Pharmacokinetic endpoints

PK parameters

The PK parameters that will be determined are shown in Table 2-10. The PK parameters for ABL001 are derived based on the non-compartmental methods using Phoenix WinNonlin® software version 6.4 in patients with full PK sampling in PAS.

Table 2-10 Non-compartmental PK parameters for ABL001 in full PK group

AUC0-12h	The area under the plasma concentration-time curve from time zero to 12 hours ($ng*hr*mL^{-1}$)
AUClast	The AUC from time zero to the last measurable plasma concentration sampling time (Tlast) ($ng*hr*mL^{-1}$)
Cmax	The maximum (peak) observed plasma concentration after dose administration (ng/mL)
Tmax	The time to reach maximum (peak) plasma concentration after dose administration (hr)
Tlast	The time to reach the last measurable plasma concentration after dose administration (hr)
CL/F	The total apparent body clearance of drug from the plasma after oral administration ($L*hr^{-1}$)

Descriptive statistics (n, arithmetic mean, CV% mean, standard deviation (SD), median, geometric mean, CV% geo-mean, minimum and maximum) will be presented by treatment for PAS for all PK parameters defined in Table 2-10 except Tmax, where only n, median, minimum and maximum will be presented.

All individual PK parameters will be listed for patients treated with ABL001 and with full PK sampling in the safety set.

PK concentrations

Descriptive statistics (n, m (number of non-zero concentrations), arithmetic mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum) for ABL001 concentration will be presented at each scheduled time point for the PAS.

The mean (+/- SD) and geometric mean concentration-time profiles for ABL001 over time will be displayed graphically for PAS on the linear and semi-log view.

All individual plasma ABL001 concentration data will be listed for patients treated with ABL001 in the Safety Set.

Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ, 1 ng/mL) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing values for any PK data will not be imputed and will be treated as missing.

2.10 PD and PK/PD analyses

The potential relationship between ABL001 exposure (e.g. trough concentration) and efficacy, pharmacodynamics (PD) or safety endpoints may be assessed by graphic exploration and/or statistical modeling, as appropriate, including effect of population covariates. Additional exposure-response analyses for ECG may be conducted. The concentration data may be analyzed by a population approach to evaluate the influence of covariates on drug exposure. If applicable, the details of the above-mentioned analyses will be described in a separate analysis plan and reported separately.

The relationship between average trough plasma concentration up to 24 weeks and BCR-ABL ratio IS (%) at 24 weeks will be assessed by graphic exploration.

2.11 Patient-reported outcomes

The FAS will be used for analyzing PRO data unless specified differently. The MDASI CML, PGIC along with EQ-5D-5L will be used to assess patient's disease-related symptoms and health-related quality of life from baseline to EOT; and the WPAI-CML will be used to assess work productivity and activity impairment related to the patient's CML. All tools require patient's direct completion and will be administered utilizing electronic device for data collection at scheduled time points from screening to end of treatment.

The baseline is defined in Section 2.1.1. Patients with an evaluable baseline score and at least one evaluable post-baseline score during the treatment period will be included in the change from baseline analyses. Missing data items in a scale will be handled according to the manual for each instrument. No imputation will be applied if the total or subscale scores are missing at a visit. All measures will assess differences between the treatment arms.

Compliance to the schedule of administration of each PRO questionnaire will be summarized by treatment group, for baseline and scheduled post-baseline assessment time points. The following categories, as collected on the eCRF, will be used to describe whether the questionnaire was completed at a specific time point:

1. yes, fully completed
2. yes, partly completed
3. no

Repeated measures model for continuous scores

To best utilize the repeated assessments of a given PRO score, a repeated measures model for longitudinal data will be used to estimate differences between treatment arms. This repeated measures model will include terms for treatment, the stratification factor (major cytogenetic response status), time, baseline value as main effects, and an interaction term for treatment by time. This analysis will be restricted to patients with an evaluable baseline score and at least one evaluable post-baseline score. All data collected until end of treatment (including the end of treatment assessment) will be included in the analysis. Note that only data collected under treatment (i.e. while the patient is treated) will be included. The end of treatment assessment will be included if collected within 7 days of the last dose intake.

Time will be considered as a continuous variable expressed in weeks, i.e. considering that the PRO score follow a linear trend.

As a first approach, an unstructured correlation matrix will be used to model the correlation within patients. The structure of the correlation matrix will be investigated and simplified using likelihood ratio tested if appropriate.

2.11.1 MDASI-CML

The M.D. Anderson Symptom Inventory – Chronic Myeloid Leukemia (MDASI-CML) questionnaire is planned to be administered during screening, at weeks 4, 8, 12, 16, 24, 36, 48 and 96 after randomization.

The MDASI-CML is a 26 item self-administered questionnaire for adult CML patients. Twenty of the items measure the severity of disease-related symptoms and are scored from 0 (Not present) to 10 (As bad as you can imagine) and 6 items that measure symptom interference with daily life scored from 0 (Did not interfere) to 10 (Interfered completely).

The severity score will be calculated when a patient scores at least 11 items out of the 20 severity items using the formula: (sum of scores for the items answered) / (number of items answered). If a patient scores fewer than 11 items, the severity score will be missing.

The interference score will be calculated when a patient scores at least 4 items out of the 6 interference items using the formula: (sum of scores for the items answered) / (number of items answered). If a patient scores fewer than 4 items, the interference score will be missing.

For the severity score and interference score, descriptive statistics (n, mean, SD, median, 25th and 75th percentiles) by treatment arm will be provided for the actual scores and changes from baseline scores at each scheduled assessment time point.

Between-treatment differences for the change in severity and interference scores will be evaluated using the above-mentioned repeated measures model.

2.11.2 EQ-5D-5L

EQ-5D-5L is a two-part standardized instrument for measuring health outcomes in a wide range of health conditions and treatments. It consists of a descriptive system and a visual analogue scale (EQ VAS). The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems (or unable to perform the activity). The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'worst imaginable health state'.

The EQ-5D-5L data will be used to calcutae utility values for the economic evaluation of ABL001 and bosutinib in a separate analysis.

The EQ-5D-5L questionnaire is planned to be administered during screening, at weeks 4, 8, 12, 16, 24, 36, 48 and 96 after randomization.

Descriptive system

The number and percentage of subjects in the five levels of each EQ-5D demension will be presented by treatment group at each assessment time point.

EQ VAS

The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale from 0, labeled as 'worst imaginable health state', to 100, labeled as 'best imaginable health state'.

For the EQ VAS, descriptive statistics (n, mean, SD, median, 25th and 75th percentiles) by treatment arm will be provided for actual values and for the change from baseline at each assessment time point.

Between-treatment differences for the changes in EQ VAS score will be evaluated using the above-mentioned repeated measures model.

2.11.3 WPAI-CML

The Work Productivity and Activity Impairment Questionnaire – Chronic Myeloid Leukemia (WPAI-CML) questionnaire is planned to be administered during screening, at weeks 4, 12, 24, 48 and 96 after randomization.

The WPAI-CML is a six-item questionnaire which is intended to measure work and activity impairment associated with CML for those who self-identify as currently employed for pay. This questionnaire measures self-reported productivity loss associated with CML during the past seven days. It consists of questions about absence from work due to CML, hours spent at work, the reduction in productivity at work attributed to CML, and the reduction in productivity while performing regular activities. WPAI-CML outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes. Scoring will be done according to WPAI-CML instrument guidance resulting in four scores including: Percent work time missed due to problem; percent impairment while working due to problem; Percent overall work impairment due to problem; and, percent activity impairment due to problem.

Descriptive statistics (n, mean, SD, median, 25th and 75th percentiles) for each of the four derived outcome scores and changes from baseline scores will be presented by treatment arm at each scheduled assessment time point with .

Between-treatment differences for the changes in each of the four outcome scores will be evaluated using the above-mentioned repeated measures model.

2.11.4 PGIC

The Patient Global Impression of Change (PGIC) instrument is planned to be administered during screening, at weeks 4, 8, 12, 16, 24, 36, 48 and 96 after randomization

The PGIC is comprised of a single question intended to measure a patient's perspective of improvement or deterioration over time relative to treatment. The PGIC uses a seven-point

scale where one (1) equals very much improved and seven (7) equals very much worse. Missing values will not be imputed.

The number and percentage of subjects in each of the seven categories for PGIC will be presented by treatment group at each assessment time point.

2.12 Resource utilization

Data relating to resource utilization (described in trial protocol Section 7.2.5) from the FAS will be used for the purpose of economic evaluation, which will be carried out and reported as a separate activity outside the CSR.

The measures of healthcare resource utilization (HCRU) include: hospitalization (H), emergency room (ER) visit, general practitioner (GP) visits, specialist (Sp) visit and urgent care (UC) visit. HCRU will be assessed as follows: frequency and duration of hospitalization from baseline up to end of treatment; frequency of emergency room visits from baseline up to end of treatment; frequency of additional outpatient office visits general practitioner, specialist, and urgent care visits from baseline up to end of treatment. Hospitalization visits will also record the number of days on ward and the type of ward (hospital unit) and the discharge status. At each HCRU collected, the reason for the visit, i.e. related to CML, AE related to CML therapy or other reason, will be collected, in order to quantify the impact of treatment on healthcare resources.

HCRU data by treatment arm will be summarized in the primary analysis CSR and the end of study treatment CSR, with descriptive statistics (n, mean, median, SD, min, max) for quantitative variables, and count and percentage for qualitative variables.

2.13 Biomarkers

As a project standard, Novartis will analyze only biomarkers collected in the clinical database. For exploratory markers, since the studies are not adequately powered to assess specific biomarker-related hypotheses, the goal of these exploratory statistical analyses should be considered as the generation of new scientific hypotheses. No adjustment for multiple comparisons is usually planned for exploratory analyses. Furthermore, additional post hoc exploratory assessments are expected and may be performed.

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue their analysis due to either practical or strategic reasons. Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

If not otherwise specified, the FAS will be used for all biomarker analyses on patients with biomarker data.

Exploratory biomarker objectives

- To characterize mutations in the BCR-ABL1 gene at baseline and at end of treatment and examine their association with molecular and cytogenetic response for ABL001 vs bosutinib
- To correlate gene expression profiles in leukemic stem cell (LSC)-enriched blood and bone marrow with response to ABL001 vs. bosutinib
- To characterize the effect of ABL001 vs. bosutinib treatment on CML LSC and normal progenitor cells (e.g. growth and differentiation) and their bone marrow microenvironment niches
- To assess clonal evolution during treatment with ABL001 vs. bosutinib
- To evaluate soluble factors that correlate with response to ABL001 vs. bosutinib treatment in terms of tumor immunogenicity status

Only some analyses for the first exploratory biomarker objective about BCR-ABL1 mutation listed above are described here and the results will be included in the respective CSRs. Additional analyses for this and other exploratory biomarker objectives will be described in separate analyses plans, with results reported separately.

List of biomarkers evaluated and the collection time points

The biomarkers evaluated in the study are listed in Table 2-11 below.

Table 2-11 Sample biomarker summary table

Biomarker	Time point	Sample	Method
Immune markers PD-L1 and CD8	Screening and end of treatment	Bone marrow biopsy	Immunohisto-chemistry
$CD34^+$ enriched leukemic stem cells	Screening, week 24 and end of treatment	Bone marrow aspirate	RNA analysis
Leukemic stem cells characterization	Screening, week 24 and end of treatment	Bone marrow aspirate	Flow cytometry
BCR-ABL1 gene mutation	W1D1 pre-dose and end of treatment. If mutation is present at baseline, then also every 12 weeks after baseline	Peripheral blood	Sanger Sequencing
$CD34^+$ enriched leukemic stem cells	W1D1 pre-dose and end of treatment	Peripheral blood	RNA analysis
Low level mutations in BCR-ABL1 gene	W1D1 pre-dose and end of	Peripheral blood	Mass spectrometry

Biomarker	Time point	Sample	Method
	treatment		and NGS
ABL001 mode of action in patients treated with ABL001: T-cell maturation, activation and differentiation along with maturing myeloid and leukemic stem cell panels	W1D1 pre-dose, Week 4, 8, 12, 24, 36, 48, 60, 72, 84, 96 and end of treatment	Peripheral blood	Flow cytometry
Circulating cytokines in plasma	W1D1 pre-dose, Week 48 and end of treatment	Peripheral blood	MSD and ELISA
Genetic variant analysis of the UGT1A1 gene	W1D1	Peripheral blood	Sanger Sequencing

General data handling and preprocessing

For bone marrow samples the latest assessment during screening period will be used as the baseline value, while for blood samples the week 1 day 1 (W1D1) pre-dose assessment will be used as the baseline value.

When more than one biomarker data value are available for a subject at any time point, the mean of the replicate values will be used for all statistical analyses.

2.13.1 Somatic mutation biomarker data handling and analysis

Handling of somatic biomarker data

Overall, somatic mutation status (wild type or mutant) will be derived from the mutational status of the interrogated exons for the BCR-ABL1 gene by Sanger Sequencing. These may be non-exclusive and the presence of mutation across more than one exon will be reported in separate categories.

Mutation summary statistics

All somatic mutation data will be reported using counts and percentages by the mutation type in the form of contingency tables with the rows containing the different mutations assayed, and the treatment groups in the columns. All the mutation categories for a gene will also be aggregated into mutant, wild type or missing/unknown groups and counts/percentages will be reported by these three categories as well. A summary table will be presented for baseline mutations and another summary table for post-baseline new mutations (not present at baseline).

All the mutation data will be listed for each subject ordered by treatment group.

Association between biomarkers and clinical outcome

This analysis does not adjust for multiple comparisons and results may have higher false positive rates.

The relationship between baseline BCR-ABL1 gene mutation data (wild type or mutant) and outcome data (with or without MMR at and by 24 and 96 weeks using FAS, with or without CCyR at and by 24 and 96 weeks using CCyR analysis set) will be explored by reporting contingency tables and by applying a logistic regression including treatment group, baseline BCR-ABL1 gene mutation and their interaction as covariates. Treatment group will be included in this summary table.

In addition, the same analysis will be performed for

- the relationship between post-baseline new BCR-ABL1 mutation (with or without new mutation) up to 48 weeks and outcome data (with or without MMR at 48 and 96 weeks using FAS, with or without CCyR at 48 and 96 weeks using CCyR analysis set).
- the relationship between post-baseline new BCR-ABL1 mutation (with or without new mutation) up to end of treatment and outcome data (with or without MMR at 96 weeks using FAS, with or without CCyR at 96 weeks using CCyR analysis set).

The odds ratios bewteen treatment groups with 95% confidence intervals will be reported, for each biomarker category and overall. If treatment by biomarker interaction is significant (e.g. when $p < 0.1$), overall odds ratio for treatment will not be reported.

2.14 Other exploratory analyses

MMR rate at 24 weeks

The FAS will be used for the following exploratory analyses:

1. A logistic regression model adjusted for the stratification factor will be fit to assess treatment effect. An adjusted odds ratio for the treatment effect with associated 95% confidence intervals will be presented. Mantel-Haenszel estimates of the common odds ratio and the corresponding 95% confidence interval will also be provided.
2. Based on the subgroups specified in Section 2.2.1, the following analyses will be performed for each subgroup:
   - Proportion of patients with MMR at 24 weeks and its 95% confidence interval based on the Pearson-Clopper method within each treatment group
   - The difference in MMR rate at 24 weeks between treatment groups and the corresponding Wald 95% confidence interval

   Efficacy analyses in subgroups will be purely exploratory and are intended to explore the consistency of treatment effect. Forest plot (n, risk difference, Wald 95% confidence interval) will be produced to graphically depict the treatment effect estimates in different subgroups. No inferential statistics (p-values) will be produced for the subgroups.
3. A logistic regression model adjusted for the stratification factor and other important variables identified by the subgroup analyses above will be fit to assess treatment effect. An adjusted odds ratio for the treatment effect with associated 95% confidence intervals will be presented.

Association between historical BCR-ABL1 mutations and clinical outcome

The relationship between historical BCR-ABL1 gene mutation data (with or without mutation) from local lab and outcome data (with or without MMR at and by 24 and 96 weeks using FAS, with or without CCyR at and by 24 and 96 weeks using CCyR analysis set) will be explored by reporting contingency tables and by applying a logistic regression including treatment group, baseline BCR-ABL1 gene mutation and their interaction as covariates. Treatment group will be included in this summary table.

Influence of early molecular response levels on long term molecular response levels

The relationship between MMR status at 24 weeks and MMR status at 48 and 96 weeks will be explored using FAS by reporting contingency tables and by applying a logistic regression including treatment group, MMR status at 24 weeks and their interaction as covariates. Treatment group will be included in this summary table. The odds ratios between treatment groups with 95% confidence intervals will be reported, for each category of MMR status at 24 weeks and overall. If the interaction of treatment by MMR status at 24 weeks is significant (e.g. when $p < 0.1$), overall odds ratio for treatment will not be reported.

2.15 Interim analysis

No formal interim analysis is planned for this trial.

3 Sample size calculation

3.1 Primary analysis

To test the null hypothesis that the MMR rate at 24 weeks is equal in the two treatment arms, based on two-sided 5% level of significance and with 90% power, 222 patients will be needed in total (i.e. 148 patients in the ABL001 arm and 74 patients in the bosutinib arm based on 2:1 randomization allocation). The calculations were made using the software package PASS (2008).

It is assumed that ABL001 leads to a 20% improvement in the MMR rate at 24 weeks over bosutinib from 15% to 35% which corresponds to an odds ratio of 3.05. The assumed bosutinib MMR rate of 15% at 24 weeks is based on previous trials evaluating bosutinib therapy ([Kuoury et al. 2012], [Gambacorti-Passerini et al. 2014], [García-Gutiérrez et al. 2015]).

3.2 Power for analysis of key secondary variables

If the primary analysis of MMR rate at 24 weeks is statistically significant, then the key secondary endpoint MMR rate at 96 weeks will be tested, with the overall alpha controlled at the 5% two-sided level using a gatekeeping strategy.

Table 3-1 below summarizes the treatment effects of the key secondary endpoint which can be detected with 80% and 90% power, based on the specified assumptions regarding the bosutinib effect. The calculations were made using the software package PASS (2008).

Table 3-1 Detectable effect sizes for key secondary endpoint

Endpoint	Anticipated effect with bosutinib	2-sided alpha	Power	Detectable effect size§
MMR rate at 96 weeks	30%*	0.05	90%	≥ 23%
			80%	≥ 20%

*: [Gambacorti-Passerini et al. 2014], Figure 1D.
§: Absolute difference from the anticipated effect with bosutinib.

For MMR rate at 96 weeks, if the anticipated effect with bosutinib is 30%, then the given sample size with 2-sided alpha=0.05 would allow to detect an absolute difference of at least 23% (i.e. MMR rate at 96 weeks with ABL001 is at least 53%) for 90% power and of at least 20% (i.e. MMR rate at 96 weeks with ABL001 is at least 50%) for 80% power.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rules should be used for the imputation of the dose end date for a given study treatment component.

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

- Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.
- Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

  Use Dec31yyyy

- Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

  Use EOT date
- Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date:

  Use last day of the Month (mm)
- All other cases should be considered as a data issue and the statistician should contact the data manager of the study.
- After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

  Use the treatment start date

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE, ConMeds and safety assessment date imputation

The imputations specified in this section are only used for analyses of time to and duration of AEs and concomitant medications.

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	**Rule**
day, month, and year	• No imputation will be done for completely missing dates
day, month	• If available year = year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY o Else set start date = study treatment start date. • If available year > year of study treatment start date then 01JanYYYY • If available year < year of study treatment start date then 01JulYYYY
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	**Rule** (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawl of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as ‘ongoing’ rather than the end date provided.

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

5.2 AEs coding/grading

Adverse events are coded using the latest available version of Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters (embedded below). The latest available version of the document based on the underlying CTCAE version v4.03 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

EASE LAB - CTC grades in Novartis On

Imputation Rules

CTCAE grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of white blood cells (WBC).

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

The following rules will be applied to derive the WBC differential percentages when only differential counts are available for a xxx differential

xxx %value = (xxx count × 100) / WBC count

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1 and calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTCAE grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTCAE grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

5.4 Derivation of PCR results and loss of response

Scaling towards an international standard will be performed for all molecular results using laboratory specific conversion factors. In this process, the raw ratio between BCR-ABL and the control gene ABL is calculated and multiplied by the lab-specific conversion factor ([Branford and Hughes 2006]). Therefore, using the international unit, the BCR-ABL ratio will be presented in %. The MRDx assay using PAXgene™ Blood RNA tubes from MMD laboratory will be used in this study. The lab conversion factor for this assay is 1.1.

The BCR-ABL ratio in IS % is calculated by multiplying the raw BCR-ABL ratio with the lab-specific conversion factor and then by 100:

BCR-ABL ratio (in %) = (BCR-ABL / ABL) * conversion factor * 100

For consistency with elsewhere reported molecular response rates, the result may be expressed also as log-reduction. This is defined as the following:

BCR-ABL Log-Reduction = $-\log_{10}$ (BCR-ABL ratio in %)

For example, $-\log_{10}$ (0.001) = 3 log reduction for a ratio of 0.1%.

The following binary variables will be used when molecular response is reported.

Table 5-3 Response categories for molecular response

MR (Molecular Response)	BCR-ABL ratio (%)	Log-reduction category

MMR	Yes	≤ 0.1%	≥ 3-log reduction
	No	> 0.1%	< 3-log reduction
MR4.5	Yes	≤ 0.0032%	≥ 4.5-log reduction
	No	> 0.0032%	< 4.5-log reduction

Loss of MMR is defined in Section 2.7.1.1.

5.5 Statistical models

5.5.1 Primary analysis

The null hypothesis of equality of MMR rate at 24 weeks in the two treatment arms will be tested against two-sided alternative. The statistical hypotheses are:

$$H0: RA_{24wk} = RB_{24wk} \text{ versus } HA: RA_{24wk} \neq RB_{24wk}, \text{ for a two-sided test}$$

where RA_{24wk} is the probability of MMR rate at 24 weeks in ABL001 arm and RB_{24wk} is the probability of MMR rate at 24 weeks in bosutinib arm.

The Cochran-Mantel-Haenszel chi-square test X^2_{CMH} (implemented via SAS procedure FREQ with CMH option in the TABLES statement) will be used to test the difference in response rates between the treatment arms. The p-value corresponding to the CMH test for "general association" will be used which follows a Chi-square distribution with one degree of freedom.

The 95% confidence interval for the difference in MMR rate at 24 weeks between treatment groups will be provided using the Wald method (implemented via SAS procedure FREQ with RISKDIFF option in the TABLES statement, under the default METHOD=WALD and VAR=SAMPLE). If the 2×2 table is with ABL001 in row 1, bosutinib in row 2, MMR in column 1 and No MMR in column 2, then the SAS output will give the estimate of (risk for MMR at 24 weeks in ABL001 – risk for MMR at 24 weeks in bosutinib). The corresponding Mantel-Haenszel estimate of common risk difference and 95% confidence interval will also be presented (with RISKDIFF(COMMON) option in the TABLES statement, taking the Mantel-Haenszel estimate from the SAS output table).

If the sampling assumptions for chi-square test is not met (i.e. the expected frequencies should exceed 5 for all of table cells), the exact Cochran-Mantel-Haenszel test will be used (implemented via SAS procedure MULTTEST). The test is performed by running a stratified version of the Cochran-Armitage permutation test [Armitage et al. 1969]. In studies with stratified randomization, the chi-square approximation is considered appropriate for the X^2_{CMH} statistics if the rule of Mantel and Fleiss [Mantel and Fleiss 1980] is satisfied.

Confidence interval for MMR rate within each treatment arm

MMR will be summarized in terms of percentage rates with 95% confidence interval using exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table [Clopper and Pearson 1934]).

5.5.2 Key secondary analysis

The null hypothesis of equality of MMR rate at 96 weeks in the two treatment arms will be tested against two-sided alternative. The statistical hypotheses are:

$$H0: RA_{96wk} = RB_{96wk} \text{ versus } HA: RA_{96wk} \neq RB_{96wk}, \text{ for a two-sided test}$$

where RA_{96wk} is the probability of MMR rate at 96 weeks in ABL001 arm and RB_{96wk} is the probability of MMR rate at 96 weeks in bosutinib arm.

The same approaches as for the primary endpoint (Section 5.5.1) will be applied here for the Cochran-Mantel-Haenszel chi-square test X^2_{CMH}, the 95% Wald confidence interval for the difference in MMR rate at 96 weeks between treatment groups, the Mantel-Haenszel estimate of common risk difference with 95% confidence interval, and the confidence interval for MMR rate within each treatment arm.

Multiplicity adjustment

Formal statistical testing of the key secondary endpoint will be performed with $\alpha = 0.05$ (two-sided) only if the primary endpoint is significant by means of a gatekeeping procedure to control the overall alpha level.

5.5.3 Other analyses

Mantel-Haenszel common odds ratio

To obtain Mantel-Haenszel estimates of the common odds ratio and the corresponding 95% confidence interval in exploratory analyses, it requires SAS procedure FREQ with CMH and RELRISK options in the TABLES statement.

Logistic Regression

Odds ratio will be used as a measure of association between treatment and response in exploratory analyses (Section 2.14). The odds ratio will be derived from the logistic regression model (implemented using SAS procedure LOGISTIC, with treatment specified as an explanatory variable in the CLASS statement) which allows for including not only the stratification factor but also for adjustments for other covariates (both categorical and continuous). The odds ratio will be presented with 95% Wald confidence limits.

In cases where an exact test has been used to compare response rates, the odds ratio should be determined using exact logistic regression, and the odds ratio presented with exact 95% confidence limits. In these cases, SAS PROC LOGISTIC with EXACTONLY option will be used.

Kaplan-Meier estimates

An estimate of the survival function in each treatment group will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with

METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

Hazard ratio

Hazard ratio will be estimated by fitting the Cox proportional hazards model using SAS procedure PHREG (with TIES=EXACT option in the MODEL statement).

A stratified unadjusted Cox model will be, i.e. the MODEL statement will include the treatment group variable as the only covariate and the STRATA statement will include stratification variable(s). Hazard ratio with two-sided 95% confidence interval will be based on Wald test.

6 Reference

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NOVARTIS

Clinical Development

ABL001/asciminib

CABL001A2301

A phase 3, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors

Statistical Analysis Plan (SAP) – Amendment 3

Author: Statistician, [redacted]

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
25-Aug-2017	Prior to DB lock for primary analysis	Creation of final version	N/A - First version	NA
26-Mar-2020	Prior to DB lock for primary analysis	Implementation of protocol amendments 2 and 3.	ABL001 has been replaced by International Nonproprietary Name (INN) asciminib.	Throughout the SAP amendment
			Introduction of the switch to asciminib option for patients experiencing treatment failure on bosutinib treatment	Section 1.1, Figure 1-1 Sections 2.1, 2.3 Analyses added throughout the document
			Update of the definition of end of study treatment	Section 1.1
			Added a potential End-of-Study-Treatment analysis different from the 96-week analysis	
			Addition/removal of secondary safety objectives and exploratory efficacy objectives	Table 1-1
		Additional analyses, clarification	Clarification on which data are included in the analyses, which assessments are considered for safety and efficacy analyses	Section 2.1
			Addition of the treatment arms and definition of the date of end of study treatment Removal of windows defined for ECGs, LVEF and PK assessments as they are not needed.	Section 2.1.1

	As per Health Authorities request, addition of the breakdown per different time points of the number (%) of patients who discontinued the study treatment phase and of the primary reason for study treatment phase discontinuation	Section 2.3.1
	PAS: Removal of the condition related to vomiting to consider a concentration evaluable as the occurrence and time of vomiting is not collected in the CRF.	Section 2.2
	Addition of a subgroup "Stratum reported in the CRF" for the analysis by subgroup of the primary endpoint (to take into account the mistratification cases)	Section 2.2.1
	Removal of the subgroup "with or without historical BCR-ABL1 mutation by local lab" as this is not considered clinically relevant	
	Additional analyses of prior TKI and non TKI antineoplastic therapies	Section 2.4.2
	Implementation of the estimand language for the primary and key secondary objectives	Sections 2.5 and 2.6
	Addition of a sensitivity analysis of the primary estimand stratifying by the stratum recorded in the CRF to take into account that many stratification errors occurred	Section 2.5.5
	Addition of Time-to-event analyses for time to MMR and time to CCyR	Section 2.7.2

			Added how time is censored for time to MMR/CCyR, clarification on how to handle missing BMA assessments due to MMR being achieved	Section	2.7.3
			Added analyses AEs and SAEs incidence rates by adjusting for exposure and by reporting by time intervals to account for potential difference in exposure between the treatment arms	Section	2.8.1
			Clarified handling of unscheduled ECG measurements in the analyses	Section	2.8.4.1
4-June-2020	Prior to DB lock for primary analysis	Creation of amendment 2.0	Clarified baseline for mutations	Section	2.1.1
			Clarified EOT is mapped to defined time points		
			Modified age subgroup, added Line of therapy subgroup and moved Without T315I/V299L to Supplementary analysis (All patients with T315I/V299L mutations identified at the Week 1 Day 1 visit are discontinued from study treatment when the mutation results become available). Clarified Mutation subgroup doesn't include T315I/V299L mutations.	Section	2.2.1
			Modified age categories	Section	2.3
			Added COVID-19 related PDs analysis	Section	2.3.1
			Added definitions of time on treatment, duration of exposure in patient-years and average daily dose	Section	2.4.1

	Additional analyses of prior TKI therapy	Section	2.4.2
	Added summary of concomitant therapies for on-switched treatment period.	Sections	2.5.5, 2.6.5
	Added COVID-19 sensitivity analyses for the primary and key secondary endpoints	Section	2.5.6
	Added a supplementary analysis to the primary endpoint (Patients without T315I/V299L mutations at Week 1 Day 1 visit)	Section	2.9
	Added new graph for Ctrough values of asciminib	Section	4
	Updated the list of changes to the protocol specified analyses	Section	5.3
	Added imputation rules for immature cells		
	Removed imputation rules for corrected calcium as corrected calcium is collected		
	Clarified all available values for BUN and UREA will be reported under the parameter name BUN in listing to avoid double reporting of same information	Section	5.4.1
	Definition of loss of MMR: Removed reference to confirmation of loss of CHR/CCyR	Section	5.4.3
	Loss of CHR: clarified "Progressive splenomegaly refractory to therapy" is ≥ 5cm below left intercostal margin"	Section	5.4.4
	Implemented change to definition of treatment failure (Protocol amendment 3)	Section	5.4.5

			Clarified what "Thrombocytopenia (<100 x 109/L) that is unrelated to therapy" is.	Section 5.5.
			Added derivation of response rates and categories section	
7-Aug-2020	Prior to DB lock for primary analysis	Creation of amendment 3.0 after FDA type C teleconference on 28 July 2020	As agreed with FDA, added sensitivity analyses of the primary and key secondary endpoints without the imputation rule used in the main analyses in case of missing PCR evaluations at 24/96 weeks.	Section 2.5.5
			Per FDA request, added another subgroup of interest: BCR-ABL ratio at baseline ≥ 1% or <1%.	Section 2.2.1
			Added calculation rules for duration of interrruption.	Section 2.4.1
			Added derivation rule for corrected calcium using the reported total calcium value and albumin.	Section 5.3
			Aligned the definition of loss of CCyR with the definition of loss of CHR by adding the requirement that loss of CCyR (Ph+ bone marrow cells to > 0%) must have led to treatment discontinuation because of lack of efficacy.	Section 5.4.2

Table of contents

List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AP	Accelerated phase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic classification
AUC	Area under the curve
BC	Blast crisis
bid	bis in diem/twice a day
CCyR	Complete cytogenetic response
CHR	Complete hematologic response
CMH	Cochrane-Mantel-Haenszel
CML	Chronic myelogenous leukemia
CML-CP	Chronic myelogenous leukemia in chronic phase
CRO	Contract research organization
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
DAR	Dosage administration record
DI	Dose intensity
DMC	Data monitoring committee
DRL	Drug reference listing
DSUR	Development safety update report
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End of treatment in the treatment phase (patient level)
EOsT	End of study treatment (study level)
ER	Emergency room
FAS	Full analysis set
FD	First dose date of study treatment during the treatment phase
FD_{switch}	First dose date of asciminib during the treatment switch phase
GP	General practitioner
H	Hospitalization
HCRU	Health care resource utilization
HLT	High level term
HLGT	High level group term
IRT	Interactive response technology
IS	International scale
LD	Last dose date of study treatment during the treatment phase
LD_{switch}	Last dose date of asciminib during the treatment switch phase

LLOQ	Lower limit of quantitation
LPFT	Last patient first treatment
LSC	Leukemic stem cell
LVEF	Left ventricular ejection fraction
MCyR	Major cytogenetic response
mCyR	Minor cytogenetic response
MedDRA	Medical dictionary for regulatory activities
MMR	Major molecular response
NCI	National Cancer Institute
NGS	Next generation sequencing
NMQ	Novartis MedDRA Query
OS	Overall survival
PAS	Pharmacokinetic analysis set
PCR	Polymerase chain reaction
PCyR	Partial cytogenetic response
PD	Pharmacodynamic
PDI	Planned dose intensity
PFS	Progression-free rurvival
Ph+	Philadelphia chromosome positive
PK	Pharmacokinetics
PPS	Per-protocol set
PRO	Patient-reported outcomes
PSUR	Periodic safety update report
PT	Preferred term
qd	Qua'que di'e / once a day
RDI	Relative dose intensity
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
S-EoT	End of treatment in the treatment switch phase (patient level)
SMQ	Standardized MedDRA query
SOC	System organ class
Sp	Specialist
TBL	Total bilirubin
TKI	Tyrosine kinase inhibitor
TTF	Time to treatment failure
UC	Urgent care
ULN	Upper limit of norm
VAS	Visual analogue scale
W1D1	Week 1 Day 1
WBC	White blood cells
WHO-DD	World Health Organization Drug Dictionary

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses of primary objective, secondary objectives and selected exploratory objectives for the clinical study reports (CSR) of study CABL001A2301, a phase 3, multi-center, open-label, randomized study of oral asciminib versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors.

The content of this SAP is based on protocol CABL001A2301 version 03. All decisions regarding safety monitoring analysis for the data monitoring committee, 24-week primary analysis, 96-week analysis, end of study treatment analysis, 5-year progression-free survival (PFS)/overall survival (OS) update analysis, and postings for ClinTrial.gov and EudraCT, as defined in this SAP document, have been made prior to the first database lock of the study data for the primary analysis.

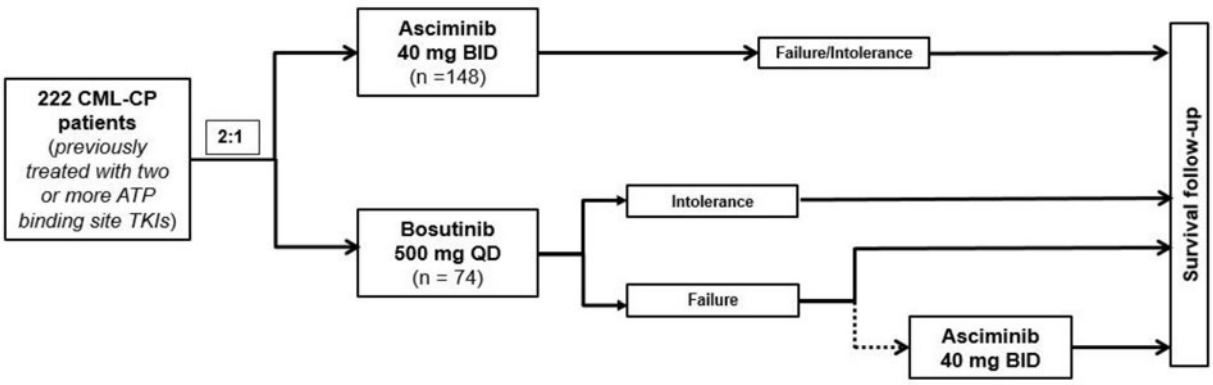
1.1 Study design

This is a randomized, Phase III , open-label, active-controlled, multi-center study comparing safety and efficacy of asciminib to bosutinib in patients with CML-CP, previously treated with 2 or more tyrosine kinase inhibitors (Figure 1-1). Approximately 220 patients will be randomized to one of the following treatment arms in 2:1 ratio:

- asciminib 40 mg BID
- Bosutinib 500 mg QD

Randomization will be stratified by the following factor: cytogenetic response status (with or without major cytogenetic response).

Figure 1-1 Schematic of Study Design



Patients with documented treatment failure (as per the 2013 ELN guidelines, Baccarani et al 2013) while on bosutinib treatment will have the option to switch to asciminib treatment within

96 weeks after the last patient has been randomized on study. The patients who switch to asciminib will be able to receive asciminib up to the end of study treatment (EOsT) period.

Patients will be treated up to the EOsT defined as up to 96 weeks after the last patient received the first study dose (LPFT) or up to 48 weeks after the last patient has switched to asciminib treatment whichever is longer, if they do not discontinue study treatment earlier. After the EOsT, the assigned study treatment will be made available to patients who in the opinion of the investigators are still deriving clinical benefit. This may be outside of this study through alternative options including, but not limited to, an expanded access/compassionate use/managed access program or access to commercial supplies in applicable countries.

Major Molecular Response (MMR) rate at 24 weeks is the primary endpoint in this study. MMR rate at 96 weeks is the key secondary endpoint.

Four analyses are planned for this study, including the 24-week primary analysis, the 96-week analysis, the End-of-Study-Treatment (EOsT) analysis, and Progression-Free survival/Overall survival (PFS/OS) update analysis The timing when those analyses are conducted is summarized in Section 2.1.

No formal interim efficacy analysis is planned in this study. A data monitoring committee (DMC) will monitor unblinded safety data approximately 6 months after the first randomized patient has started study treatment. Subsequent reviews will be conducted approximately every 6 months and when needed thereafter (ie. if significant safety findings are noted) until the primary analysis.

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary	
To compare the MMR rate at 24 weeks of asciminib versus bosutinib	Major Molecular Response (MMR) rate at 24 weeks
Key secondary	
To compare additional parameters of the efficacy of asciminib versus bosutinib	MMR rate at 96 weeks
Other secondary	
To compare additional parameters of the efficacy of asciminib versus bosutinib	• Cytogenetic response rate (Complete, Partial, Major, Minor, Minimal, no response) at and by all scheduled data collection time points including 24, 48 and 96 weeks • MMR rate at all scheduled data collection time points (except 24 and 96 weeks which are already covered by primary and key secondary endpoints) • MMR rate by all scheduled data collection time points including 24, 48 and 96 weeks • Time to MMR • Duration of MMR • Time to CCyR • Duration of CCyR • Time to treatment failure • Progression free survival

Objective	Endpoint
	• Overall survival
To compare the safety and tolerability profile of asciminib versus bosutinib	Type, frequency and severity of adverse events, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG and other safety data (vital signs)
To characterize the PK of asciminib in the CML-CP population	Trough plasma concentrations, PK parameters in full PK group: Cmax, Tmax, AUC0-12h, CL/F
To assess the safety of asciminib when administered as treatment after bosutinib failure according to the 2013 ELN Guidelines	Type, frequency and severity of adverse events, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG and other safety data (vital signs)

Objective	Endpoint
Exploratory	
To evaluate the influence of factors such as cytogenetic response at baseline, failure/intolerance to prior TKIs, line of therapy, gender, race and age on the effect of asciminib with respect to the primary efficacy endpoint	Major Molecular Response (MMR) rate at 24 weeks
To explore the exposure-response relationships of asciminib; evaluate the effect of population covariates	Exposure-safety, exposure-PD analyses
To characterize mutations in the BCR-ABL1 gene at Week 1 Day 1, upon confirmed loss of MMR and/or at end of treatment and examine their association with molecular and cytogenetic response for asciminib vs bosutinib	BCR-ABL1 gene mutations at Week 1 Day 1, upom confirmed loss of MMR and/or at end of treatment as determined by Sanger Sequencing
To understand biology of CML and bone marrow microenvironment on leukemic stem cells (LSCs) eradication, including patients' immunogenicity	Bone marrow biopsies characterization for adaptive immune response by immunohistochemistry (IHC); bone marrow aspirates to evaluate the effect of treatments on LSCs burden and immune cells subsets changes by flow cytometry
To assess clonal evolution during treatment with asciminib vs. bosutinib	Low level BCR-ABL1 mutation profiles assessed by mass spectrometry at Week 1 Day 1, upon confirmed loss of MMR and/or at EOT. Clonal evolution of several genes implicated in CML assessed by Next Generation Sequencing (NGS) methods
To evaluate soluble/inflammarory factors that correlate with response to asciminib vs. bosutinib treatment	Baseline and changes from baseline of cytokine expression in plasma
To compare the impact of treatment on patient reported outcomes (PRO) including CML-specific symptoms, patient quality of life, and impact on work productivity and activity impairment from baseline and EOT between treatment arms in all patients	Change in symptom burden and interference from baseline over time according to the MDASI-CML PRO instrument Change in patient's impression of CML symptoms according to Patient Global Impression of Change (PGIC) Change in health utility from baseline over time according to EQ-5D-5L Change in work productivity and activity impairment over time according to WPAI
To compare the impact of treatment on health care resource utilization between treatment arms in all patients	Health care resource burden over time

2 Statistical methods

2.1 Data analysis general information

The planned analyses will be performed by Novartis and/or a designated CRO. SAS version 9.4 or later will be used to perform all data analyses and to generate tables, figures and listings.

There is no planned interim efficacy analysis. Prior to the database lock for the primary analysis, tables and figures aggregated by treatment arm for safety data review by the data monitoring committee or for other reporting activities will be produced by an independent statistician and independent statistical programmers.

For between-treatment comparisons of efficacy endpoints, randomization stratification factor, i.e. cytogenetic response status (MCyR vs no MCyR) at screening, will be included in respective stratified statistical tests.

Data included in the analyses

The analysis data cut-off dates for the planned analyses are:

- Primary analysis: After all randomized patients have been on study treatment for 24 weeks or discontinued earlier, i.e., LPFT + 24 weeks.
- 96-week analysis: After all randomized patients have been on study treatment for 96 weeks or discontinued earlier, i.e., LPFT + 96 weeks
- End of study treatment analysis: 30 days after the EOsT. (Note: After the study treatment period, the assigned study treatment will be made available, may be outside of this study, to patients who in the opinion of the investigators are still deriving clinical benefit.)
- PFS/OS update analysis: 5 years from the date when the last randomized patient received the first study dose (irrespective of treatment switch for patients failing bosutinib).

All statistical analyses will be performed using all data collected in the database up to the respective data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the respective cut-off date and end date after the respective cut-off date will be reported as ongoing. The same rule will be applied to events starting before or on the respective cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by treatment group; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment group. For pharmacokinetics (PK) concentration and parameters descriptive statistics also include coefficient of variation (CV)%, geo-mean and geo-CV%.

2.1.1 General definitions

Investigational drug and study treatment

Investigational drug, will refer to the asciminib only. Whereas, ***study treatment*** will refer to asciminib or control treatment, i.e. bosutinib, received during the treatment phase. Switched treatment will refer to asciminib received during treatment switch phase.

Treatment arms

- Asciminib (Subjects randomized to asciminib arm at the beginning of the study)
- Bosutinib (Subjects randomized to bosutinib arm at the beginning of the study)

Date of end of study treatment (EOsT)

The EOsT date is the date that the study treatment is ended for the entire study. On this date, patients are treated for at least 96 weeks if they are not eligible to switch study treatment or are treated for at least 48 weeks after they have switched to asciminib treatment, unless patients have discontinued study treatment earlier

Date of first administration of randomized study treatment

The date of first administration of randomized study treatment (FD) is derived as the first date when a non-zero dose of study treatment was administered as per the Dosage Administration Record (DAR) electronic case report form (eCRF). The date of first administration of study treatment will also be referred as ***start of study treatment***.

The date of first administration of randomized study treatment is the same as the date of first administration of investigational drug or control drug.

Date of first administration of switched treatment

For subjects switching from bosutinib to asciminib, the date of first administration of switched treatment (FD_{switch}) is derived as the first date when a non-zero dose of asciminib was administered as per the DAR eCRF. The date of first administration of switched treatment (asciminib) will also be referred as ***start of switched treatment***.

Date of last administration of randomized study treatment

The date of last administration of randomized study treatment (LD) is defined as the last date when a non-zero dose of study treatment was administered as per DAR eCRF. For subjects switching from bosutinib to asciminib, this includes the dose of bosutinib administered as bridging therapy between their treatment failure and the first dose of asciminib administered.

The date of last administration of randomized study treatment is the same as the date of last administration of investigational drug or control drug.

Date of last administration of switched treatment

The date of last administration of switched treatment (LD_{switch}) is defined as the last date when a non-zero dose of switched treatment (asciminib) was administered as per DAR eCRF.

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date, etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date, etc.) − reference start date if event precedes the reference start date.

The reference start date for safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, PK, etc.) is the start of study treatment.

The reference start date for all other, non-safety assessments (e.g. molecular response, survival time, disease progression, ECOG performance status, patient reported outcomes (PRO), etc.) is the date of randomization.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Switch study day

The switch study day, describes the day of the event or assessment date, relative to the start of switched treatment.

Switch study day = date of event ‑ start of switched treatment + 1, if event is on or after the start of switched treatment

Switch study day = date of event ‑ start of switched treatment, if event precedes the start of switched treatment

The switch study day will be displayed in the data listings if an event starts on or after the start of switched treatment.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 (=365.25/12) days. If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

A week length is defined as 7 days. If duration is reported in weeks, duration in days will be divided by 7.

Baseline for the treatment period

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as “baseline” value or “baseline” assessment. In

the context of baseline definition, the efficacy evaluations also include PRO and performance status.

For safety evaluations, the last available assessment, including unscheduled assessments before the date of start of study treatment is taken as ‘‘baseline” assessment.

For pre-dose electrocardiogram (ECG), the last available assessment before the treatment start date/time is used for baseline.

For ECGs, where study requires multiple replicates per time point, the average of theses measurements would be calculated for baseline (if not already available in the database).

For mutations, the Week 1 Day 1 assessment is taken as “baseline” assessment.

In rare cases where multiple laboratory measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline.

If patients have no value as defined above, the baseline result will be missing.

Baseline for the treatment switch period

For subjects switching from bosutinib to asciminib, the last non-missing assessment, including unscheduled assessments before the date of first administration of asciminib is taken as ‘‘baseline” assessment for the switched treatment period, and denoted as baseline_switch for short.

On-treatment assessment/event and observation periods

For adverse event reporting the overall observation period will be divided into three mutually exclusive segments for subjects without treatment switching and into up to five mutually exclusive segments for subjects switching treatment:

For subjects without treatment switching:

1. ***pre-treatment period***: from day of patient’s informed consent to the day before first administration of study treatment (FD)
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of study treatment (including start and stop date) (LD). Note: Patients will be treated up to the end of study treatment period (EOsT). This will be the last actual administration of study treatment for each patient if the patient has not discontinued study treatment earlier. On this date, all patients without treatment switching will have been treated for at least 96 weeks unless patients have discontinued study treatment earlier. After this period, the assigned study treatment will be made available, may be outside of this study, to patients who in the opinion of the investigators are still deriving clinical benefit.
3. ***post-treatment period***: starting at day 31 after last administration of study treatment.

For subjects with treatment switching from bosutinib to asciminib:

1. ***pre-treatment period***: from day of patient's informed consent to the day before first administration of study treatment (FD)
2. ***on-treatment period***: from date of first administration of study treatment to either the day before the first administration of asciminib (FD_{switch}) or 30 days after the date of last actual administration of bosutinib (LD), whichever comes first.
3. ***post-treatment period***: from day 31 after last administration of bosutinib to the day before the first administration of asciminib (FD_{switch}). If the end date is before the start date, this period is not applicable.
4. ***on-switched treatment period***: from date of first administration of asciminib (FD_{switch}) to 30 days after date of last actual administration of asciminib (LD_{switch}).
   NOTE: Subjects are treated in the study up to end of study treatment period (EOsT). On this date, all subjects with treatment switching will have been treated for at least 48 weeks after switching unless they have discontinued the switched treatment earlier.
5. ***Post-switched treatment period:*** from day 31 after last actual administration of asciminib (LD_{switch}).

If dates are incomplete in a way that clear assignment to pre-, on-, post-, on-switched-, post-switched-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

Safety summaries (tables, figures) on the Safety set (respectively on the Switch Analysis Set) include only data from the on-treatment (resp. on-switched treatment) period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In particular, summary tables for adverse events (AEs) will summarize only on-treatment (resp. on-switched treatment) events, with a start date during the on-treatment (resp. on-switched treatment) period (***treatment-emergent*** AEs) (resp. switched-treatment-emergent AEs). In addition, a separate summary for death including on-treatment and post-treatment deaths will be provided.

However, all safety data (including those from the pre-treatment, post-treatment and post-switched treatment period) will be listed and flagged as appropriate.

Efficacy summaries on the FAS (apart from OS and PFS) include data from baseline up to either the last assessment on or before the EoT visit or before or on treatment failure, whichever is the earliest.

Efficacy summaries on the Switch Analysis Set include data from baseline_switch up to the last assessment on or before the S-EoT visit or before or on treatment failure during the switched treatment period, whichever is the earliest.

The efficacy assessments collected post-treatment failure, post-EoT or post S-EoT visit are not included in any efficacy analyses (except for OS and PFS analyses). However, they will be listed and flagged as appropriate.

Windows for multiple assessments

Data such as molecular response, cytogenetic response collected over time (including unscheduled visits) will be summarized by scheduled time point. As patients do not always adhere to the visit schedule, visits will be remapped according to visit windows defined in Tables 2-1 to Table 2-4 of this document to enable by-visit analysis. Only those protocol-defined visits will have the visit window defined. Each assessment (including the end of treatment assessment), either scheduled or unscheduled, will have a mapped visit assigned, as long as study day is available, according to the defined visit window up to the date with data included.

If more than one assessment is assigned to the same time window, the assessment performed closest to the target date will be used for by-visit statistical analyses. If 2 assessments within a visit window are equidistant from the target date, then the average of the 2 assessments will be used. If multiple assessments on the same date, then the the average will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Table 2-1 Time windows for molecular response

Assessment	Target day of assessment	Time Interval
Baseline	≤ 1	≤ Day 1#
Week 4	29	Day 2 to day 43
Week 8	57	Day 44 - 71
Week 12	85	Day 72 - 99
Week 16	113	Day 100 to day 141
Week 24	169	Day 142 to day 211
Week k (k=36, 48, …)	kx7 + 1	Day kx7-40 – kx7+43

Day 1 = Date of randomization
EOT assessments are mapped to the time points as needed.

Table 2-2 Time windows for cytogenetic response

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1#
Week 24	169	Day 2 to day 253
Week 48	337	Day 254 to day 421
Week 72	505	Day 422 to day 589
Week 96	673	Day 590 to day 700

Day 1 = Date of randomization
EOT assessments are mapped to the time points as needed.

For PRO data time windows will be defined for descriptive summary by visit and longitudinal data analysis. If more than one assessment is available in the same time window, the assessment closest to the planned date will be considered. If two assessments are obtained with the same time difference compared to the scheduled visit day, the assessment obtained prior to visit will be considered.

Table 2-3 Time windows for PRO: MDASI-CML, EQ-5D-5L, PGIC

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1#
Week 4	29	Day 2 - 43
Week 8	57	Day 44 - 71
Week 12	85	Day 72 - 99
Week 16	113	Day 100 - 141
Week 24	169	Day 142 - 211
Week 36	253	Day 212 - 295
Week 48	337	Day 296 - 505
Week 96	673	Day 506 - 700

Day 1 = Date of randomization

Table 2-4 Time windows for PRO: WPAI-CML

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1#
Week 4	29	Day 2 - 57
Week 12	85	Day 58 -127
Week 24	169	Day 128- 253
Week 48	337	Day 254 - 505
Week 96	673	Day 506 - 700

Day 1 = Date of randomization

Here's the general rule for the target day of assessment and time interval: For Week k visit, target day of assessment is defined as k*7+1. For the time interval, "Lower limit" = "upper limit

of prior applicable visit" +1. "Upper limit" = "target day of current visit" + integer part of ("target day of next applicable visit" – "target day of current visit")/2.

Visit window for the switched treatment period will use the same rules as described above but with Day 1 being the date of first administration of asciminib. Visit name for the switched treatment period will be defined similarly with annotated by beginning with "S-" (e.g. S-Week 4) to differentiate from those used for the randomized treatment period.

Last contact date

The last contact date will be derived for patients not known to have died at the respective analysis data cut-off date using the last complete date among the following:

Table 2-5 Last contact date data sources

Source data	Conditions
Date of randomization	No condition
Last contact date/last date patient was known to be alive from Survival Follow-up page	Patient status is reported to be alive, lost to follow-up or unknown
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term
Start/End dates from drug administration record	Non-missing dose. Doses of 0 are allowed
End of treatment date from end of treatment page	No condition
Any specific efficacy (molecular or cytogenetic) assessment date if available	Evaluation is marked as 'done'
Laboratory/PK collection dates	Sample collection marked as 'done'
Vital signs date	At least one non-missing parameter value
Performance status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the respective data cut-off date. The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post the cut-off date will be used. Completely imputed dates (e.g. the analysis data cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date.

The last contact date will be used for censoring of patients in the analysis of overall survival.

2.2 Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment and stratum they have been assigned to during the randomization procedure.

Safety Set

The **Safety Set** includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment actually received.

The actual treatment received corresponds to:

- the randomized treatment if patients took at least one dose of that treatment;
- the first treatment received if the randomized treatment was never received.

Pharmacokinetic Analysis Set

The **Pharmacokinetic Analysis Set (PAS)** includes all patients who provide at least one evaluable PK concentration. For a concentration to be evaluable, patients are required to:

- Take a dose of asciminib prior to sampling
- Take the same dose of asciminib for at least 3 consecutive days without dose interruption or dose modification prior to sampling
- Have the pre-dose sample collected before the next dose administration

Other analysis sets

- For duration of MMR and time to MMR (descriptive analysis), the **MMR Responder Set** will be used that is a subset of FAS and includes patients who achieve MMR at any time on study treatment.
- For CCyR rates at and by scheduled time points and time to CCyR (Kaplan-Meier analysis), the **CCyR Analysis Set** will be used that is a subset of FAS and includes patients who are not in CCyR at baseline.
- For duration of CCyR and time to CCyR (descriptive analysis), the **CCyR Responder Set** will be use that is a subset of FAS and includes patients who do not have CCyR at baseline and achieve CCyR at any time on study treatment.
- For analyses of patients switched to asciminib, the **Switch Analysis Set** will be used that is a subset of FAS and includes patients who switched from bosutinib to asciminib and received at least one dose of asciminib.

Patient Classification

Patients may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific subject classification rules defined in Table 2-6.

Table 2-6 Subject classification based on protocol deviations and non protocol deviation criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written inform consent	Not applicable
Safety set	No written inform consent	No dose of study medication
PK analysis set	No written inform consent	See definition of PAS
MMR Responder Set	Not applicable	See definition of MMR Responder Set
CCyR Analysis Set	Not applicable	See definition of CCyR Analysis Set
CCyR Responder Set	Not applicable	See definition of CCyR Responder Set
Switch Analysis Set	Not applicable	See definition of Switch Analysis Set

Withdrawal of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the eCRF.

2.2.1 Subgroup of interest

Subgroup analyses will use the same method as for the analysis in the respective overall analysis set.

The objective for carrying out these subgroup analyses is to identify potential issues that may be limited to a subgroup of patients, or that are more commonly observed in a subgroup of patients.

Summary tables and figures will be generated only for subgroups with at least 15 patients.

Efficacy

The primary efficacy endpoint will be summarized by the following subgroups to examine the homogeneity of treatment effect provided that the primary efficacy analysis based on the FAS is statistically significant:

- Stratification factor (based on randomization data from Interactive Response Technology [IRT]): “Major Cytogenetic Response” or “No Major Cytogenetic Response”
- Stratum reported in the CRF (derived using the data collected on the Bone Marrow Aspirate eCRF at baseline: see Appendix): “Major Cytogenetic Response” or “No Major Cytogenetic Response”

- Sex: Female or male
- Race: Asian, Caucasian, or others
- Age category (≥18-< 65 years, ≥ 65 years, ≥ 75 years,)
- Reason for discontinuation of the last prior Tyrosine Kinase Inhibitor (TKI): Failure (i.e. lack of efficacy) or intolerance (i.e. adverse event, lack of tolerability). Note: Only one reason for discontinuation is allowed for each prior therapy.
- Number of prior TKI therapies: 2, 3 or ≥4
- Line of therapy of randomized treatment: 3rd, 4th or ≥5th
- With or without Week 1 Day 1 BCR-ABL1 mutation (other than T315I or V299L) by Sanger Sequencing at central lab: Wild type or mutant
- BCR-ABL ratio at baseline ≥ 1% or <1%

No formal statistical test of hypotheses will be performed for the subgroups, only point estimate of the treatment effect and 95%-confidence intervals will be provided (see Section 2.14 for further analysis details). The objective of the efficacy subgroup analysis is to demonstrate homogeneity of treatment effect in the above subgroups.

Safety

Subgroup analyses for selected safety endpoints will be defined when required.

Japan-specific subgroup analyses

Two subgroups will be formed based on geographic region: Japan or other region (this is not based on ethinicity). These subgroup analyses will be only used for submission to Japan health authority.

Summary tables and figures will be presented for the two subgroups for the following outcome measures:

- Baseline characteristics: Tables of demographics, diagnosis and extent of cancer, extramedullary involvement, bone marrow analysis, molecular response, prior TKI and non-TKI, patient disposition, analysis sets by stratum
- Exposure: Tables of duration of exposure, dose received
- Tables of concomitant medications as well as surgical and medical procedures
- PK (only in asciminib arm): Table and figure of asciminib concentration by time, table of asciminib PK parameters (patients with full PK sampling), figure of average trough asciminib concentration from week 2, 4, 12 and 24 vs. BCR-ABL ratio IS (%) at 24 weeks
- AEs: Tables of all AEs, treatment-related AEs, AEs requiring dose adjustment or interruption, AEs requiring additional therapies, serious adverse events (SAEs), adverse events of special interest (AESIs), overview table of AEs and death
- ECG: Tables of Notable ECG values, change from baseline in ECG parameters values
- Lab: Hematology shift table, biochemistry shift table
- Efficacy: Tables of molecular response categories at and by each time point, MMR rate at and by each time point, time to MMR, duration of MMR, cytogenetic response

categories at and by each time point, time to CCyR, duration of CCyR, TTF, PFS, OS. Figures of cumulative incidence of MMR and of CCyR, association between Week 1 Day 1 BCR-ABL1 gene mutation and clinical outcome.

2.3 Patient disposition, demographics and other baseline characteristics

The FAS will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries will be reported by treatment arm and for all patients, and listings will be reported by treatment arm to assess baseline comparability. No inferential statistics will be provided.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by treatment arm. Categorical data (e.g. age groups: 18 - <65, 65 - <75, and ≥ 75 years and 18 - <65, ≥ 65 years, sex, race, ethnicity, ECOG performance status) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height, body mass index) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum), where BMI (kg/m^2) will be calculated as weight[kg] / (height[m]^2) using weight at screening.

For the Switch Analysis Set, the initial baseline and "baseline_switch" value will be summarized. Weight, BMI, age and ECOG performance status will be summarized using the "baseline_switch" value defined in Section 2.1.2.

In addition, a summary table by sex, age group (18 - <65, 65 - <85, and ≥ 85 years) and treatment group and another summary table by race and treatment group will be generated using the safety set for DSUR/PSUR.

Baseline stratification factors

The number (%) of patients in each stratum ("Major Cytogenetic Response" or "No Major Cytogenetic Response") based on data obtained from the IRT system will be summarized overall and by treatment arm for the FAS. Discordances between the stratum recorded in IRT at the time of randomization and the stratum recorded in the clinical database through the data collected on eCRF will be cross-tabulated and listed. In case the baseline bone marrow aspirate is missing or not evaluable (i.e. < 20 metaphases), the stratum recorded in the clinical database will be imputed following the rule described in Appendix 5.1.2.1.

Baseline cytogenetic response and molecular response

Baseline and Baseline_switch will be summarized for cytogenetic response and molecular response for the FAS and Switch Analysis Set respectively.

Diagnosis and extent of cancer

All diagnosis and extent of cancer data will be summarized and listed by treatment arm. One summary table will include time (years) since initial diagnosis (descriptive statistics with N, mean, median, standard deviation, minimum and maximum) and historical mutation: present

(unknown, yes, no), historical CML-associated mutation status (E225K, E255V, E355G, etc.) (frequency counts and percentages). Another table will include extramedullary involvement: any extramedullary involvement (Yes/No) and location of extramedullary involvement (Spleen, Liver) (frequency counts and percentages).

For the Switch Analysis Set, the above information will be based on the last observation prior to the Baseline_switch.

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on eCRF will be summarized and listed by treatment arm. The summary will be presented by primary system organ class (SOC), preferred term (PT) and treatment arm. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

In addition, separate listings will be produced for medical history possibly contributing to liver dysfunction, and medical history of protocol solicited cardiovascular events.

The cardiovascular risk factors, heavy smoking, low physical activity, unhealthy diet, and other, are collected prior to randomization and the EoT visit. A listing by treatment arm will be presented.

Family medical history of each patient for ischemic heart disease, cardiac arrhythmia, sudden death, high cholesterol, diabetes mellitus, heart defects (congenital heart disease), and heart failure is also collected prior to randomization and at the EoT visit. A listing by treatment arm will be presented.

Other

All data collected at baseline, including child bearing potential as well as informed consent for additional research on study data and biological samples, will be listed.

2.3.1 Patient disposition

Enrollment by country and center will be summarized for all screened patients and also by treatment arm using the FAS. The number (%) of randomized patients included in the FAS will be presented overall and by treatment group. The number (%) of screened and not-randomized patients and the reasons for screening failure will also be displayed. The eligibility criteria will be also summarized. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment group.

The following summaries will be provided (with % based on the total number of FAS patients):

- Number (%) of patients who were randomized (based on data from IRT system)
- Number (%) of patients who were randomized but not treated (based on DAR eCRF page not completed for any study treatment component)
- Primary reason for not being treated (based on “End of Treatment Phase Disposition” eCRF page)

- Number (%) of patients who were treated (based on DAR eCRF pages of each study treatment completed with non-zero dose administered)
- Number (%) of patients who are still on-treatment (based on the "End of Treatment Phase Disposition" page not completed);
- Number (%) of patients who discontinued the study treatment phase overall, before Week 24, Week 48 and Week 96 (based on the "End of Treatment Phase Disposition" page)
- Primary reason for study treatment phase discontinuation overall, before Week 24, Week 48 and Week 96 (based on the "End of Treatment Phase Disposition" page)
- Number (%) of patients who have entered the survival follow-up (based on the "End of Treatment Phase Disposition" page)
- Number (%) of patients in the FAS randomized to the bosutinib arm who switched to receive asciminib (based on DAR – ABL0001 eCRF page completed with non-zero dose administered during the Treatment switch phase);

The following summaries will be provided with % based on the total number patients in the Switch Analysis Set:

- Number (%) of patients who switched from bosutinib arm to receive asciminib and are still receiving asciminib (based on the "End of Treatment Disposition" eCRF not completed during the Treatment switch phase);Number (%) of patients who switched from bosutinib arm to receive asciminib and discontinued asciminib (based on the "End of Treatment Disposition" eCRF during the Treatment switch phase);
- Primary reason for treatment switch phase discontinuation (based on the "End of Treatment Disposition" eCRF during the Treatment switch phase)
- Number (%) of patients who have entered the survival follow-up (based on the "End of Treatment Disposition" eCRF during the Treatment switch phase)

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the Study Specification Document) overall and by treatment group for the FAS. All protocol deviations will be listed. In addition, the number (%) of patients in the FAS with any COVID-19 related protocol deviation (COVID-19 specific protocol deviations as well as non-specific COVID-19 protocol deviations with a COVID-19 relationship) will be tabulated by deviation category (as specified in the Study Specification Document) overall and by treatment group.

Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized by treatment group and stratum. Reasons leading to exclusion from analysis sets will be listed by treatment group and stratum as well as tabulated overall and by treatment group.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, average daily dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment arm. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of subjects in each interval. The number (%) of subjects who have dose reductions or interruptions, and the reasons, will be summarized by treatment group.

Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set and Switch Analysis Set will be used for all summaries and listings of randomized and switched treatments respectively.

To summarize exposure data for the randomized treatment period, this will be based on patients in the Safety set with the date of last administration of study treatment and the date of first administration of study treatment being FD and LD respectively.

To summarize exposure data for the switched treatment period, this will be based on patients in the Switch Analysis Set with the date of last administration of study treatment and the date of first administration of study treatment being FD_{switch} and LD_{switch} respectively.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to the investigational drug or control:

Duration of exposure to study treatment (weeks) = ((date of last administration of study treatment) – (date of first administration of study treatment) + 1) / 7.

The **duration of exposure in patient-years** is the total of the duration of exposure in years from all the patients in a treatment group.

The date of last administration of study treatment is defined in Section 2.1.1.

Summary of duration of exposure to study treatment will include categorical summaries based on intervals (<24 weeks, ≥24 weeks, ≥48 weeks, ≥96 weeks) and continuous summaries (i.e. mean, standard deviation etc.).

Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure.

The **planned cumulative dose** for a study treatment refers to the total planned dose as per the protocol up to the last date of study treatment administration. The calculations for the two study treatments are:

- ABL001: 40 mg/administration × 2 (administration/day) × duration of exposure (day)

- Bosutinib: 500 mg/day × duration of exposure prior to dose escalation (day) + 600 mg/day × duration of exposure since dose escalation (day), where the starting day of dose escalation is identified as the first record in the DAR eCRF with dose increased and reason "As per protocol".

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the DAR eCRF. It is the sum of the non-zero total daily doses recorded over the dosing period. For patients who did not take any drug the actual cumulative dose is by definition equal to zero. The actual cumulative dose will be summarized for each of the study treatment.

Dose intensity and relative dose intensity

Average Daily Dose (ADD) is defined as:

ADD (mg/day) = Actual cumulative dose (mg) / Time on treatment (day).

Time on treatment (weeks) = ((date of last administration of study treatment) – (date of first administration of study treatment) + 1 – number of days with dose interruption*) / 7

*For subjects in the asciminib arm, this includes the half days before and after the period with 0 dose if the treatment was interrupted after the morning dose and/or resumed in the evening (1 day record with QD dose administered before or after a record with 0 dose).

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (mg/day) = Actual cumulative dose (mg) / Duration of exposure to study treatment (day).

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as:

PDI (mg/day) = Planned cumulative dose (mg) / Duration of exposure (day).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg/day) / PDI (mg/day).

ADD, DI and RDI will be summarized separately for the two study treatments.

Dose changes, interruptions or permanent discontinuations

The number of subjects who have dose increase (allowed for bosutinib starting week 8, see protocol Section 6.2), dose reductions, dose interruptions or permanent discontinuations, and the reasons, as well as the duration of dose interruption due to any reason will be summarized separately for the two study treatments. For any subjects, duration of dose interruption will be calculated by adding all individual episodes of dose interruption for that patient. For subjects in the asciminb arm, this includes the half days before and after the period with 0 dose if the treatment was interrupted after the morning dose and/or resumed in the evening (1 day record with QD dose administered before or after a record with 0 dose).

'Dose Changed', 'Dose Interrupted' and 'Dose Permanently Discontinued' fields from the DAR eCRF pages will be used to determine the dose changes, dose interruptions, and permanent discontinuations, respectively.

The corresponding fields 'Reason for Dose Change/Dose Interrupted' and 'Reason for Permanent Discontinuation' will be used to summarize the reasons.

A dose change occurs when total daily dose is different from the most recently planned dose. For patients in asciminib arm, there is only one planned dose, i.e. 80 mg/day. For patients in bosutinib arm, the initial planned dose is 500 mg/day and could be changed to 600 mg/day in week 8 or later.

For the purpose of summarizing interruptions and reasons, multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in the mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Reduction: A dose change where the actual total daily dose is lower than the most recently planned dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the eCRF, while number of reductions will be derived programmatically based on the change and the direction of the change.

Increase: A dose change where the actual total daily dose is greater than the most recently planned dose. Therefore any dose change to correct a dosing error will not be considered a dose increase. Only dose change is collected in the eCRF, while number of increase will be derived programmatically based on the change and the direction of the change.

2.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

The number and percentage of patients who received any prior anti-neoplastic medications will be summarized by treatment arm for the lowest anatomical therapeutic classification (ATC) class and preferred term. A listing will also be produced.

Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD). Details regarding WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS.

The following information will be summarized for the FAS and Switch Analysis Set:

- Prior TKI by medication (e.g. imatinib, dasatinib, nilotinib, ponatinib, bosutinib, etc.)
- Number of prior TKI (e.g. 2, 3, 4, etc.)
- Number of lines of prior TKI therapy (2, 3, 4, 5+)

  A new line of therapy is considered each time a change in TKI occured. Multiple entries for the same TKI will be counted as separate lines of therapy if a different TKI is received between the different entries.
- Time on each line of prior TKI therapy (in years)
- Time on last prior TKI (in years)
- Reason to discontinue the most recent TKI therapy at the time of screening

- Prior non-TKI therapies (Yes, No).

A Sankey-like plot showing the sequence of prior TKIs will be provided.

Note: In case the last TKI given prior to enrollment in the study was a bridging therapy (i.e. reason for discontinuation includes a wording related to bridging), it will not be considered in the analysis of prior TKIs. In particular, it will not be considered as the last or most recent TKI therapy at the time of screening and will not count as an additional line of therapy.

For the Switch Analysis Set, bosutinib received during the randomized treatment period and other TKIs received since discontinuation of bosutinib and before first administration of asciminib (FD_{switch}) should be considered as prior TKIs.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by the lowest anatomical therapeutic classification (ATC) class, preferred term, overall and by treatment group by means of frequency counts and percentages using FAS.

Anti-neoplastic medications will be coded using the WHO-DD. Details regarding WHO-DD version will be included in the footnote in the tables/listings.

Concomitant therapies

Concomitant therapies are defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapies include medications (other than study drugs) and medical procedures starting on or after the start date of study treatment, or starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO ATC classification system and summarized by the lowest ATC class and PT using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and PT.

The summaries for the on-treatment period using the Safety Set will include:

- Therapies starting on or after the start of randomized study treatment but no later than the end of the on-treatment period and
- Therapies starting prior to start of randomized study treatment and continuing after the start of randomized study treatment.

These summaries for the on-switched treatment period using the Switch Analysis Set will include:

- Medications starting on or after the start of switched treatment but no later than the end of the on-switched treatment period and
- Medications starting prior to start of switched treatment and continuing after the start of switched treatment.

All concomitant therapies will be listed using the Safety Set. Any concomitant therapies starting and ending prior to the start of randomized study treatment or starting beyond end of the on-treatment period if not switched, or starting beyond end of on-switched treatment period if switched will be flagged in the listing.

The prohibited concomitant medications will be summarized by lowest ATC class and preferred term up to the end of on-treatment and on-switched treatment periods, respectively.

2.5 Analysis of the primary objective/estimand

In this section, the targeted treatment effect corresponding to the primary objective as well as the primary objective is clarified using the estimand language.

The primary clinical question of interest is: Is the efficacy of asciminib (40 mg bid) superior to bosutinib (500 mg qd) in CML patients in chronic phase, previously treated with 2 or more tyrosine kinase inhibitors, with regards to achieving MMR at 24 weeks while on study treatment and without meeting any treatment failure criteria (defined in section 5.4.4) prior to 24 weeks, regardless of dose modification, dose interruption, or deviation in any intake of concomitant medications.

The primary estimand is described by the following attributes:

Population: CML patients in chronic phase, previously treated with 2 or more tyrosine kinase inhibitors. Further details about the population are provided in Section 5 of the protocol.

Endpoint: Major Molecular Response (MMR) achieved at 24 weeks while on study treatment without meeting any treatment failure criteria (defined in section 5.4.4) prior to 24 weeks. A patient will be counted as having achieved MMR at 24 weeks if he/she meets the MMR criterion (BCR-ABL ratio $\leq$ 0.1%) at 24 weeks while on study treatment unless the patient met any treatment failure criteria (defined in section 5.4.4) prior to 24 weeks.

Intercurrent events:

- Treatment discontinuation (i.e. having performed an EOT visit) prior to 24 weeks due to any reason (e.g. intolerance, treatment failure, death, etc.): non response
- Meeting any treatment failure criteria (defined in section 5.4.4) prior to 24 weeks: non response
- Dose modification, dose interruption, or deviation in any intake of concomitant medications: ignore (treatment policy strategy)

Treatment of interest: the randomized treatment (the investigational treatment asciminib or the control treatment bosutinib) received for at least 24 weeks with or without dose modification, dose interruption or deviation in any intake of concomitant medications. Further details about the investigational treatment and control treatment are provided in Section 6 of the protocol.

Handling of remaining intercurrent events : no other IE foreseen

The summary measure: difference in MMR rate and its 95% confidence interval at week 24 between the two treatment arms.

2.5.1 Primary endpoint/estimand

The primary endpoint is Major Molecular Response (MMR) achieved at 24 weeks while on study treatment without meeting any treatment failure criteria (defined in section 5.4.4) prior to 24 weeks. A patient will be counted as having achieved MMR at 24 weeks if he/she meets the MMR criterion (BCR-ABL ratio $\leq$ 0.1%) at 24 weeks while on study treatment unless the patient met any treatment failure criteria (defined in section 5.4.4) prior to 24 weeks.

MMR will be considered as a binary variable with patients achieving MMR grouped as 'responders' and patients not achieving MMR grouped as 'non responders'. Only patients with MMR at 24 weeks are considered responders. In other words, any patient who achieves MMR before 24 weeks, but is no longer in MMR at 24 weeks, will be considered as a non-responder in this primary analysis.

Patients discontinuing treatment (i.e. having performed an EOT visit) prior to 24 weeks due to any reason (e.g. intolerance, treatment failure, death, etc.) and patients meeting any treatment failure criteria (defined in section 5.4.4) prior to 24 weeks will be considered as not having achieved MMR at 24 weeks.

Details of derivation of Polymerase Chain Reaction (PCR) results and calculation of BCR-ABL ratio are presented in Section 5.4.

2.5.2 Statistical hypothesis, model, and method of analysis

The MMR rate at 24 weeks will be calculated based on the FAS and according to the Intent To Treat (ITT) principle. MMR rate and its 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. The 95% confidence interval for the unstratified difference in MMR rate between treatment groups will be provided using the Wald method.

The null hypothesis is that there is no difference between the treatment groups with respect to MMR rate at 24 weeks. The Cochrane-Mantel-Haenszel (CMH) chi-square test, stratified by the randomization stratification factor, i.e. cytogenetic response status (MCyR vs no MCyR) at screening, will be used to compare MMR rate between the two treatment groups, at the two-sided 5% level of significance. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will be presented.

2.5.3 Handling of remaining intercurrent events of primary estimand

No remaining intercurrent events.

2.5.4 Handling of missing values not related to intercurrent event

Patients with missing PCR evaluations at 24 weeks will be considered as non-responders. However, if the 24-week PCR evaluation is missing, but both a PCR evaluation at 16 weeks and a PCR evaluation at 36 weeks indicate MMR, the 24-week assessment is imputed as a 'Response', assuming that MMR is maintained between 16 and 36 weeks.

2.5.5 Sensitivity analyses

The following sensitivity analyses will be performed:

- The CMH chi-square test of MMR rate at 24 weeks will be repeated stratifying by the stratum recorded in the CRF (MCyR vs no MCyR at baseline).
- Due to the COVID-19 (Coronavirus) pandemic, there is a risk that planned hospital visits are cancelled, potentially resulting in missing PCR evaluations. In order to assess the impact of COVID-19 (including potential missing data) on the primary endpoint, the CMH chi-square test of MMR rate at 24 weeks will be repeated on the FAS excluding the patients with planned 24-week visit (start of study treatment + 161 days) after the start date of COVID-19 epidemic. As per Novartis guidance, the start date, in a given country or region, is being defined as the approximate time point at which, according to the WHO situation reports and the Johns Hopkins database, the number of confirmed COVID-19 infections started to increase significantly (around 100 confirmed cases) and/or governments started to take measures (such as stay-at-home orders) to contain the epidemic, whichever occurred first (China: January 1, 2020; South Korea: February 20, 2020; Japan: February 21, 2020; Italy: February 23, 2020 and Rest of the World: March 1, 2020).
- The CMH chi-square test of MMR rate at 24 weeks will be repeated without the imputation rule used in the main analysis in case of missing PCR evaluations at 24 weeks.

2.5.6 Supplementary analyses

Additional supplemental logistic regression and subgroup analyses are described in Section 2.14.

Assess whether the efficacy of asciminib (40 mg bid) is superior to bosutinib (500 mg qd) in CML patients in chronic phase, without T315I or V299L mutation detected at Week 1 Day 1 visit and previously treated with 2 or more tyrosine kinase inhibitors, with regards to achieving MMR at 24 weeks while on study treatment and without meeting any treatment failure criteria (defined in section 5.4.4) prior to 24 weeks, regardless of dose modification, dose interruption, or deviation in any intake of concomitant medications.

The corresponding estimand attributes are the same as the ones of the primary estimand except that the population excludes patients detected with T315I or V299L at Week 1 Day 1 visit (As per protocol, these patients were discontinued from study treatment when the mutation results became available).

The CMH chi-square test of MMR rate at 24 weeks will be repeated on the FAS excluding patients detected with T315I or V299L at Week 1 Day 1 visit.

2.6 Analysis of the key secondary objective/estimand

The key secondary clinical question of interest is: Is the efficacy of asciminib (40 mg bid) superior to bosutinib (500 mg qd) in CML patients in chronic phase, previously treated with 2 or more tyrosine kinase inhibitors, with regards to achieving MMR at 96 weeks while on study treatment and without meeting any treatment failure criteria (defined in section 5.4.4) prior to 96 weeks, regardless of dose modification, dose interruption, or deviation in any intake of concomitant medications.

The key secondary estimand is described by the following attributes:

Population: CML patients in chronic phase, previously treated with 2 or more tyrosine kinase inhibitors. Further details about the population are provided in Section 5 of the protocol.

Endpoint: Major Molecular Response (MMR) achieved at 96 weeks while being treated without meeting any treatment failure criteria (defined in section 5.4.4) prior to 96 weeks. A patient will be counted as having achieved MMR at 96 weeks if he/she meets the MMR criterion (BCR-ABL ratio $\leq$ 0.1%) at 96 weeks while on study treatment unless the patient met any treatment failure criteria (defined in section 5.4.4) prior to 96 weeks.

Intercurrent events:

- Treatment discontinuation (i.e. having performed an EOT visit) prior to 96 weeks due to any reason (e.g. intolerance, treatment failure, death, etc.): non response
- Meeting any treatment failure criteria (defined in section 5.4.4) prior to 96 weeks: non response
- Dose modification, dose interruption, or deviation in any intake of concomitant medications: ignore (treatment policy strategy)

Treatment of interest: the randomized treatment (the investigational treatment asciminib or the control treatment bosutinib) received for at least 96 weeks with or without dose modification, dose interruption or deviation in any intake of concomitant medications. Further details about the investigational treatment and control treatment are provided in Section 6 of the protocol.

Handling of remaining intercurrent events : no other IE foreseen

The summary measure: difference in MMR rate and its 95% confidence interval at week 96 between the two treatment arms

The analysis of the key secondary objective will be performed at the time of the 96-week analysis.

2.6.1 Key secondary endpoint/estimand

The key secondary endpoint is MMR achieved at 96 weeks while on study treatment without meeting any treatment failure criteria (defined in section 5.4.4) prior to 96 weeks. A patient will be counted as having achieved MMR at 96 weeks if he/she meets the MMR criterion (BCR-ABL ratio $\leq$ 0.1%) at 96 weeks while on study treatment unless the patient met any treatment failure criteria (defined in section 5.4.4) prior to 96 weeks.

MMR will be considered as a binary variable with patients achieving MMR grouped as ‘responders’ and patients not achieving MMR grouped as ‘non responders’. Only patients with MMR at 96 weeks are considered responders. In other words, any patient who achieves MMR before 96 weeks, but is no longer in MMR at 96 weeks, will be considered as a non-responder in this key secondary analysis.

Patients discontinuing treatment (i.e. having performed an EOT visit) prior to 96 weeks due to any reason (e.g. intolerance, treatment failure, death, etc.) and patients meeting any treatment failure criteria (defined in section 5.4.4) prior to 96 weeks will be considered as not having achieved MMR at 96 weeks.

2.6.2 Statistical hypothesis, model, and method of analysis

The null hypothesis is that there is no difference between the treatment groups with respect to MMR rate at 96 weeks. Following a gatekeeping procedure to control the overall alpha level, only if the primary endpoint is significant, formal statistical testing of the key secondary endpoint with two-sided 5% level of significance will be performed using the CMH chi-square test, stratified by the randomization stratification factor, i.e. cytogenetic response status (MCyR vs no MCyR) at screening.

MMR rate and its 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. The 95% confidence interval for the difference in MMR rate between treatment groups will be provided using the Wald method. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be presented.

2.6.3 Handling of remaining intercurrent events of primary estimand

No remaining intercurrent events.

2.6.4 Handling of missing values not related to intercurrent event

Patients with missing PCR evaluations at 96 weeks will be considered as non-responders. However, if the 96-week PCR evaluation is missing, but both a PCR evaluation at 84 weeks and a PCR evaluation at 108 weeks indicate MMR, the 96-week assessment is imputed as a 'Response', assuming that MMR is maintained between 84 and 108 weeks.

2.6.5 Sensitivity analysis

- In order to assess the impact of COVID-19 (including potential missing data) on the key secondary endpoint, the CMH chi-square test of MMR rate at 96 weeks will be repeated on the FAS excluding the patients with planned 96-week visit (start of study treatment + 665 days) between the start date of the COVID-19 epidemic (China: January 1, 2020; South Korea: February 20, 2020; Japan: February 21, 2020; Italy: February 23, 2020 and Rest of the World: March 1, 2020) and its end date (to be defined in the future).
- The CMH chi-square test of MMR rate at 96 weeks will be repeated without the imputation rule used in the main analysis in case of missing PCR evaluations at 96 weeks.

2.7 Analysis of secondary efficacy objective(s)

The other secondary efficacy objective is to compare additional parameters (defined below) of the efficacy of asciminib versus bosutinib.

2.7.1 Secondary endpoints

2.7.1.1 Molecular response

MMR rates at all scheduled data collection time points, i.e., the protocol-planned visits except for 24 weeks and 96 weeks which are already covered by primary and key secondary endpoints. Such rates are defined as the proportion of patients with MMR at the respective time points.

MMR rates by all scheduled data collection time points, i.e., the protocol-planned visits. These are cumulative MMR rates by time points and are defined as the proportion of patients who achieve MMR at or before specified visits, i.e. if a patient achieves an MMR but then loses it before or at a specific visit, he/she will still be classed as achieving MMR by that specific time point.

Molecular response category at specific time points, i.e., the protocol-planned visits. Categories of molecular response are defined in Appendix.

Molecular response category by specific time points, i.e., the protocol-planned visits. This is defined as the best (lowest) molecular response category up to the specific time points.

Time to MMR (in weeks) is defined as: (date of first documented MMR - date of randomization + 1)/7.

Duration of MMR is defined for patients in the MMR Responder Set as the time between the date of the first documented MMR and the end date of MMR, i.e. the earliest date of confirmed loss of MMR, progression to accelerated phase (AP)/blast crisis (BC), or CML-related death.

Loss of MMR and progression to accelerated phase (AP)/blast crisis (BC) are defined in Appendix.

For patients for whom none of the events above is reported, the duration will be censored (see Section 2.7.3). The duration of MMR (in weeks) is calculated as: (end date or censoring date of MMR - date of first MMR + 1)/7.

2.7.1.2 Cytogenetic response

At each assessment time point the cytogenetic response status of each patient is classified as complete, partial, major, minor, minimal response and none (a review of a minimum of 20 metaphases is required):

- Complete response (CCyR): 0% Philadelphia chromosome positive (Ph+) metaphases
- Partial response (PCyR): >0 to 35% Ph+ metaphases
- Major response (MCyR = CCyR + PCyR): 0 to 35% Ph+ metaphases
- Minor response (mCyR): >35 to 65% Ph+ metaphases
- Minimal response: >65 to 95% Ph+ metaphases
- None: >95 to 100% Ph+ metaphases.

As per protocol, bone marrow aspirate for cytogenetic analyses will be performed as long as subjects have not achieved MMR. Therefore, in case no bone marrow aspirate was performed but the subject is in MMR at a specific time-point, the subject is considered to have achieved CCyR at that time-point. The date of CCyR is imputed by the date of MMR at the same scheduled time-point.

CCyR rates at all scheduled data collection time points, i.e., the protocol-planned visits. Such rates are defined as the proportion of patients in CCyR at the respective time points among patients in the CCyR Analysis Set, which excludes patients who are in CCyR at baseline.

CCyR rates by all scheduled data collection time points, i.e., the protocol-planned visits. Such rates are defined as the proportion of patients who achieve CCyR at or before the respective time points among patients in the CCyR Analysis Set.

Cytogenetic response category at specific time points, i.e., the protocol-planned visits. At each assessment time point the cytogenetic response status of each patient is classified as complete, partial, major, minor, minimal response and none (a review of a minimum of 20 metaphase is required) as defined in Appendix.

Cytogenetic response category by specific time points, i.e., the protocol-planned visits. This is defined as the best (lowest) cytogenetic response category up to the specific time points.

Time to CCyR (in weeks) is defined for patients as: (date of first documented CCyR - date of randomization + 1)/7.

Duration of CCyR is defined for patients in the CCyR Responder Set as the time between date of first documented CCyR and the end date of CCyR, i.e. the earliest date of loss of CCyR, progression to AP/BC, or CML-related death. Loss of CCyR and progression to AP/BC are defined in Appendix. For patients for whom none of the events above is reported, the duration will be censored (see Section 2.7.3). The duration of CCyR (in weeks) is calculated as: (end date or censoring date of CCyR - date of first CCyR + 1)/7.

2.7.1.3 Other secondary efficacy endpoints

Time to treatment failure (TTF) is defined for patients in FAS as the time from date of randomization to an event of treatment failure. The events that constitute 'treatment failure' are described in the Appendix. They are based on the ELN criteria [Baccarani et al. 2013] defining failure of a second line treatment adapted to include discontinuation of randomized treatment as an event.

TTF (in months) is calculated as: (date of treatment failure or censoring date (see Section 2.7.3) - date of randomization + 1)/30.4375.

Progression-Free-Survival (PFS) is defined for patients in FAS as the time from the date of randomization to the earliest occurrence of documented disease progression to AP/BC or the date of death from any cause (including progressions and deaths observed during the survival follow-up period).

PFS (in months) is calculated as: (date of disease progression/death or censoring date (see Section 2.7.3) - date of randomization + 1)/30.4375.

Overall survival (OS) is defined for patients in FAS as the time from the date of randomization to the date of death (including the survival follow-up period).

OS (in months) is calculated as: (date of death or censoring date (see Section 2.7.3) - date of randomization + 1)/30.4375, regardless whether the patient switched from bosutinib to asciminib.

2.7.2 Statistical hypothesis, model, and method of analysis

No confirmatory statistical testing of non-key secondary efficacy endpoints will be performed, however, nominal p-values will be presented for exploratory purposes (as specified in protocol Section 10.5.2).

MMR rates at and by time points

The FAS will be used for these endpoints. For each time point the MMR rate and the associated 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. The descriptive p-value obtained via CMH chi-square tests stratified by the randomization strata, i.e. MCyR vs no MCyR at screening, will be presented. A 95% confidence interval for the difference in each MMR rate between treatment groups will be provided using the Wald method. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

The cumulative incidence of MMR by treatment group will be graphically displayed by an increasing step function. Each curve will increase each time (after randomization) at which a new responder is observed and thus will increase up to the best observed response rate (e.g. up to 50% if half of the patients in the analysis population are able to achieve MMR).

Molecular response at and by time points

Frequency and percentage of all molecular response categories (defined in Appendix) by treatment arm using FAS will be presented for each time point.

For the by-time-points summary, the within-patient best molecular response category up to the specific time points is used to calculate the frequency and percentage.

Time to MMR

The MMR Responder Set will be used. Descriptive statistics (minimum, maximum, median, quartiles, mean, sd) of time to MMR will be provided for the two treatment groups separately.

The FAS will be also used to perform similar Time-to-Event analyses as described below for duration of MMR.

Duration of MMR

The MMR Responder Set will be used. The survival distribution of duration of MMR will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals [Brookmeyer and Crowley 1982] of the medians, along with the proportion of patients who are still in MMR at 24, 48, 72 and 96 weeks and the associated 95% confidence intervals, will be presented for each treatment group.

CCyR rates at and by time points

The CCyR Analysis Set will be used for these endpoints.

For each time point the CCyR rate and the associated 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. The descriptive p-value obtained via CMH chi-square tests stratified by the randomization strata, i.e. MCyR vs no

MCyR at screening, will be presented. A 95% confidence interval for the difference in each CCyR rate between treatment groups will be provided using the Wald method. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

The cumulative incidence of CCyR by treatment group will be graphically displayed by an increasing step function. Each curve will increase each time (after randomization) at which a new responder is observed and thus will increase up to the best observed response rate (e.g. up to 50% if half of the patients in the analysis population are able to achieve CCyR).

Cytogenetic response at and by time points

Frequency and percentage of all cytogenetic response categories (defined in Section 2.7.1.2) by treatment arm using FAS will be presented for each time point. A shift table comparing baseline and best post-baseline cytogenetic response categories by treatment will also be presented. All assessments of cytogenetic response categories will also be listed by treatment arm.

For the by-time-points summary, the within-patient best cytogenetic response category up to the specific time points is used to calculate the frequency and percentage.

Assessments of bone marrow aspirate at different time points will also be summarized.

Time to CCyR

The CCyR Responder Set will be used. Descriptive statistics (minimum, maximum, median, quartiles, mean, sd) of time to CCyR will be provided for the two treatment groups separately.

The CCyR analysis set will be also used to perform similar Time-to-Event analyses as described below for duration of CCyR.

Duration of CCyR

The CCyR Responder Set will be used. The survival distribution of duration of CCyR will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals [Brookmeyer and Crowley 1982] of the medians, along with the proportion of patients who are still in CCyR at 24, 48, 72 and 96 weeks and the associated 95% confidence intervals, will be presented for each treatment group.

TTF, PFS and OS

For each endpoint the survival distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals [Brookmeyer and Crowley 1982] of the medians, along with the proportion of patients who have not experienced the respective events at 1, 3 and 5 years and the associated 95% confidence intervals, will be presented for each treatment group. The hazard ratio between the two treatments will be calculated, along with its 95% confidence interval, using a stratified Cox model. The descriptive p-value obtained using a stratified log-rank test will be also presented. The stratification will be based on the randomization stratification factor, i.e. cytogenetic response status (MCyR vs no MCyR) at screening.

2.7.3 Handling of missing values/censoring/discontinuations

MMR rates at specific time points: Patients discontinuing the randomized treatment prior to a specific time point due to any reason or patients without an available assessment at that time point will be considered as non-responders for that time point.

MMR rates by specific time points:

Patients without any documented response for which an evaluable response assessment was never provided will be considered as non-responders for the period of time up to that time point.

Molecular response at specific time points: The category "Missing" will be assigned to

- Ongoing cases, i.e. patients without assessment at the specific time point who have not discontinued study treatment and have not been treated sufficiently long for a specific time point
- Discontinued due to progressive disease/death prior to a specific time point
- Discontinued due to other reasons prior to a specific time point

- **Molecular response category by specific time points**: The category "Missing" will be assigned to patients for whom an evaluable response assessment was never provided.

Time to MMR: For patients in the FAS who have not experienced any MMR, the time will be censored as follows in the Kaplan-Meier analysis:

- If a patient does not achieve the specified response before the cut-off date for the analysis, censoring time will be the last molecular assessment (PCR) date on treatment prior to the cut-off date or the EoT visit, whichever comes first.
- If a patient discontinues study treatment prior to achieving a response for a reason other than disease progression or death, then the patient will be censored at the last molecular assessment (PCR) date on treatment prior to the cut-off date or the EoT visit, whichever comes first.
- If a patient discontinues study treatment prior to achieving a response due to progression or death, then the censoring time will be set to the longest follow-up time in the treatment group, that is, consider the response is impossible to reach.
- In case no on-treatment response assessment was performed, the patient will be censored at day 1.

Duration of MMR: For patients in the MMR responder set who have not experienced any event (loss of MMR, progression to AP/BC, or CML-related death), the duration will be censored at the last molecular assessment (PCR) date on treatment.

CCyR rates at specific time points: Patients discontinuing the randomized treatment prior to a specific time point due to any reason will be considered as non-responders for that time point.

CCyR rates by specific time points: This will be handled similarly as MMR, but with CCyR instead.

Cytogenetic response at specific time points: This will be handled similarly as molecular response category.

Cytogenetic response category by specific time points: This will be handled similarly as molecular response category.

Time to CCyR: For patients in the CCyR analysis set who have not experienced any CCyR, the time will be censored in the same manner as Time to MMR.

Duration of CCyR: For patients in the CCyR responder set who have not experienced any event (loss of CCyR, progression to AP/BC, or CML-related death) the duration will be censored at the last cytogenetic assessment date on treatment or the last PCR evaluation on treatment indicating MMR, whichever is the latest.

TTF: For patients in the FAS who have not reached treatment failure, their TTFs will be censored at the time of their last study assessment (PCR, cytogenetic, hematologic or extramedullary) before the cut-off date.

PFS: For patients who have not experienced an event (disease progression to AP/BC or death from any cause), their PFS times will be censored at the date of last study assessment (PCR, cytogenetic, hematologic or extramedullary) before the cut-off date, regardless of subsequent intake of treatment(s) after randomization.

OS: Patients who are alive at the time of the analysis data cutoff date will be censored at the date of last contact (see Section 2.1.1) before the cut-off date, regardless of subsequent intake of treatment(s) after randomization.

2.8 Safety analyses

All safety analyses will be based on the safety set, except that the summary of safety data during the switched treatment period will be based on the Switch Analysis Set. All listings and tables will be presented by treatment group.

2.8.1 Adverse events (AEs)

AE summaries will include all AEs occurring during the on-treatment period (or the on-switched treatment period). All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome, etc. AEs with start date outside of the on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades or the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sorting order for the preferred term will be based on their frequency in the asciminib arm.

The following adverse event summaries will be produced by treatment arm for the Safety set and Switch Analysis Set: overview of adverse events and deaths, AEs by SOC and PT,

summarized by relationship, seriousness, leading to treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy, and leading to fatal outcome. The study treatment-related AEs/SAEs/AEs leading to treatment discontinuation as well as SAE with fatal outcome are summarized for the Safety set and Switch Analysis set.

For posting to ClinTrial.gov and EudraCT, a summary table of on-treatment deaths and serious AEs and another summary table of non serious AEs by treatment, both including occurrences (an occurrence is defined as >1 day between start and prior end date of record of same preferred term) and sorted by SOC and PT, will be presented as well.

In order to account for differences in exposure between the treatment arms, incidence rates of AEs and SAEs will be presented by adjusting for duration of treatment period in patient-years. They will also be reported by time intervals (i.e. period of emergence: the event is assigned to the interval when it first started): 0 to 2 months, > 2 months to 6 months, > 6 months to 12 months, >12 months and more after the start of study treatment.

2.8.1.1 Adverse events of special interest / grouping of AEs

Data analysis of AESIs

An adverse event of special interest (AESI) is a grouping of adverse events that are of scientific and medical concern specific to compound asciminib. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HLGTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. The latest approved version of CRS prior to the respective database lock will be used.

For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during the on-treatment period (or the on-switched treatment period) will be summarized.

Summaries of these AESIs will be provided by treatment arm (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, death, etc.). If sufficient number of events occurred, analysis of time to first occurrence will be applied.

A listing of all grouping levels down to the MedDRA PTs used to define each AESI will be generated.

2.8.2 Deaths

Separate summaries for on-treatment and all deaths *(including post-treatment deaths)* will be produced on the Safety set by treatment arm, system organ class and preferred term.

Similarly, a separate summary for on-switched treatment deaths will be produced on the Switch Analysis Set.

All deaths will be listed, where deaths occurring during the post-treatment, the on-switched treatment or post-switched treatment periods will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

2.8.3 Laboratory data

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. Details of CTCAE grading and imputation rules are presented in Appendix 5.3.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

On analyzing laboratory data, all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date.

The following summaries will be produced on the Safety set separately for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline in the on-treatment period.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

The same summaries will be produced on the Switch Analysis Set for the on-switched treatment period.

The following listings will be produced separately for hematology and biochemistry for the laboratory data:

- Listings of all laboratory data, with CTCAE grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTCAE grade 3 or 4 laboratory toxicities

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis DILI Clinical safety guidelines will be summarized for the criteria defined by single lab parameter. For combination of various parameters, the worst post-baseline values from each single parameter are taken into consideration, i.e. it may not come from the concurrent measurement (i.e. same assessment). :

The following summaries will be produced:

- ALT or AST > 3x upper limit of norm (ULN)
- ALT or AST > 5xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP >= 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

12-lead ECGs including PR, QRS, QT, QTcF and RR intervals will be obtained centrally for each subject during the study. ECG data will be read and interpreted centrally.

The echocardiogram will be performed and evaluated locally to assess the left ventricular ejection fraction (LVEF).

Data handling

The average of the triplicate ECG parameters at each time point will be used in the analyses.

For unscheduled visits, ECGs that are reported on the same day and within 30 minutes apart from each other will be assumed to be sequential ECGs and thus will be used to compute the mean of the ECG parameters.

Unscheduled ECG measurements will not be used in computing the summary statistics for change from Baseline at each post-baseline time point. However, they will be used in the outlier analyses (e.g. QTc > 450 ms, > 480 ms, or > 500 ms at any time point, or an increase from Baseline in QTc > 30 ms or > 60 ms). End of treatment ECG measurements for discontinued patients will be considered as an unscheduled measurement in case it occurs outside a scheduled visit.

Data analysis

The number and percentage of subjects with notable ECG values will be presented by treatment arm for the Safety set and Switched Analysis Set. Notable values are defined below:

- QT, QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- HR

  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

A listing of all ECG assessments will be produced by treatment arm and notable values will be flagged. A separate listing of only the subjects with notable ECG values will also be produced. In each listing the assessments collected during the post-treatment period will be flagged.

Change from baseline ECG parameters by timepoint will also be summarized by treatment.

A listing of all LVEF assessments will be produced by treatment arm. In the listing, the assessments collected outside of on-treatment period will be flagged.

A summary table by treatment arm with descriptive statistics for LVEF at different timepoints (baseline, week 20) and for change from baseline will be presented. A shift table for LVEF categories (≤40%, 41-49%, ≥50%) at baseline versus worst value on treatment will also be presented.

2.8.4.2 Cardiovascular risk factor assessment

Prior to randomization and at the end of treatment, for each patient information of the following risk factors is collected: heavy smoking, low physical activity, unhealthy diet, and other. A listing by treatment arm will be presented.

Family medical history of each patient for ischemic heart disease, cardiac arrhythmia, sudden death, high cholesterol, diabetes mellitus, heart defects (congenital heart disease), and heart failure is also collected prior to randomization and at the end of treatment. A listing by treatment arm will be presented.

2.8.4.3 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

The number and percentage of subjects with notable vital sign values (high/low) in systolic blood pressure, diastolic blood pressure, pulse rate, weight and temperature will be presented by treatment arm.

A listing of all vital sign assessments will be produced by treatment arm and notable values will be flagged. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.8.4.4 Liver events

There are separate eCRF pages to collect acetaminophen/paracetamol, autoimmune, drug use 6 months prior to liver event, immunoglobulin, liver function tests, pathology, related imaging, viral serology and potential impact of alcohol use, and an overview eCRF page. Data on the overview eCRF page will be listed by treatment arm. Assessments collected during the post-treatment period will be flagged.

2.8.4.5 Pulmonary function tests

Data of pulmonary function tests will be listed by treatment arm. Assessments collected during the post-treatment period will be flagged.

2.8.5 Additional Analyses

2.8.5.1 ECOG performance status

ECOG performance status collected on treatment will be summarized. Shift tables will be provided comparing baseline with best and worst values during study for each treatment group.

2.9 Pharmacokinetic endpoints

PK parameters

The PK parameters that will be determined are shown in Table 2-7. The PK parameters for asciminib are derived based on the non-compartmental methods using Phoenix WinNonlin® software version 6.4 in patients with full PK sampling in PAS.

Table 2-7 Non-compartmental PK parameters for asciminib in full PK group

AUC0-12h	The area under the plasma concentration-time curve from time zero to 12 hours ($ng*hr*mL^{-1}$)
AUClast	The AUC from time zero to the last measurable plasma concentration sampling time (Tlast) ($ng*hr*mL^{-1}$)
Ctrough	Trough plasma concentration (measured concentration at the end of a dosing interval at steady state [taken directly before next administration])
Cmax	The maximum (peak) observed plasma concentration after dose administration (ng/mL)
Tmax	The time to reach maximum (peak) plasma concentration after dose administration (hr)
Tlast	The time to reach the last measurable plasma concentration after dose administration (hr)
CL/F	The total apparent body clearance of drug from the plasma after oral administration ($L*hr^{-1}$)

Descriptive statistics (n, arithmetic mean, CV% mean, standard deviation (SD), median, geometric mean, CV% geo-mean, minimum and maximum) will be presented by treatment for PAS for all PK parameters defined in Table 2-7 except Tmax, where only n, median, minimum and maximum will be presented.

All individual PK parameters will be listed for patients treated with asciminib and with full PK sampling in the safety set.

PK concentrations

Descriptive statistics (n, m (number of non-zero concentrations), arithmetic mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum) for asciminib concentration will be presented at each scheduled time point for the PAS.

The mean (+/- SD) and geometric mean concentration-time profiles for asciminib over time will be displayed graphically for PAS on the linear and semi-log view (Week 2 Day 1; for patients with full PK sampling only).

The mean (±SD) and median Ctrough values of asciminib over time will be displayed graphically for PAS on the linear scale only (Patients with full and sparse PK sampling).

All individual plasma asciminib concentration data will be listed for patients treated with asciminib in the Safety Set.

Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ, 1 ng/mL) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the

calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing values for any PK data will not be imputed and will be treated as missing.

2.10 PD and PK/PD analyses

The potential relationship between asciminib exposure (e.g. trough concentration) and efficacy, pharmacodynamics (PD) or safety endpoints may be assessed by graphic exploration and/or statistical modeling, as appropriate, including effect of population covariates. Additional exposure-response analyses for ECG may be conducted. The concentration data may be analyzed by a population approach to evaluate the influence of covariates on drug exposure. If applicable, the details of the above-mentioned analyses will be described in a separate analysis plan and reported separately.

The relationship between average trough plasma concentration up to 24 weeks and BCR-ABL ratio IS (%) at 24 weeks will be assessed by graphic exploration.

2.11 Patient-reported outcomes

The FAS will be used for analyzing PRO data unless specified differently. The MDASI CML, PGIC along with EQ-5D-5L will be used to assess patient's disease-related symptoms and health-related quality of life from baseline to EOT; and the WPAI-CML will be used to assess work productivity and activity impairment related to the patient's CML. All tools require patient's direct completion and will be administered utilizing electronic device for data collection at scheduled time points from screening to end of treatment.

The baseline is defined in Section 2.1.1. Patients with an evaluable baseline score and at least one evaluable post-baseline score during the treatment period will be included in the change from baseline analyses. Missing data items in a scale will be handled according to the manual for each instrument. No imputation will be applied if the total or subscale scores are missing at a visit. All measures will assess differences between the treatment arms.

Compliance to the schedule of administration of each PRO questionnaire will be summarized by treatment group, for baseline and scheduled post-baseline assessment time points. The following categories, as collected on the eCRF, will be used to describe whether the questionnaire was completed at a specific time point:

1. yes, fully completed
2. yes, partly completed
3. no

Repeated measures model for continuous scores

To best utilize the repeated assessments of a given PRO score, a repeated measures model for longitudinal data will be used to estimate differences between treatment arms. This repeated measures model will include terms for treatment, the stratification factor (major cytogenetic response status), time, baseline value as main effects, and an interaction term for treatment by time. This analysis will be restricted to patients with an evaluable baseline score and at least

one evaluable post-baseline score. All data collected until end of treatment (including the end of treatment assessment) will be included in the analysis. Note that only data collected under treatment (i.e. while the patient is treated) will be included. The end of treatment assessment will be included if collected within 7 days of the last dose intake.

Time will be considered as a continuous variable expressed in weeks, i.e. considering that the PRO score follow a linear trend.

As a first approach, an unstructured correlation matrix will be used to model the correlation within patients. The structure of the correlation matrix will be investigated and simplified using likelihood ratio tested if appropriate.

2.11.1 MDASI-CML

The M.D. Anderson Symptom Inventory – Chronic Myeloid Leukemia (MDASI-CML) questionnaire is planned to be administered during screening, at weeks 4, 8, 12, 16, 24, 36, 48 and 96 after randomization.

The MDASI-CML is a 26 item self-administered questionnaire for adult CML patients. Twenty of the items measure the severity of disease-related symptoms and are scored from 0 (Not present) to 10 (As bad as you can imagine) and 6 items that measure symptom interference with daily life scored from 0 (Did not interfere) to 10 (Interfered completely).

The severity score will be calculated when a patient scores at least 11 items out of the 20 severity items using the formula: (sum of scores for the items answered) / (number of items answered). If a patient scores fewer than 11 items, the severity score will be missing.

The interference score will be calculated when a patient scores at least 4 items out of the 6 interference items using the formula: (sum of scores for the items answered) / (number of items answered). If a patient scores fewer than 4 items, the interference score will be missing.

For the severity score and interference score, descriptive statistics (n, mean, SD, median, 25th and 75th percentiles) by treatment arm will be provided for the actual scores and changes from baseline scores at each scheduled assessment time point.

Between-treatment differences for the change in severity and interference scores will be evaluated using the above-mentioned repeated measures model.

2.11.2 EQ-5D-5L

EQ-5D-5L is a two-part standardized instrument for measuring health outcomes in a wide range of health conditions and treatments. It consists of a descriptive system and a visual analogue scale (EQ VAS). The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems (or unable to perform the activity). The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'worst imaginable health state'.

The EQ-5D-5L data will be used to calcutae utility values for the economic evaluation of asciminib and bosutinib in a separate analysis.

The EQ-5D-5L questionnaire is planned to be administered during screening, at weeks 4, 8, 12, 16, 24, 36, 48 and 96 after randomization.

Descriptive system

The number and percentage of subjects in the five levels of each EQ-5D demension will be presented by treatment group at each assessment time point.

EQ VAS

The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale from 0, labeled as 'worst imaginable health state', to 100, labeled as 'best imaginable health state'.

For the EQ VAS, descriptive statistics (n, mean, SD, median, 25th and 75th percentiles) by treatment arm will be provided for actual values and for the change from baseline at each assessment time point.

Between-treatment differences for the changes in EQ VAS score will be evaluated using the above-mentioned repeated measures model.

2.11.3 WPAI-CML

The Work Productivity and Activity Impairment Questionnaire – Chronic Myeloid Leukemia (WPAI-CML) questionnaire is planned to be administered during screening, at weeks 4, 12, 24, 48 and 96 after randomization.

The WPAI-CML is a six-item questionnaire which is intended to measure work and activity impairment associated with CML for those who self-identify as currently employed for pay. This questionnaire measures self-reported productivity loss associated with CML during the past seven days. It consists of questions about absence from work due to CML, hours spent at work, the reduction in productivity at work attributed to CML, and the reduction in productivity while performing regular activities. WPAI-CML outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes. Scoring will be done according to WPAI-CML instrument guidance resulting in four scores including: Percent work time missed due to problem; percent impairment while working due to problem; Percent overall work impairment due to problem; and, percent activity impairment due to problem.

Descriptive statistics (n, mean, SD, median, 25th and 75th percentiles) for each of the four derived outcome scores and changes from baseline scores will be presented by treatment arm at each scheduled assessment time point with .

Between-treatment differences for the changes in each of the four outcome scores will be evaluated using the above-mentioned repeated measures model.

2.11.4 PGIC

The Patient Global Impression of Change (PGIC) instrument is planned to be administered during at weeks 4, 8, 12, 16, 24, 36, 48 and 96 after randomization

The PGIC is comprised of a single question intended to measure a patient's perspective of improvement or deterioration over time relative to treatment. The PGIC uses a seven-point scale

where one (1) equals very much improved and seven (7) equals very much worse. Missing values will not be imputed.

The number and percentage of subjects in each of the seven categories for PGIC will be presented by treatment group at each assessment time point.

2.12 Resource utilization

Data relating to resource utilization (described in trial protocol Section 7.2.5) from the FAS will be used for the purpose of economic evaluation, which will be carried out and reported as a separate activity outside the CSR.

The measures of healthcare resource utilization (HCRU) include: hospitalization (H), emergency room (ER) visit, general practitioner (GP) visits, specialist (Sp) visit and urgent care (UC) visit. HCRU will be assessed as follows: frequency and duration of hospitalization from baseline up to end of treatment; frequency of emergency room visits from baseline up to end of treatment; frequency of additional outpatient office visits general practitioner, specialist, and urgent care visits from baseline up to end of treatment. Hospitalization visits will also record the number of days on ward and the type of ward (hospital unit) and the discharge status. At each HCRU collected, the reason for the visit, i.e. related to CML, AE related to CML therapy or other reason, will be collected, in order to quantify the impact of treatment on healthcare resources.

HCRU data by treatment arm will be summarized in the primary analysis CSR and the end of study treatment CSR, with descriptive statistics (n, mean, median, SD, min, max) for quantitative variables, and count and percentage for qualitative variables.

2.13 Biomarkers

As a project standard, Novartis will analyze only biomarkers collected in the clinical database. For exploratory markers, since the studies are not adequately powered to assess specific biomarker-related hypotheses, the goal of these exploratory statistical analyses should be considered as the generation of new scientific hypotheses. No adjustment for multiple comparisons is usually planned for exploratory analyses. Furthermore, additional post hoc exploratory assessments are expected and may be performed.

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue their analysis due to either practical or strategic reasons. Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

If not otherwise specified, the FAS will be used for all biomarker analyses on patients with biomarker data.

Exploratory biomarker objectives

- To characterize mutations in the BCR-ABL1 gene at Week 1 Day 1, upon confirmed loss of molecular response and/or at end of treatment and examine their association with molecular and cytogenetic response for asciminib vs bosutinib

- To understand biology of CML and bone marrow microenvironment on leukemic stem cells (LSCs) eradication, including patients' immunogenicity
- To assess clonal evolution during treatment with asciminib vs. bosutinib
- To evaluate soluble/inflammatory factors that correlate with response to asciminib vs. bosutinib treatment

Only some analyses for the first exploratory biomarker objective about BCR-ABL1 mutation listed above are described here and the results will be included in the respective CSRs. Additional analyses for this and other exploratory biomarker objectives will be described in separate analyses plans, with results reported separately.

List of biomarkers evaluated and the collection time points

The biomarkers evaluated in the study are listed in Table 2-8 below.

Table 2-8 Sample biomarker summary table

Biomarker	Time point	Sample	Method
Immune markers PD-L1 and CD8	Screening and end of treatment	Bone marrow biopsy	Immunohisto-chemistry
Leukemic stem cells characterization	Screening, week 24 and end of treatment	Bone marrow aspirate	Flow cytometry
BCR-ABL1 gene mutation	W1D1 pre-dose and end of treatment. If mutation is present at baseline, then also every 12 weeks after baseline	Peripheral blood	Sanger Sequencing
Low level mutations in BCR-ABL1 gene	W1D1 pre-dose and end of treatment	Peripheral blood	Mass spectrometry and NGS
Circulating cytokines in plasma	W1D1 pre-dose, Week 48 and end of treatment	Peripheral blood	MSD and ELISA
Genetic variant analysis of the UGT2B7 and UGT2B17 gene	W1D1	Peripheral blood	Genechip

General data handling and preprocessing

For bone marrow samples the latest assessment during screening period will be used as the baseline value, while for blood samples the week 1 day 1 (W1D1) pre-dose assessment will be used as the baseline value.

When more than one biomarker data value are available for a subject at any time point, the mean of the replicate values will be used for all statistical analyses.

2.13.1 Somatic mutation biomarker data handling and analysis

Handling of somatic biomarker data

Overall, somatic mutation status (wild type or mutant) will be derived from the mutational status of the interrogated exons for the BCR-ABL1 gene by Sanger Sequencing. These may be non-exclusive and the presence of mutation across more than one exon will be reported in separate categories.

Mutation summary statistics

All somatic mutation data will be reported using counts and percentages by the mutation type in the form of contingency tables with the rows containing the different mutations assayed, and the treatment groups in the columns. All the mutation categories for a gene will also be aggregated into mutant, wild type or missing/unknown groups and counts/percentages will be reported by these three categories as well. A summary table will be presented for baseline mutations and another summary table for post-baseline new mutations (not present at baseline).

All the mutation data will be listed for each subject ordered by treatment group.

Association between biomarkers and clinical outcome

This analysis does not adjust for multiple comparisons and results may have higher false positive rates.

The relationship between Week 1 Day 1 BCR-ABL1 gene mutation data (wild type or mutant) and outcome data (with or without MMR at and by 24 and 96 weeks using FAS, with or without CCyR at and by 24 and 96 weeks using CCyR analysis set) will be explored by reporting contingency tables and by applying a logistic regression including treatment group, Week 1 Day 1 BCR-ABL1 gene mutation and their interaction as covariates. Treatment group will be included in this summary table.

In addition, the same analysis will be performed for

- the relationship between post-baseline new BCR-ABL1 mutation (with or without new mutation) up to 48 weeks and outcome data (with or without MMR at 48 and 96 weeks using FAS, with or without CCyR at 48 and 96 weeks using CCyR analysis set).
- the relationship between post-baseline new BCR-ABL1 mutation (with or without new mutation) up to end of treatment and outcome data (with or without MMR at 96 weeks using FAS, with or without CCyR at 96 weeks using CCyR analysis set).

The odds ratios bewteen treatment groups with 95% confidence intervals will be reported, for each biomarker category and overall. If treatment by biomarker interaction is significant (e.g. when $p < 0.1$), overall odds ratio for treatment will not be reported.

2.14 Other exploratory analyses

MMR rate at 24 weeks

The FAS will be used for the following exploratory analyses:

1. A logistic regression model adjusted for the stratification factor (based on the randomization platform data IRT) will be fit to assess treatment effect. An adjusted odds ratio for the treatment effect with associated 95% confidence intervals will be presented. Mantel-Haenszel estimates of the common odds ratio and the corresponding 95% confidence interval will also be provided.
   Some subjects were mistratified. To assess the impact of this mistratification on the treatment effect assessment, a logistic regression adjusting for major cytogenetic status at baseline based on CRF data will also be run.
2. Based on the subgroups specified in Section 2.2.1, the following analyses will be performed for each subgroup:
   - Proportion of patients with MMR at 24 weeks and its 95% confidence interval based on the Pearson-Clopper method within each treatment group
   - The difference in MMR rate at 24 weeks between treatment groups and the corresponding Wald 95% confidence interval

   Efficacy analyses in subgroups will be purely exploratory and are intended to explore the consistency of treatment effect. Forest plot (n, risk difference, Wald 95% confidence interval) will be produced to graphically depict the treatment effect estimates in different subgroups. No inferential statistics (p-values) will be produced for the subgroups.
3. A logistic regression model adjusted for the stratification factor (baseline major cytogenetic response status based on randomization data) and other important variables identified by the subgroup analyses above will be fit to assess treatment effect. An adjusted odds ratio for the treatment effect with associated 95% confidence intervals will be presented.
   To assess the impact of mistratifications on the treatment effect assessment, the same analysis will be repeated, adjusting for major cytogenetic status at baseline based on CRF data instead of based on randomization data.

Influence of early molecular response levels on long term molecular response levels

The relationship between MMR status at 24 weeks and MMR status at 48 and 96 weeks will be explored using FAS by reporting contingency tables and by applying a logistic regression including treatment group, MMR status at 24 weeks and their interaction as covariates. Treatment group will be included in this summary table. The odds ratios between treatment groups with 95% confidence intervals will be reported, for each category of MMR status at 24 weeks and overall. If the interaction of treatment by MMR status at 24 weeks is significant (e.g. when $p < 0.1$), overall odds ratio for treatment will not be reported.

Efficacy Analysis on Switch Analysis Set

Efficacy analyses on the Switch Analysis Set will be performed at the time of the 96-week analysis. Unless otherwise specified, endpoints are defined and analyzed similarly as specified in Sections 2.5, 2.6, and 2.7 on Switch Analysis Set, but with baseline, FD, LD, and EoT replaced by baseline_switch, FD_{switch}, LD_{switch}, and S-EoT. The below are the efficacy endpoints to be analyzed:

1. MMR rate at and by all protocol-planned visits.
2. CCyR rate at and by all protocol-planned visits.
3. Time to MMR
4. Duration of MMR
5. Time to CCyR
6. Duration of CCyR
7. Time to Treatment Failure

The analysis of time-to-event endpoints will be conducted only if at least 5 events are observed.

2.15 Interim analysis

No formal interim analysis is planned for this trial.

Three to four analyses are planned with the analysis data cut-off dates and the scope of analyses as follows:

- **24-week Primary analysis**: Formal testing of the primary endpoint with full alpha will be performed. Analyses of other efficacy endpoints at and by 24 weeks will also be performed.
- **96-week analysis**: Formal statistical testing of the key secondary endpoint will be performed with $\alpha = 0.05$ (two-sided) only if the primary endpoint (i.e. MMR rate at 24 weeks) is significant. Otherwise, no statistical testing will be performed, and any analysis will be considered exploratory. Analyses of other efficacy endpoints will also be performed.
- **End of study treatment (EOsT) analysis (if required)**: similar to the 96-week analysis without formal statistical testing.

  NOTE: This analysis may be conducted at the same time as 96-week analysis.
- **5-year PFS/OS update analysis**: PFS and OS.

In addition, DMC safety analyses will be conducted. Prior to the database lock for the primary analysis, tables and figures aggregated by treatment arm for safety data review by the DMC or for other reporting activities will be produced by an independent statistician and independent statistical programmers.

3 Sample size calculation

3.1 Primary analysis

To test the null hypothesis that the MMR rate at 24 weeks is equal in the two treatment arms, based on two-sided 5% level of significance and with 90% power, 222 patients will be needed in total (i.e. 148 patients in the asciminib arm and 74 patients in the bosutinib arm based on 2:1 randomization allocation). The calculations were made using the software package PASS (2008).

It is assumed that asciminib leads to a 20% improvement in the MMR rate at 24 weeks over bosutinib from 15% to 35% which corresponds to an odds ratio of 3.05. The assumed bosutinib MMR rate of 15% at 24 weeks is based on previous trials evaluating bosutinib therapy ([Kuoury et al. 2012], [Gambacorti-Passerini et al. 2014], [García-Gutiérrez et al. 2015]).

3.2 Power for analysis of key secondary variables

If the primary analysis of MMR rate at 24 weeks is statistically significant, then the key secondary endpoint MMR rate at 96 weeks will be tested, with the overall alpha controlled at the 5% two-sided level using a gatekeeping strategy.

Table 3-1 below summarizes the treatment effects of the key secondary endpoint which can be detected with 80% and 90% power, based on the specified assumptions regarding the bosutinib effect. The calculations were made using the software package PASS (2008).

Table 3-1 Detectable effect sizes for key secondary endpoint

Endpoint	Anticipated effect with bosutinib	2-sided alpha	Power	Detectable effect size§
MMR rate at 96 weeks	30%*	0.05	90%	≥ 23%
			80%	≥ 20%

*: [Gambacorti-Passerini et al. 2014], Figure 1D.
§: Absolute difference from the anticipated effect with bosutinib.

For MMR rate at 96 weeks, if the anticipated effect with bosutinib is 30%, then the given sample size with 2-sided alpha=0.05 would allow to detect an absolute difference of at least 23% (i.e. MMR rate at 96 weeks with asciminib is at least 53%) for 90% power and of at least 20% (i.e. MMR rate at 96 weeks with asciminib is at least 50%) for 80% power.

4 Change to protocol specified analyses

Pharmacokinetic analysis set: Removal of the condition related to vomiting to consider a concentration evaluable as the occurrence and time of vomiting is not collected in the CRF.

The estimand langage was implemented in sections 2.5 and 2.6. Then, the PPS and analyses based on PPS were removed.

The subgroup considering historical BCR-ABL1 mutations was removed as not considered clinically relevant.

A definition for loss of CHR was provided.

Definition of loss of MMR: removed any reference to confirmation of CHR and CCyR as confirmation of CHR and CCyR was not mandated by protocol and was therefore not performed in practise.

The following analyses were added:

ECOG status, time to event analyses for duration of MMR and CCyR, exposure adjusted AE incidence and yearly AE incidence, COVID-19 related sensitivity analyses.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rules should be used for the imputation of the dose end date for a given study treatment component.

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 2: If the dose end date is completely missing and the EOT page is available:

The EOT completion date should be used.

- All other cases should be considered as a data issue and the statistician should contact the data manager of the study.
- After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

  Use the treatment start date

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE, ConMeds and safety assessment date imputation

The imputations specified in this section are only used for analyses of time to and duration of AEs and concomitant medications.

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

Missing Element	Rule
day, month	• If available year = year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY o Else set start date = study treatment start date. • If available year > year of study treatment start date then 01JanYYYY • If available year < year of study treatment start date then 01JulYYYY
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Stratum reported in the CRF

This will be derived from the Bone Marrow Aspirate data recorded in the corresponding eCRF pages at baseline. In some case the baseline sample may be missing or not evaluable (i.e. <20 metaphases).

The following imputation rule will be applied to derive the missing or non evaluable values:

- Major cytogenetic response (MCyR) (0 to 35% Ph+ metaphases) will be assumed if BCR-ABL1 levels ≤10% (IS).

Rationale:

ELN 2013 recommendations are providing treatment milestones with response categories for cytogenetic and molecular response, which we can refer to for the imputation:

6 mo	BCR-ABL1 <1% and/or Ph+ 0	BCR-ABL1 1-10% and/or Ph+ 1-35%	BCR-ABL1 >10% and/or Ph+ >35%

MCyR is roughly corresponding to BCR-ABL1 levels ≤10% (IS) (Ross et al 2009).

5.2 AEs coding/grading

Adverse events are coded using the latest available version of Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters (embedded below). The latest available version of the document based on the underlying CTCAE version v4.03 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values,

summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

EASE LAB - CTC grades in Novartis Or

Imputation Rules

Hematology

Immature cells (promyelocytes, myelocytes, metamyelocytes and blasts) will not be displayed in shift tables and will only be listed.

Immature cells are manually counted only if anomalies are detected during the automatic testing. Therefore, when the automatic testing was performed but no data is transferred for immature cells, this means there was no immature cells and their values can be imputed to 0. Note that there should not be any imputation in case the automatic testing was not performed or the test of immature cells is present with missing value in the database (this would mean the test was to be performed but couldn't).

CTCAE grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of white blood cells (WBC).

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

The following rules will be applied to derive the WBC differential percentages when only differential counts are available for a xxx differential

xxx %value = (xxx count × 100) / WBC count

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mmol/L) = Calcium (mmol/L) +0.02 (40 – [Albumin (g/L)]

For calculation of laboratory CTCAE grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mmol/L) as for calcium.

CTCAE grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

Biochemistry

In order to avoid double reporting of the same information, all available values for BUN and UREA will be reported under the parameter name BUN (mmol/L) in listing using the following conversion rule: UREA (mmol/L)=2.14 BUN (mmol/L) ([Lamb E et al 2012]).

5.4 Efficacy variables

5.4.1 Molecular response

Scaling towards an international standard will be performed for all molecular results using laboratory specific conversion factors. In this process, the raw ratio between BCR-ABL and the control gene ABL is calculated and multiplied by the lab-specific conversion factor ([Branford and Hughes 2006]). Therefore, using the international unit, the BCR-ABL ratio will be presented in %. The MRDx assay using PAXgene^{TM} Blood RNA tubes from MMD laboratory will be used in this study. The lab conversion factor for this assay was 1.1 until 1 June 2020 and 1 thereafter.

The BCR-ABL ratio in IS % is calculated by multiplying the raw BCR-ABL ratio with the lab-specific conversion factor and then by 100:

BCR-ABL ratio (in %) = (BCR-ABL / ABL) * conversion factor * 100

The BCR-ABL ratio in IS% provided by the central laboratory will be use in the analyses. However, to calculate the fold change in BCR-ABL1/ABL used to derive the loss of MMR criteria, in case the BCR-ABL number of copies is reported as a 0 value and the patient doesn't have atypical transcript at baseline, then the value will be replaced by 1, and the BCR-ABL ratio will be calculated.

Molecular response is categorized as follows:

- 10% > BCR-ABL ratio
- 1% < BCR-ABL ratio ≤ 10%
- 0.1% < BCR-ABL ratio ≤ 1%
- 0.01% < BCR-ABL ratio ≤ 0.1%
- 0.0032% < BCR-ABL ratio ≤ 0.01%
- BCR-ABL ratio ≤ 0.0032%

Major molecular response (MMR)

Major molecular response (MMR) is defined as a value of ≤ 0.1% of BCR-ABL ratio on the IS. This endpoint corresponds to a ≥ 3 log reduction in BCR-ABL transcripts from a standardized baseline value for untreated CML patients which was established in the IRIS study (STI5710106). MMR will be considered as a binary variable with patients achieving MMR grouped as 'responders' and patients not achieving MMR or patients with missing PCR evaluations grouped as 'non-responders'.

Loss of MMR

Loss of MMR is defined as an increase in BCR-ABL1/ABL to > 0.1% by international scale (IS) in association with a ≥ 5-fold rise in BCR-ABL1/ABL from the lowest value achieved up to that time point on study treatment and replicated by a second analysis of the same sample. Loss of MMR must be confirmed by a subsequent sample analysis within 4-6 weeks showing loss of MMR associated with a ≥ 5-fold rise in BCR-ABL1/ABL from the lowest value achieved up to that time point on study treatment.

If there is any assessment in between indicating a BCR-ABL ratio of ≤ 0.1% or a < 5-fold increase in BCR-ABL ratio from the lowest value achieved up to that time point on study treatment, then the initial indication of loss of MMR cannot be confirmed. However, an assessment indicating (unconfirmed) loss of MMR will be considered as confirmed loss of MMR if the patient had loss of CHR or loss of complete cytogenetic response (CCyR) after the achievement of MMR. CML-related death or progression to AP or BC will be considered as confirmed loss of MMR in any case (if they occurred on treatment) (given that the patient achieved prior MMR).

5.4.2 Cytogenetic response

Cytogenetic response will be based on the percentage of Ph+ metaphases in the bone marrow. Cytogenetic evaluations will be considered for response assessment only if the number of metaphases examined is ≥ 20 in each bone marrow sample. As per protocol, fluorescent *in-situ* hybridization (FISH) assessments will not be considered for any evaluation of cytogenetic response during treatment.

Cytogenetic response is categorized as follows (a review of a minimum of 20 metaphases is required):

- Complete response (CCyR): 0% Philadelphia chromosome positive (Ph+) metaphases
- Partial response (PCyR): >0 to 35% Ph+ metaphases
- Major response (MCyR = CCyR + PCyR): 0 to 35% Ph+ metaphases
- Minor response (mCyR): >35 to 65% Ph+ metaphases
- Minimal response: >65 to 95% Ph+ metaphases
- None: >95 to 100% Ph+ metaphases.

If bone marrow aspirate blast percentage is provided as '<X' (i.e. below limit of detection), the numeric value is set to X for summary tables. In the listing '<X' will be presented.

Complete cytogenetic response (CCyR)

CCyR is defined as a value of 0% Ph+ metaphases in bone marrow.

CCyR will be considered as a binary variable with patients achieving CCyR grouped as 'responders' and patients not achieving CCyR, patients with missing cytogenetic evaluations grouped as 'non-responders'.

Loss of CCyR

Loss of CCyR is defined as an increase in the Ph+ bone marrow cells to > 0%.

Loss of CCyR must have led to treatment discontinuation because of lack of efficacy (based on the "End of Treatment Phase Disposition" eCRF or "End of Treatment Disposition" eCRF during the Treatment switch phase with Subject status="lack of efficacy" and Reason of treatment failure = "After start of therapy, loss of CHR, CCyR or PCyR").

In addition, CML-related death or progression to AP or BC will be considered as loss of CCyR in any case (if they occurred on treatment).

Major cytogenetic response (MCyR)

MCyR is defined as a value of 0% to 35% Ph+ metaphases in bone marrow.

MCyR will be considered as a binary variable with patients achieving MCyR grouped as 'responders' and patients not achieving MCyR, patients with missing cytogenetic evaluations grouped as 'non-responders'.

Loss of MCyR is defined as an increase in the Ph+ bone marrow cells to > 35%. For patients with response = PCyR, this would constitute loss of PCyR.

CML-related death or progression to AP or BC will be considered as confirmed loss of MCyR in any case (if they occurred on treatment).

5.4.3 Hematologic response

Loss of CHR

Loss of CHR is defined by meeting any of the following:

- WBC count > 20×10^9/L
- Platelet count ≥ 600×10^9/L
- Appearance of blasts or promyelocytes in peripheral blood
- Appearance of myelocytes + metamyelocytes ≥ 5% in peripheral blood
- Progressive splenomegaly refractory to therapy (i.e. ≥ 5cm below left intercostal margin)

Loss of CHR must have led to treatment discontinuation because of lack of efficacy (based on the "End of Treatment Phase Disposition" eCRF or "End of Treatment Disposition" eCRF during the Treatment switch phase with Subject status="lack of efficacy" and Reason of treatment failure = "After start of therapy, loss of CHR, CCyR or PCyR").

In addition, CML-related death or progression to AP or BC will be considered as loss of CHR in any case (if they occurred on treatment).

Complete hematologic response (CHR)

CHR is defined when all of the following criteria are present at any assessment which is confirmed by another assessment at least after 4 weeks:

- White blood cells (WBC) count < 10×10^9 /L
- Platelet count < 450×10^9 /L
- Basophils < 5%
- No blasts and promyelocytes in peripheral blood
- Myelocytes + metamyelocytes < 5% in peripheral blood

- No evidence of extramedullary disease, including spleen and liver. As extramedullary disease is evaluated less frequently than hematology, the results of these evaluations are carried forward until the next assessment (unless extramedullary disease was not present at the current assessment but present at the next).

The assessment is not considered CHR, if there are any values indicative of CML in AP or BC (i.e. by blasts in bone marrow). The information used for hematological assessment will be obtained from the laboratory, extramedullary and bone marrow data, all merged by patient and date. To accommodate for missing parameters, specific laboratory results may be carried forward up to 14 days such that assessments performed within a two-week period can combined into one complete evaluation of hematological response. A value will be carried forward for no more than up to the subsequent valid assessment of the respective laboratory parameter. If even after applying this carry-forward algorithm, any of the above laboratory parameters is not available at a given assessment date, the response assessment will be considered missing, unless any of the available values (including those carried forward) indicates that there is no response in which case the assessment will be 'No response'.

For confirmation of CHR, both the initial CHR as well as the confirming assessment (at least 4 weeks after the initial assessment) must satisfy all the criteria mentioned above and no assessment in between indicates 'No response'. The terms "confirmed CHR" and "CHR" are used as synonymous given that the definition of CHR mentioned above already includes a requirement for confirmation.

5.4.4 Treatment Failure

The following events will constitute 'treatment failure', and are based on the ELN criteria (Baccarani et al 2013) defining failure of a second line treatment adapted to include discontinuation of randomized treatment as an event:

- No CHR or > 95% Ph+ metaphases at three months after initiation of therapy or thereafter
- BCR-ABL1 ratio > 10% IS and/or > 65% Ph+ metaphases at six months after initiation of therapy or thereafter
- BCR-ABL1 ratio > 10% IS and/or > 35% Ph+ metaphases at 12 months after initiation of therapy or thereafter
- Loss of CHR, CCyR or PCyR at any time after initiation of therapy
- Detection of new BCR-ABL1 mutations which potentially cause resistance to study treatment (T315I and V299L), at any time after initiation of therapy
- Confirmed loss of MMR in 2 consecutive tests
- New clonal chromosome abnormalities in Ph+ cells: CCA/Ph+: at any time after initiation of therapy
- Discontinuation from randomized treatment for any reason* (Note that Reason for treatment discontinuation="completed" doesn't indicate a premature treatment discontinuation)

5.4.5 CML progression to accelerated phase (AP) or blast crisis (BC)

For the evaluation of CML progression to AP or BC, the following criteria will be used. Accelerated phase (AP) is defined by any of the following:

- ≥ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate
- ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate
- ≥ 20% basophils in the peripheral blood
- Thrombocytopenia (<100 x 10^9/L) that is unrelated to therapy*

*As thrombocytopenia is a known adverse reaction to CML therapy, platelets <100 × 109/L are only considered as CML-AP if the patient had these values within 30 days of treatment discontinuation due to disease progression. In this case, comments are to be provided on the termination page that thrombocytopenia is indicative of progression to AP and an adverse event (AE) entered with relationship to study treatment = 'Not suspected'

Blast crisis (BC) is defined by any of the following:

- ≥ 30% blasts in peripheral blood or bone marrow aspirate
- Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma).
  The second bullet criteria can't be considered in this study as this information was not collected.

5.4.6 CML-related deaths

CML-related death is considered as any death during treatment or follow-up (safety or survival)

- if the principal cause of death is marked as "study indication" in the eCRF by the investigator,
- or if the death occurred subsequent to documented progression to AP/BC and the cause of death is reported as "unknown" or not reported by the investigator.

With respect to the second bullet, as "unknown" cause of death will be coded to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term 'Death', this MedDRA coding will be used in the derivation of CML-related death.

5.4.7 Disease progression

The following events are considered disease progression

- CML-related deaths
- Accelerated phase (AP)
- Blast crisis (BC)

5.4.8 Overall survival

This includes all-cause deaths.

5.5 Derivation of response rates and categories

5.5.1 Response rate at a specific time point

The molecular and cytogenetic response evaluations will be summarized by the following mutually exclusive categories which are based on the respective assessment within the time window:

- **Response categories** (sections 5.4.1 and 5.4.2)**:** Patients with an available assessment at that time point (+/- time window) indicating any of the response categories.
- **No response:** Patients with assessment at that time point (+/- time window) indicating 'no response'
- **Missing:** Patients without an evaluable response assessment at that time point (+/- time window). This category is then further split into patients who are ongoing without treatment failure at the beginning of the relevant time window, patients who are ongoing with treatment failure at the beginning of the relevant time window, patients who discontinued due to lack of efficacy, disease progression (PD) or death and patients who discontinued due to other reasons.

5.5.2 Response rate by a specific time point (best response)

In this analysis, patients who had achieved any response at or before the time point will be displayed in their best response category, no matter if they lost the response/discontinued or not. Therefore this response rate represents the best observed response rate up to that specific time point (including the time window).

Patients for whom an evaluable response assessment was never provided will be classified as 'Missing'.

5.6 Statistical models

5.6.1 Primary analysis

The null hypothesis of equality of MMR rate at 24 weeks in the two treatment arms will be tested against two-sided alternative. The statistical hypotheses are:

$$H0: RA_{24wk} = RB_{24wk} \text{ versus } HA: RA_{24wk} \neq RB_{24wk}, \text{ for a two-sided test}$$

where RA_{24wk} is the probability of MMR rate at 24 weeks in asciminib arm and RB_{24wk} is the probability of MMR rate at 24 weeks in bosutinib arm.

The Cochran-Mantel-Haenszel chi-square test X^2_{CMH} (implemented via SAS procedure FREQ with CMH option in the TABLES statement), stratified by the randomization stratification factor, i.e. cytogenetic response status (MCyR vs no MCyR) at screening, will be used to test the difference in response rates between the treatment arms. The p-value corresponding to the CMH test for "general association" will be used which follows a Chi-square distribution with one degree of freedom.

The 95% confidence interval for the unstratified difference in MMR rate at 24 weeks between treatment groups will be provided using the Wald method (implemented via SAS procedure FREQ with RISKDIFF option in the TABLES statement, under the default

METHOD=WALD and VAR=SAMPLE). If the 2×2 table is with asciminib in row 1, bosutinib in row 2, MMR in column 1 and No MMR in column 2, then the SAS output will give the estimate of (risk for MMR at 24 weeks in asciminib – risk for MMR at 24 weeks in bosutinib). The corresponding Mantel-Haenszel estimate of common risk difference and 95% confidence interval will also be presented (with RISKDIFF(COMMON) option in the TABLES statement, taking the Mantel-Haenszel estimate from the SAS output table).

If the sampling assumptions for chi-square test is not met (i.e. the expected frequencies should exceed 5 for all of table cells), the exact Cochran-Mantel-Haenszel test will be used (implemented via SAS procedure MULTTEST). The test is performed by running a stratified version of the Cochran-Armitage permutation test [Armitage et al. 1969]. In studies with stratified randomization, the chi-square approximation is considered appropriate for the X^2_{CMH} statistics if the rule of Mantel and Fleiss [Mantel and Fleiss 1980] is satisfied.

Confidence interval for MMR rate within each treatment arm

MMR will be summarized in terms of percentage rates with 95% confidence interval using exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table [Clopper and Pearson 1934]).

5.6.2 Key secondary analysis

The null hypothesis of equality of MMR rate at 96 weeks in the two treatment arms will be tested against two-sided alternative. The statistical hypotheses are:

$$H0: RA_{96wk} = RB_{96wk} \text{ versus } HA: RA_{96wk} \neq RB_{96wk}, \text{ for a two-sided test}$$

where RA_{96wk} is the probability of MMR rate at 96 weeks in asciminib arm and RB_{96wk} is the probability of MMR rate at 96 weeks in bosutinib arm.

The same approaches as for the primary endpoint (Section 5.5.1) will be applied here for the Cochran-Mantel-Haenszel chi-square test X^2_{CMH}, the 95% Wald confidence interval for the difference in MMR rate at 96 weeks between treatment groups, the Mantel-Haenszel estimate of common risk difference with 95% confidence interval, and the confidence interval for MMR rate within each treatment arm.

Multiplicity adjustment

Formal statistical testing of the key secondary endpoint will be performed with $\alpha = 0.05$ (two-sided) only if the primary endpoint is significant by means of a gatekeeping procedure to control the overall alpha level.

5.6.3 Other analyses

Mantel-Haenszel common odds ratio

To obtain Mantel-Haenszel estimates of the common odds ratio and the corresponding 95% confidence interval in exploratory analyses, it requires SAS procedure FREQ with CMH and RELRISK options in the TABLES statement.

Logistic Regression

Odds ratio will be used as a measure of association between treatment and response in exploratory analyses (Section 2.14). The odds ratio will be derived from the logistic regression model (implemented using SAS procedure LOGISTIC, with treatment specified as an explanatory variable in the CLASS statement) which allows for including not only the stratification factor but also for adjustments for other covariates (both categorical and continuous). The odds ratio will be presented with 95% Wald confidence limits.

In cases where an exact test has been used to compare response rates, the odds ratio should be determined using exact logistic regression, and the odds ratio presented with exact 95% confidence limits. In these cases, SAS PROC LOGISTIC with EXACTONLY option will be used.

Kaplan-Meier estimates

An estimate of the survival function in each treatment group will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

Hazard ratio

Hazard ratio will be estimated by fitting the Cox proportional hazards model using SAS procedure PHREG (with TIES=EXACT option in the MODEL statement).

A stratified unadjusted Cox model will be, i.e. the MODEL statement will include the treatment group variable as the only covariate and the STRATA statement will include stratification variable(s). Hazard ratio with two-sided 95% confidence interval will be based on Wald test.

5.6.4 Calculation of exposure-adjusted incidence rate

To adjust for different durations of exposure across treatment arms, the incidence rate per 100 patient-years of exposure (exposure-adjusted incidence rates of adverse events) will be calculated.

The IR/100 pyr is defined as numerator/denominator, where

- Numerator = number of patients with the adverse events of interest (not the number of events; one patient may have more than one event).
- Denominator = patient-years = total time at risk in years = among all patients in the population, sum of the duration of exposure (in days) until the first onset of the event of interest, if the patient experienced the event, or until the date of last dose if the patient did not experience the event / 365.25.

The patient-years (i.e. total time at risk in years) will be calculated as the sum of times at risk in days over all patients in the population / 365.25.

The time at risk for a patient in days will be calculated as follows:

- If the patient experienced the event of interest, the time at risk for this patient is the duration of exposure from the first dose of treatment until the first onset of the event.
- For patients without an event of interest, the time at risk is the total duration of exposure during core study, as applicable.

6 Reference

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NOVARTIS

Clinical Development

ABL001/asciminib

CABL001A2301

A phase 3, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors

Statistical Analysis Plan (SAP) – Addendum 1

Document type:	SAP Documentation
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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
25-Aug-2017	Prior to DB lock for primary analysis	Creation of final version	N/A - First version	NA
26-Mar-2020	Prior to DB lock for primary analysis	Implementation of protocol amendments 2 and 3.	ABL001 has been replaced by International Nonproprietary Name (INN) asciminib.	Throughout the SAP amendment
			Introduction of the switch to asciminib option for patients experiencing treatment failure on bosutinib treatment	Section 1.1, Figure 1-1 Sections 2.1, 2.3 Analyses added throughout the document
			Update of the definition of end of study treatment	Section 1.1
			Added a potential End-of-Study-Treatment analysis different from the 96-week analysis	
			Addition/removal of secondary safety objectives and exploratory efficacy objectives	Table 1-1
		Additional analyses, clarification	Clarification on which data are included in the analyses, which assessments are considered for safety and efficacy analyses	Section 2.1
			Addition of the treatment arms and definition of the date of end of study treatment Removal of windows defined for ECGs, LVEF and PK assessments as they are not needed.	Section 2.1.1

	As per Health Authorities request, addition of the breakdown per different time points of the number (%) of patients who discontinued the study treatment phase and of the primary reason for study treatment phase discontinuation	Section 2.3.1
	PAS: Removal of the condition related to vomiting to consider a concentration evaluable as the occurrence and time of vomiting is not collected in the CRF.	Section 2.2
	Addition of a subgroup "Stratum reported in the CRF" for the analysis by subgroup of the primary endpoint (to take into account the mistratification cases)	Section 2.2.1
	Removal of the subgroup "with or without historical BCR-ABL1 mutation by local lab" as this is not considered clinically relevant	
	Additional analyses of prior TKI and non TKI antineoplastic therapies	Section 2.4.2
	Implementation of the estimand language for the primary and key secondary objectives	Sections 2.5 and 2.6
	Addition of a sensitivity analysis of the primary estimand stratifying by the stratum recorded in the CRF to take into account that many stratification errors occurred	Section 2.5.5
	Addition of Time-to-event analyses for time to MMR and time to CCyR	Section 2.7.2

			Added how time is censored for time to MMR/CCyR, clarification on how to handle missing BMA assessments due to MMR being achieved	Section	2.7.3
			Added analyses AEs and SAEs incidence rates by adjusting for exposure and by reporting by time intervals to account for potential difference in exposure between the treatment arms	Section	2.8.1
			Clarified handling of unscheduled ECG measurements in the analyses	Section	2.8.4.1
4-June-2020	Prior to DB lock for primary analysis	Creation of amendment 2.0	Clarified baseline for mutations	Section	2.1.1
			Clarified EOT is mapped to defined time points		
			Modified age subgroup, added Line of therapy subgroup and moved Without T315I/V299L to Supplementary analysis (All patients with T315I/V299L mutations identified at the Week 1 Day 1 visit are discontinued from study treatment when the mutation results become available). Clarified Mutation subgroup doesn't include T315I/V299L mutations.	Section	2.2.1
			Modified age categories	Section	2.3
			Added COVID-19 related PDs analysis	Section	2.3.1
			Added definitions of time on treatment, duration of exposure in patient-years and average daily dose	Section	2.4.1

	Additional analyses of prior TKI therapy	Section	2.4.2
	Added summary of concomitant therapies for on-switched treatment period.	Sections	2.5.5, 2.6.5
	Added COVID-19 sensitivity analyses for the primary and key secondary endpoints	Section	2.5.6
	Added a supplementary analysis to the primary endpoint (Patients without T315I/V299L mutations at Week 1 Day 1 visit)	Section	2.9
	Added new graph for Ctrough values of asciminib	Section	4
	Updated the list of changes to the protocol specified analyses	Section	5.3
	Added imputation rules for immature cells		
	Removed imputation rules for corrected calcium as corrected calcium is collected		
	Clarified all available values for BUN and UREA will be reported under the parameter name BUN in listing to avoid double reporting of same information	Section	5.4.1
	Definition of loss of MMR: Removed reference to confirmation of loss of CHR/CCyR	Section	5.4.3
	Loss of CHR: clarified "Progressive splenomegaly refractory to therapy" is ≥ 5cm below left intercostal margin"	Section	5.4.4
	Implemented change to definition of treatment failure (Protocol amendment 3)	Section	5.4.5

			Clarified what "Thrombocytopenia (<100 x 109/L) that is unrelated to therapy" is.	Section 5.5.
			Added derivation of response rates and categories section	
7-Aug-2020	Prior to DB lock for primary analysis	Creation of amendment 3.0 after FDA type C teleconference on 28 July 2020	As agreed with FDA, added sensitivity analyses of the primary and key secondary endpoints without the imputation rule used in the main analyses in case of missing PCR evaluations at 24/96 weeks.	Section 2.5.5
			Per FDA request, added another subgroup of interest: BCR-ABL ratio at baseline ≥ 1% or <1%.	Section 2.2.1
			Added calculation rules for duration of interrruption.	Section 2.4.1
			Added derivation rule for corrected calcium using the reported total calcium value and albumin.	Section 5.3
			Aligned the definition of loss of CCyR with the definition of loss of CHR by adding the requirement that loss of CCyR (Ph+ bone marrow cells to > 0%) must have led to treatment discontinuation because of lack of efficacy.	Section 5.4.2
14-Oct-2020	Post DB lock for primary analysis	Creation of addendum 1.0 to include post-hoc analyses added after FIR results review	Added that protocol deviations during the treatment switch period will be reported separately and clarified .	Section 2.3.1
			Clarified how to identify prohibited concomitant medications.	Section 2.4.2
			Added an analysis of time to MMR considering	Sections 2.7.2 and 5.6.3

	discontinuation from treatment due to any reason, without prior achievement of MMR as a competing risk. Added an analysis of the MMR rate using the number of subjects with adequate follow-up as the denominator, i.e. for each time point (week x), only patients randomized at least x weeks prior to the cut-off date will be considered.		
	Added that post-hoc exploration of the treatment effect in different subgroups and assessment of the possible effect of differences in distribution of baseline characteristics were conducted (e.g. distribution of reasons for discontinuation of last prior TKI by gender and treatment, distribution of MCyR status at baseline by reasons for discontinuation of last prior TKI, distribution of mutation status at Week 1 Day 1 by reasons for discontinuation of last prior TKI).	Section	2.14

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List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AP	Accelerated phase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic classification
AUC	Area under the curve
BC	Blast crisis
bid	bis in diem/twice a day
CCyR	Complete cytogenetic response
CHR	Complete hematologic response
CMH	Cochrane-Mantel-Haenszel
CML	Chronic myelogenous leukemia
CML-CP	Chronic myelogenous leukemia in chronic phase
CRO	Contract research organization
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
DAR	Dosage administration record
DI	Dose intensity
DMC	Data monitoring committee
DRL	Drug reference listing
DSUR	Development safety update report
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End of treatment in the treatment phase (patient level)
EOsT	End of study treatment (study level)
ER	Emergency room
FAS	Full analysis set
FD	First dose date of study treatment during the treatment phase
FD_{switch}	First dose date of asciminib during the treatment switch phase
GP	General practitioner
H	Hospitalization
HCRU	Health care resource utilization
HLT	High level term
HLGT	High level group term
IRT	Interactive response technology
IS	International scale
LD	Last dose date of study treatment during the treatment phase
LD_{switch}	Last dose date of asciminib during the treatment switch phase

LLOQ	Lower limit of quantitation
LPFT	Last patient first treatment
LSC	Leukemic stem cell
LVEF	Left ventricular ejection fraction
MCyR	Major cytogenetic response
mCyR	Minor cytogenetic response
MedDRA	Medical dictionary for regulatory activities
MMR	Major molecular response
NCI	National Cancer Institute
NGS	Next generation sequencing
NMQ	Novartis MedDRA Query
OS	Overall survival
PAS	Pharmacokinetic analysis set
PCR	Polymerase chain reaction
PCyR	Partial cytogenetic response
PD	Pharmacodynamic
PDI	Planned dose intensity
PFS	Progression-free rurvival
Ph+	Philadelphia chromosome positive
PK	Pharmacokinetics
PPS	Per-protocol set
PRO	Patient-reported outcomes
PSUR	Periodic safety update report
PT	Preferred term
qd	Qua'que di'e / once a day
RDI	Relative dose intensity
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
S-EoT	End of treatment in the treatment switch phase (patient level)
SMQ	Standardized MedDRA query
SOC	System organ class
Sp	Specialist
TBL	Total bilirubin
TKI	Tyrosine kinase inhibitor
TTF	Time to treatment failure
UC	Urgent care
ULN	Upper limit of norm
VAS	Visual analogue scale
W1D1	Week 1 Day 1
WBC	White blood cells
WHO-DD	World Health Organization Drug Dictionary

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses of primary objective, secondary objectives and selected exploratory objectives for the clinical study reports (CSR) of study CABL001A2301, a phase 3, multi-center, open-label, randomized study of oral asciminib versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors.

The content of this SAP is based on protocol CABL001A2301 version 03. All decisions regarding safety monitoring analysis for the data monitoring committee, 24-week primary analysis, 96-week analysis, end of study treatment analysis, 5-year progression-free survival (PFS)/overall survival (OS) update analysis, and postings for ClinTrial.gov and EudraCT, as defined in this SAP document, have been made prior to the first database lock of the study data for the primary analysis.

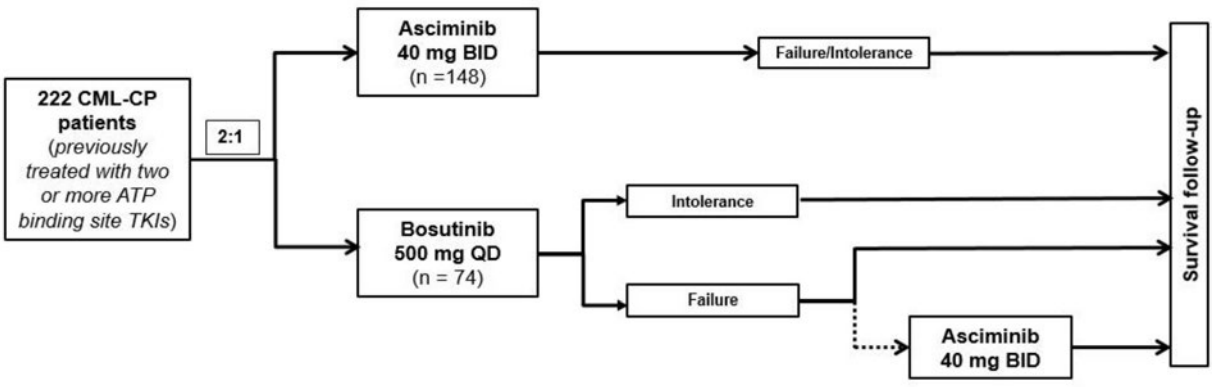
1.1 Study design

This is a randomized, Phase III , open-label, active-controlled, multi-center study comparing safety and efficacy of asciminib to bosutinib in patients with CML-CP, previously treated with 2 or more tyrosine kinase inhibitors (Figure 1-1). Approximately 220 patients will be randomized to one of the following treatment arms in 2:1 ratio:

- asciminib 40 mg BID
- Bosutinib 500 mg QD

Randomization will be stratified by the following factor: cytogenetic response status (with or without major cytogenetic response).

Figure 1-1 Schematic of Study Design



Patients with documented treatment failure (as per the 2013 ELN guidelines, Baccarani et al 2013) while on bosutinib treatment will have the option to switch to asciminib treatment within

96 weeks after the last patient has been randomized on study. The patients who switch to asciminib will be able to receive asciminib up to the end of study treatment (EOsT) period.

Patients will be treated up to the EOsT defined as up to 96 weeks after the last patient received the first study dose (LPFT) or up to 48 weeks after the last patient has switched to asciminib treatment whichever is longer, if they do not discontinue study treatment earlier. After the EOsT, the assigned study treatment will be made available to patients who in the opinion of the investigators are still deriving clinical benefit. This may be outside of this study through alternative options including, but not limited to, an expanded access/compassionate use/managed access program or access to commercial supplies in applicable countries.

Major Molecular Response (MMR) rate at 24 weeks is the primary endpoint in this study. MMR rate at 96 weeks is the key secondary endpoint.

Four analyses are planned for this study, including the 24-week primary analysis, the 96-week analysis, the End-of-Study-Treatment (EOsT) analysis, and Progression-Free survival/Overall survival (PFS/OS) update analysis The timing when those analyses are conducted is summarized in Section 2.1.

No formal interim efficacy analysis is planned in this study. A data monitoring committee (DMC) will monitor unblinded safety data approximately 6 months after the first randomized patient has started study treatment. Subsequent reviews will be conducted approximately every 6 months and when needed thereafter (ie. if significant safety findings are noted) until the primary analysis.

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary	
To compare the MMR rate at 24 weeks of asciminib versus bosutinib	Major Molecular Response (MMR) rate at 24 weeks
Key secondary	
To compare additional parameters of the efficacy of asciminib versus bosutinib	MMR rate at 96 weeks
Other secondary	
To compare additional parameters of the efficacy of asciminib versus bosutinib	• Cytogenetic response rate (Complete, Partial, Major, Minor, Minimal, no response) at and by all scheduled data collection time points including 24, 48 and 96 weeks • MMR rate at all scheduled data collection time points (except 24 and 96 weeks which are already covered by primary and key secondary endpoints) • MMR rate by all scheduled data collection time points including 24, 48 and 96 weeks • Time to MMR • Duration of MMR • Time to CCyR • Duration of CCyR • Time to treatment failure • Progression free survival

Objective	**Endpoint**
	• Overall survival
To compare the safety and tolerability profile of asciminib versus bosutinib	Type, frequency and severity of adverse events, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG and other safety data (vital signs)
To characterize the PK of asciminib in the CML-CP population	Trough plasma concentrations, PK parameters in full PK group: Cmax, Tmax, AUC0-12h, CL/F
To assess the safety of asciminib when administered as treatment after bosutinib failure according to the 2013 ELN Guidelines	Type, frequency and severity of adverse events, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG and other safety data (vital signs)

Objective	Endpoint
Exploratory	
To evaluate the influence of factors such as cytogenetic response at baseline, failure/intolerance to prior TKIs, line of therapy, gender, race and age on the effect of asciminib with respect to the primary efficacy endpoint	Major Molecular Response (MMR) rate at 24 weeks
To explore the exposure-response relationships of asciminib; evaluate the effect of population covariates	Exposure-safety, exposure-PD analyses
To characterize mutations in the BCR-ABL1 gene at Week 1 Day 1, upon confirmed loss of MMR and/or at end of treatment and examine their association with molecular and cytogenetic response for asciminib vs bosutinib	BCR-ABL1 gene mutations at Week 1 Day 1, upom confirmed loss of MMR and/or at end of treatment as determined by Sanger Sequencing
To understand biology of CML and bone marrow microenvironment on leukemic stem cells (LSCs) eradication, including patients' immunogenicity	Bone marrow biopsies characterization for adaptive immune response by immunohistochemistry (IHC); bone marrow aspirates to evaluate the effect of treatments on LSCs burden and immune cells subsets changes by flow cytometry
To assess clonal evolution during treatment with asciminib vs. bosutinib	Low level BCR-ABL1 mutation profiles assessed by mass spectrometry at Week 1 Day 1, upon confirmed loss of MMR and/or at EOT. Clonal evolution of several genes implicated in CML assessed by Next Generation Sequencing (NGS) methods
To evaluate soluble/inflammarory factors that correlate with response to asciminib vs. bosutinib treatment	Baseline and changes from baseline of cytokine expression in plasma
To compare the impact of treatment on patient reported outcomes (PRO) including CML-specific symptoms, patient quality of life, and impact on work productivity and activity impairment from baseline and EOT between treatment arms in all patients	Change in symptom burden and interference from baseline over time according to the MDASI-CML PRO instrument Change in patient's impression of CML symptoms according to Patient Global Impression of Change (PGIC) Change in health utility from baseline over time according to EQ-5D-5L Change in work productivity and activity impairment over time according to WPAI
To compare the impact of treatment on health care resource utilization between treatment arms in all patients	Health care resource burden over time

2 Statistical methods

2.1 Data analysis general information

The planned analyses will be performed by Novartis and/or a designated CRO. SAS version 9.4 or later will be used to perform all data analyses and to generate tables, figures and listings.

There is no planned interim efficacy analysis. Prior to the database lock for the primary analysis, tables and figures aggregated by treatment arm for safety data review by the data monitoring committee or for other reporting activities will be produced by an independent statistician and independent statistical programmers.

For between-treatment comparisons of efficacy endpoints, randomization stratification factor, i.e. cytogenetic response status (MCyR vs no MCyR) at screening, will be included in respective stratified statistical tests.

Data included in the analyses

The analysis data cut-off dates for the planned analyses are:

- Primary analysis: After all randomized patients have been on study treatment for 24 weeks or discontinued earlier, i.e., LPFT + 24 weeks.
- 96-week analysis: After all randomized patients have been on study treatment for 96 weeks or discontinued earlier, i.e., LPFT + 96 weeks
- End of study treatment analysis: 30 days after the EOsT. (Note: After the study treatment period, the assigned study treatment will be made available, may be outside of this study, to patients who in the opinion of the investigators are still deriving clinical benefit.)
- PFS/OS update analysis: 5 years from the date when the last randomized patient received the first study dose (irrespective of treatment switch for patients failing bosutinib).

All statistical analyses will be performed using all data collected in the database up to the respective data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the respective cut-off date and end date after the respective cut-off date will be reported as ongoing. The same rule will be applied to events starting before or on the respective cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by treatment group; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment group. For pharmacokinetics (PK) concentration and parameters descriptive statistics also include coefficient of variation (CV)%, geo-mean and geo-CV%.

2.1.1 General definitions

Investigational drug and study treatment

Investigational drug, will refer to the asciminib only. Whereas, ***study treatment*** will refer to asciminib or control treatment, i.e. bosutinib, received during the treatment phase. Switched treatment will refer to asciminib received during treatment switch phase.

Treatment arms

- Asciminib (Subjects randomized to asciminib arm at the beginning of the study)
- Bosutinib (Subjects randomized to bosutinib arm at the beginning of the study)

Date of end of study treatment (EOsT)

The EOsT date is the date that the study treatment is ended for the entire study. On this date, patients are treated for at least 96 weeks if they are not eligible to switch study treatment or are treated for at least 48 weeks after they have switched to asciminib treatment, unless patients have discontinued study treatment earlier

Date of first administration of randomized study treatment

The date of first administration of randomized study treatment (FD) is derived as the first date when a non-zero dose of study treatment was administered as per the Dosage Administration Record (DAR) electronic case report form (eCRF). The date of first administration of study treatment will also be referred as ***start of study treatment***.

The date of first administration of randomized study treatment is the same as the date of first administration of investigational drug or control drug.

Date of first administration of switched treatment

For subjects switching from bosutinib to asciminib, the date of first administration of switched treatment (FD_{switch}) is derived as the first date when a non-zero dose of asciminib was administered as per the DAR eCRF. The date of first administration of switched treatment (asciminib) will also be referred as ***start of switched treatment***.

Date of last administration of randomized study treatment

The date of last administration of randomized study treatment (LD) is defined as the last date when a non-zero dose of study treatment was administered as per DAR eCRF. For subjects switching from bosutinib to asciminib, this includes the dose of bosutinib administered as bridging therapy between their treatment failure and the first dose of asciminib administered.

The date of last administration of randomized study treatment is the same as the date of last administration of investigational drug or control drug.

Date of last administration of switched treatment

The date of last administration of switched treatment (LD_{switch}) is defined as the last date when a non-zero dose of switched treatment (asciminib) was administered as per DAR eCRF.

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date, etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date, etc.) − reference start date if event precedes the reference start date.

The reference start date for safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, PK, etc.) is the start of study treatment.

The reference start date for all other, non-safety assessments (e.g. molecular response, survival time, disease progression, ECOG performance status, patient reported outcomes (PRO), etc.) is the date of randomization.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Switch study day

The switch study day, describes the day of the event or assessment date, relative to the start of switched treatment.

Switch study day = date of event ‑ start of switched treatment + 1, if event is on or after the start of switched treatment

Switch study day = date of event ‑ start of switched treatment, if event precedes the start of switched treatment

The switch study day will be displayed in the data listings if an event starts on or after the start of switched treatment.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 (=365.25/12) days. If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

A week length is defined as 7 days. If duration is reported in weeks, duration in days will be divided by 7.

Baseline for the treatment period

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as “baseline” value or “baseline” assessment. In

the context of baseline definition, the efficacy evaluations also include PRO and performance status.

For safety evaluations, the last available assessment, including unscheduled assessments before the date of start of study treatment is taken as ‘‘baseline” assessment.

For pre-dose electrocardiogram (ECG), the last available assessment before the treatment start date/time is used for baseline.

For ECGs, where study requires multiple replicates per time point, the average of theses measurements would be calculated for baseline (if not already available in the database).

For mutations, the Week 1 Day 1 assessment is taken as “baseline” assessment.

In rare cases where multiple laboratory measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline.

If patients have no value as defined above, the baseline result will be missing.

Baseline for the treatment switch period

For subjects switching from bosutinib to asciminib, the last non-missing assessment, including unscheduled assessments before the date of first administration of asciminib is taken as ‘‘baseline” assessment for the switched treatment period, and denoted as baseline_switch for short.

On-treatment assessment/event and observation periods

For adverse event reporting the overall observation period will be divided into three mutually exclusive segments for subjects without treatment switching and into up to five mutually exclusive segments for subjects switching treatment:

For subjects without treatment switching:

1. ***pre-treatment period***: from day of patient’s informed consent to the day before first administration of study treatment (FD)
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of study treatment (including start and stop date) (LD). Note: Patients will be treated up to the end of study treatment period (EOsT). This will be the last actual administration of study treatment for each patient if the patient has not discontinued study treatment earlier. On this date, all patients without treatment switching will have been treated for at least 96 weeks unless patients have discontinued study treatment earlier. After this period, the assigned study treatment will be made available, may be outside of this study, to patients who in the opinion of the investigators are still deriving clinical benefit.
3. ***post-treatment period***: starting at day 31 after last administration of study treatment.

For subjects with treatment switching from bosutinib to asciminib:

- ***pre-treatment period***: from day of patient's informed consent to the day before first administration of study treatment (FD)
- ***on-treatment period***: from date of first administration of study treatment to either the day before the first administration of asciminib (FD_{switch}) or 30 days after the date of last actual administration of bosutinib (LD), whichever comes first.
- ***post-treatment period***: from day 31 after last administration of bosutinib to the day before the first administration of asciminib (FD_{switch}). If the end date is before the start date, this period is not applicable.
- ***on-switched treatment period***: from date of first administration of asciminib (FD_{switch}) to 30 days after date of last actual administration of asciminib (LD_{switch}).
  NOTE: Subjects are treated in the study up to end of study treatment period (EOsT). On this date, all subjects with treatment switching will have been treated for at least 48 weeks after switching unless they have discontinued the switched treatment earlier.
- ***Post-switched treatment period:*** from day 31 after last actual administration of asciminib (LD_{switch}).

If dates are incomplete in a way that clear assignment to pre-, on-, post-, on-switched-, post-switched-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

Safety summaries (tables, figures) on the Safety set (respectively on the Switch Analysis Set) include only data from the on-treatment (resp. on-switched treatment) period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In particular, summary tables for adverse events (AEs) will summarize only on-treatment (resp. on-switched treatment) events, with a start date during the on-treatment (resp. on-switched treatment) period (***treatment-emergent*** AEs) (resp. switched-treatment-emergent AEs). In addition, a separate summary for death including on-treatment and post-treatment deaths will be provided.

However, all safety data (including those from the pre-treatment, post-treatment and post-switched treatment period) will be listed and flagged as appropriate.

Efficacy summaries on the FAS (apart from OS and PFS) include data from baseline up to either the last assessment on or before the EoT visit or before or on treatment failure, whichever is the earliest.

Efficacy summaries on the Switch Analysis Set include data from baseline_switch up to the last assessment on or before the S-EoT visit or before or on treatment failure during the switched treatment period, whichever is the earliest.

The efficacy assessments collected post-treatment failure, post-EoT or post S-EoT visit are not included in any efficacy analyses (except for OS and PFS analyses). However, they will be listed and flagged as appropriate.

Windows for multiple assessments

Data such as molecular response, cytogenetic response collected over time (including unscheduled visits) will be summarized by scheduled time point. As patients do not always adhere to the visit schedule, visits will be remapped according to visit windows defined in Tables 2-1 to Table 2-4 of this document to enable by-visit analysis. Only those protocol-defined visits will have the visit window defined. Each assessment (including the end of treatment assessment), either scheduled or unscheduled, will have a mapped visit assigned, as long as study day is available, according to the defined visit window up to the date with data included.

If more than one assessment is assigned to the same time window, the assessment performed closest to the target date will be used for by-visit statistical analyses. If 2 assessments within a visit window are equidistant from the target date, then the average of the 2 assessments will be used. If multiple assessments on the same date, then the the average will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Table 2-1 Time windows for molecular response

Assessment	Target day of assessment	Time Interval
Baseline	≤ 1	≤ Day 1#
Week 4	29	Day 2 to day 43
Week 8	57	Day 44 - 71
Week 12	85	Day 72 - 99
Week 16	113	Day 100 to day 141
Week 24	169	Day 142 to day 211
Week k (k=36, 48, …)	kx7 + 1	Day kx7-40 – kx7+43

Day 1 = Date of randomization
EOT assessments are mapped to the time points as needed.

Table 2-2 Time windows for cytogenetic response

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1#
Week 24	169	Day 2 to day 253
Week 48	337	Day 254 to day 421
Week 72	505	Day 422 to day 589
Week 96	673	Day 590 to day 700

Day 1 = Date of randomization
EOT assessments are mapped to the time points as needed.

For PRO data time windows will be defined for descriptive summary by visit and longitudinal data analysis. If more than one assessment is available in the same time window, the assessment closest to the planned date will be considered. If two assessments are obtained with the same time difference compared to the scheduled visit day, the assessment obtained prior to visit will be considered.

Table 2-3 Time windows for PRO: MDASI-CML, EQ-5D-5L, PGIC

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1#
Week 4	29	Day 2 - 43
Week 8	57	Day 44 - 71
Week 12	85	Day 72 - 99
Week 16	113	Day 100 - 141
Week 24	169	Day 142 - 211
Week 36	253	Day 212 - 295
Week 48	337	Day 296 - 505
Week 96	673	Day 506 - 700

Day 1 = Date of randomization

Table 2-4 Time windows for PRO: WPAI-CML

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1#
Week 4	29	Day 2 - 57
Week 12	85	Day 58 -127
Week 24	169	Day 128- 253
Week 48	337	Day 254 - 505
Week 96	673	Day 506 - 700

Day 1 = Date of randomization

Here's the general rule for the target day of assessment and time interval: For Week k visit, target day of assessment is defined as k*7+1. For the time interval, "Lower limit" = "upper limit

of prior applicable visit" +1. "Upper limit" = "target day of current visit" + integer part of ("target day of next applicable visit" – "target day of current visit")/2.

Visit window for the switched treatment period will use the same rules as described above but with Day 1 being the date of first administration of asciminib. Visit name for the switched treatment period will be defined similarly with annotated by beginning with "S-" (e.g. S-Week 4) to differentiate from those used for the randomized treatment period.

Last contact date

The last contact date will be derived for patients not known to have died at the respective analysis data cut-off date using the last complete date among the following:

Table 2-5 Last contact date data sources

Source data	Conditions
Date of randomization	No condition
Last contact date/last date patient was known to be alive from Survival Follow-up page	Patient status is reported to be alive, lost to follow-up or unknown
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term
Start/End dates from drug administration record	Non-missing dose. Doses of 0 are allowed
End of treatment date from end of treatment page	No condition
Any specific efficacy (molecular or cytogenetic) assessment date if available	Evaluation is marked as ‘done’
Laboratory/PK collection dates	Sample collection marked as ‘done’
Vital signs date	At least one non-missing parameter value
Performance status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the respective data cut-off date. The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post the cut-off date will be used. Completely imputed dates (e.g. the analysis data cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date.

The last contact date will be used for censoring of patients in the analysis of overall survival.

2.2 Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment and stratum they have been assigned to during the randomization procedure.

Safety Set

The **Safety Set** includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment actually received.

The actual treatment received corresponds to:

- the randomized treatment if patients took at least one dose of that treatment;
- the first treatment received if the randomized treatment was never received.

Pharmacokinetic Analysis Set

The **Pharmacokinetic Analysis Set (PAS)** includes all patients who provide at least one evaluable PK concentration. For a concentration to be evaluable, patients are required to:

- Take a dose of asciminib prior to sampling
- Take the same dose of asciminib for at least 3 consecutive days without dose interruption or dose modification prior to sampling
- Have the pre-dose sample collected before the next dose administration

Other analysis sets

- For duration of MMR and time to MMR (descriptive analysis), the **MMR Responder Set** will be used that is a subset of FAS and includes patients who achieve MMR at any time on study treatment.
- For CCyR rates at and by scheduled time points and time to CCyR (Kaplan-Meier analysis), the **CCyR Analysis Set** will be used that is a subset of FAS and includes patients who are not in CCyR at baseline.
- For duration of CCyR and time to CCyR (descriptive analysis), the **CCyR Responder Set** will be use that is a subset of FAS and includes patients who do not have CCyR at baseline and achieve CCyR at any time on study treatment.
- For analyses of patients switched to asciminib, the **Switch Analysis Set** will be used that is a subset of FAS and includes patients who switched from bosutinib to asciminib and received at least one dose of asciminib.

Patient Classification

Patients may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific subject classification rules defined in Table 2-6.

Table 2-6 Subject classification based on protocol deviations and non protocol deviation criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written inform consent	Not applicable
Safety set	No written inform consent	No dose of study medication
PK analysis set	No written inform consent	See definition of PAS
MMR Responder Set	Not applicable	See definition of MMR Responder Set
CCyR Analysis Set	Not applicable	See definition of CCyR Analysis Set
CCyR Responder Set	Not applicable	See definition of CCyR Responder Set
Switch Analysis Set	Not applicable	See definition of Switch Analysis Set

Withdrawal of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the eCRF.

2.2.1 Subgroup of interest

Subgroup analyses will use the same method as for the analysis in the respective overall analysis set.

The objective for carrying out these subgroup analyses is to identify potential issues that may be limited to a subgroup of patients, or that are more commonly observed in a subgroup of patients.

Summary tables and figures will be generated only for subgroups with at least 15 patients.

Efficacy

The primary efficacy endpoint will be summarized by the following subgroups to examine the homogeneity of treatment effect provided that the primary efficacy analysis based on the FAS is statistically significant:

- Stratification factor (based on randomization data from Interactive Response Technology [IRT]): “Major Cytogenetic Response” or “No Major Cytogenetic Response”
- Stratum reported in the CRF (derived using the data collected on the Bone Marrow Aspirate eCRF at baseline: see Appendix): “Major Cytogenetic Response” or “No Major Cytogenetic Response”

- Sex: Female or male
- Race: Asian, Caucasian, or others
- Age category (≥18-< 65 years, ≥ 65 years, ≥ 75 years,)
- Reason for discontinuation of the last prior Tyrosine Kinase Inhibitor (TKI): Failure (i.e. lack of efficacy) or intolerance (i.e. adverse event, lack of tolerability). Note: Only one reason for discontinuation is allowed for each prior therapy.
- Number of prior TKI therapies: 2, 3 or ≥4
- Line of therapy of randomized treatment: 3rd, 4th or ≥5th
- With or without Week 1 Day 1 BCR-ABL1 mutation (other than T315I or V299L) by Sanger Sequencing at central lab: Wild type or mutant
- BCR-ABL ratio at baseline ≥ 1% or <1%

No formal statistical test of hypotheses will be performed for the subgroups, only point estimate of the treatment effect and 95%-confidence intervals will be provided (see Section 2.14 for further analysis details). The objective of the efficacy subgroup analysis is to demonstrate homogeneity of treatment effect in the above subgroups.

Safety

Subgroup analyses for selected safety endpoints will be defined when required.

Japan-specific subgroup analyses

Two subgroups will be formed based on geographic region: Japan or other region (this is not based on ethinicity). These subgroup analyses will be only used for submission to Japan health authority.

Summary tables and figures will be presented for the two subgroups for the following outcome measures:

- Baseline characteristics: Tables of demographics, diagnosis and extent of cancer, extramedullary involvement, bone marrow analysis, molecular response, prior TKI and non-TKI, patient disposition, analysis sets by stratum
- Exposure: Tables of duration of exposure, dose received
- Tables of concomitant medications as well as surgical and medical procedures
- PK (only in asciminib arm): Table and figure of asciminib concentration by time, table of asciminib PK parameters (patients with full PK sampling), figure of average trough asciminib concentration from week 2, 4, 12 and 24 vs. BCR-ABL ratio IS (%) at 24 weeks
- AEs: Tables of all AEs, treatment-related AEs, AEs requiring dose adjustment or interruption, AEs requiring additional therapies, serious adverse events (SAEs), adverse events of special interest (AESIs), overview table of AEs and death
- ECG: Tables of Notable ECG values, change from baseline in ECG parameters values
- Lab: Hematology shift table, biochemistry shift table
- Efficacy: Tables of molecular response categories at and by each time point, MMR rate at and by each time point, time to MMR, duration of MMR, cytogenetic response

categories at and by each time point, time to CCyR, duration of CCyR, TTF, PFS, OS. Figures of cumulative incidence of MMR and of CCyR, association between Week 1 Day 1 BCR-ABL1 gene mutation and clinical outcome.

2.3 Patient disposition, demographics and other baseline characteristics

The FAS will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries will be reported by treatment arm and for all patients, and listings will be reported by treatment arm to assess baseline comparability. No inferential statistics will be provided.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by treatment arm. Categorical data (e.g. age groups: 18 - <65, 65 - <75, and ≥ 75 years and 18 - <65, ≥ 65 years, sex, race, ethnicity, ECOG performance status) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height, body mass index) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum), where BMI (kg/m^2) will be calculated as weight[kg] / (height[m]^2) using weight at screening.

For the Switch Analysis Set, the initial baseline and "baseline_switch" value will be summarized. Weight, BMI, age and ECOG performance status will be summarized using the "baseline_switch" value defined in Section 2.1.2.

In addition, a summary table by sex, age group (18 - <65, 65 - <85, and ≥ 85 years) and treatment group and another summary table by race and treatment group will be generated using the safety set for DSUR/PSUR.

Baseline stratification factors

The number (%) of patients in each stratum ("Major Cytogenetic Response" or "No Major Cytogenetic Response") based on data obtained from the IRT system will be summarized overall and by treatment arm for the FAS. Discordances between the stratum recorded in IRT at the time of randomization and the stratum recorded in the clinical database through the data collected on eCRF will be cross-tabulated and listed. In case the baseline bone marrow aspirate is missing or not evaluable (i.e. < 20 metaphases), the stratum recorded in the clinical database will be imputed following the rule described in Appendix 5.1.2.1.

Baseline cytogenetic response and molecular response

Baseline and Baseline_switch will be summarized for cytogenetic response and molecular response for the FAS and Switch Analysis Set respectively.

Diagnosis and extent of cancer

All diagnosis and extent of cancer data will be summarized and listed by treatment arm. One summary table will include time (years) since initial diagnosis (descriptive statistics with N, mean, median, standard deviation, minimum and maximum) and historical mutation: present

(unknown, yes, no), historical CML-associated mutation status (E225K, E255V, E355G, etc.) (frequency counts and percentages). Another table will include extramedullary involvement: any extramedullary involvement (Yes/No) and location of extramedullary involvement (Spleen, Liver) (frequency counts and percentages).

For the Switch Analysis Set, the above information will be based on the last observation prior to the Baseline_switch.

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on eCRF will be summarized and listed by treatment arm. The summary will be presented by primary system organ class (SOC), preferred term (PT) and treatment arm. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

In addition, separate listings will be produced for medical history possibly contributing to liver dysfunction, and medical history of protocol solicited cardiovascular events.

The cardiovascular risk factors, heavy smoking, low physical activity, unhealthy diet, and other, are collected prior to randomization and the EoT visit. A listing by treatment arm will be presented.

Family medical history of each patient for ischemic heart disease, cardiac arrhythmia, sudden death, high cholesterol, diabetes mellitus, heart defects (congenital heart disease), and heart failure is also collected prior to randomization and at the EoT visit. A listing by treatment arm will be presented.

Other

All data collected at baseline, including child bearing potential as well as informed consent for additional research on study data and biological samples, will be listed.

2.3.1 Patient disposition

Enrollment by country and center will be summarized for all screened patients and also by treatment arm using the FAS. The number (%) of randomized patients included in the FAS will be presented overall and by treatment group. The number (%) of screened and not-randomized patients and the reasons for screening failure will also be displayed. The eligibility criteria will be also summarized. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment group.

The following summaries will be provided (with % based on the total number of FAS patients):

- Number (%) of patients who were randomized (based on data from IRT system)
- Number (%) of patients who were randomized but not treated (based on DAR eCRF page not completed for any study treatment component)
- Primary reason for not being treated (based on “End of Treatment Phase Disposition” eCRF page)

- Number (%) of patients who were treated (based on DAR eCRF pages of each study treatment completed with non-zero dose administered)
- Number (%) of patients who are still on-treatment (based on the "End of Treatment Phase Disposition" page not completed);
- Number (%) of patients who discontinued the study treatment phase overall, before Week 24, Week 48 and Week 96 (based on the "End of Treatment Phase Disposition" page)
- Primary reason for study treatment phase discontinuation overall, before Week 24, Week 48 and Week 96 (based on the "End of Treatment Phase Disposition" page)
- Number (%) of patients who have entered the survival follow-up (based on the "End of Treatment Phase Disposition" page)
- Number (%) of patients in the FAS randomized to the bosutinib arm who switched to receive asciminib (based on DAR – ABL0001 eCRF page completed with non-zero dose administered during the Treatment switch phase);

The following summaries will be provided with % based on the total number patients in the Switch Analysis Set:

- Number (%) of patients who switched from bosutinib arm to receive asciminib and are still receiving asciminib (based on the "End of Treatment Disposition" eCRF not completed during the Treatment switch phase);Number (%) of patients who switched from bosutinib arm to receive asciminib and discontinued asciminib (based on the "End of Treatment Disposition" eCRF during the Treatment switch phase);
- Primary reason for treatment switch phase discontinuation (based on the "End of Treatment Disposition" eCRF during the Treatment switch phase)
- Number (%) of patients who have entered the survival follow-up (based on the "End of Treatment Disposition" eCRF during the Treatment switch phase)

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation during the randomized treatment period will be tabulated by deviation category (as specified in the Study Specification Document) overall and by treatment group for the FAS. All protocol deviations will be listed. In addition, the number (%) of patients in the FAS with any COVID-19 related protocol deviation (COVID-19 specific protocol deviations as well as non-specific COVID-19 protocol deviations with a COVID-19 relationship) during the randomized treatment period will be tabulated by deviation category (as specified in the Study Specification Document) overall and by treatment group. The same information will be tabulated for protocol deviations occuring during the treatment switch period for the switch analysis set.

Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized by treatment group and stratum. Reasons leading to exclusion from analysis sets will be listed by treatment group and stratum as well as tabulated overall and by treatment group.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, average daily dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment arm. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of subjects in each interval. The number (%) of subjects who have dose reductions or interruptions, and the reasons, will be summarized by treatment group.

Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set and Switch Analysis Set will be used for all summaries and listings of randomized and switched treatments respectively.

To summarize exposure data for the randomized treatment period, this will be based on patients in the Safety set with the date of last administration of study treatment and the date of first administration of study treatment being FD and LD respectively.

To summarize exposure data for the switched treatment period, this will be based on patients in the Switch Analysis Set with the date of last administration of study treatment and the date of first administration of study treatment being FD_{switch} and LD_{switch} respectively.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to the investigational drug or control:

Duration of exposure to study treatment (weeks) = ((date of last administration of study treatment) – (date of first administration of study treatment) + 1) / 7.

The **duration of exposure in patient-years** is the total of the duration of exposure in years from all the patients in a treatment group.

The date of last administration of study treatment is defined in Section 2.1.1.

Summary of duration of exposure to study treatment will include categorical summaries based on intervals (<24 weeks, ≥24 weeks, ≥48 weeks, ≥96 weeks) and continuous summaries (i.e. mean, standard deviation etc.).

Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure.

The **planned cumulative dose** for a study treatment refers to the total planned dose as per the protocol up to the last date of study treatment administration. The calculations for the two study treatments are:

- ABL001: 40 mg/administration × 2 (administration/day) × duration of exposure (day)

- Bosutinib: 500 mg/day × duration of exposure prior to dose escalation (day) + 600 mg/day × duration of exposure since dose escalation (day), where the starting day of dose escalation is identified as the first record in the DAR eCRF with dose increased and reason "As per protocol".

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the DAR eCRF. It is the sum of the non-zero total daily doses recorded over the dosing period. For patients who did not take any drug the actual cumulative dose is by definition equal to zero. The actual cumulative dose will be summarized for each of the study treatment.

Dose intensity and relative dose intensity

Average Daily Dose (ADD) is defined as:

ADD (mg/day) = Actual cumulative dose (mg) / Time on treatment (day).

Time on treatment (weeks) = ((date of last administration of study treatment) – (date of first administration of study treatment) + 1 – number of days with dose interruption*) / 7

*For subjects in the asciminib arm, this includes the half days before and after the period with 0 dose if the treatment was interrupted after the morning dose and/or resumed in the evening (1 day record with QD dose administered before or after a record with 0 dose).

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (mg/day) = Actual cumulative dose (mg) / Duration of exposure to study treatment (day).

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as:

PDI (mg/day) = Planned cumulative dose (mg) / Duration of exposure (day).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg/day) / PDI (mg/day).

ADD, DI and RDI will be summarized separately for the two study treatments.

Dose changes, interruptions or permanent discontinuations

The number of subjects who have dose increase (allowed for bosutinib starting week 8, see protocol Section 6.2), dose reductions, dose interruptions or permanent discontinuations, and the reasons, as well as the duration of dose interruption due to any reason will be summarized separately for the two study treatments. For any subjects, duration of dose interruption will be calculated by adding all individual episodes of dose interruption for that patient. For subjects in the asciminb arm, this includes the half days before and after the period with 0 dose if the treatment was interrupted after the morning dose and/or resumed in the evening (1 day record with QD dose administered before or after a record with 0 dose).

'Dose Changed', 'Dose Interrupted' and 'Dose Permanently Discontinued' fields from the DAR eCRF pages will be used to determine the dose changes, dose interruptions, and permanent discontinuations, respectively.

The corresponding fields 'Reason for Dose Change/Dose Interrupted' and 'Reason for Permanent Discontinuation' will be used to summarize the reasons.

A dose change occurs when total daily dose is different from the most recently planned dose. For patients in asciminib arm, there is only one planned dose, i.e. 80 mg/day. For patients in bosutinib arm, the initial planned dose is 500 mg/day and could be changed to 600 mg/day in week 8 or later.

For the purpose of summarizing interruptions and reasons, multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in the mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Reduction: A dose change where the actual total daily dose is lower than the most recently planned dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the eCRF, while number of reductions will be derived programmatically based on the change and the direction of the change.

Increase: A dose change where the actual total daily dose is greater than the most recently planned dose. Therefore any dose change to correct a dosing error will not be considered a dose increase. Only dose change is collected in the eCRF, while number of increase will be derived programmatically based on the change and the direction of the change.

2.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

The number and percentage of patients who received any prior anti-neoplastic medications will be summarized by treatment arm for the lowest anatomical therapeutic classification (ATC) class and preferred term. A listing will also be produced.

Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD). Details regarding WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS.

The following information will be summarized for the FAS and Switch Analysis Set:

- Prior TKI by medication (e.g. imatinib, dasatinib, nilotinib, ponatinib, bosutinib, etc.)
- Number of prior TKI (e.g. 2, 3, 4, etc.)
- Number of lines of prior TKI therapy (2, 3, 4, 5+)
  A new line of therapy is considered each time a change in TKI occured. Multiple entries for the same TKI will be counted as separate lines of therapy if a different TKI is received between the different entries.
- Time on each line of prior TKI therapy (in years)
- Time on last prior TKI (in years)
- Reason to discontinue the most recent TKI therapy at the time of screening
- Prior non-TKI therapies (Yes, No).

A Sankey-like plot showing the sequence of prior TKIs will be provided.

Note: In case the last TKI given prior to enrollment in the study was a bridging therapy (i.e. reason for discontinuation includes a wording related to bridging), it will not be considered in the analysis of prior TKIs. In particular, it will not be considered as the last or most recent TKI therapy at the time of screening and will not count as an additional line of therapy.

For the Switch Analysis Set, bosutinib received during the randomized treatment period and other TKIs received since discontinuation of bosutinib and before first administration of asciminib (FD_{switch}) should be considered as prior TKIs.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by the lowest anatomical therapeutic classification (ATC) class, preferred term, overall and by treatment group by means of frequency counts and percentages using FAS.

Anti-neoplastic medications will be coded using the WHO-DD. Details regarding WHO-DD version will be included in the footnote in the tables/listings.

Concomitant therapies

Concomitant therapies are defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapies include medications (other than study drugs) and medical procedures starting on or after the start date of study treatment, or starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO ATC classification system and summarized by the lowest ATC class and PT using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and PT.

The summaries for the on-treatment period using the Safety Set will include:

- Therapies starting on or after the start of randomized study treatment but no later than the end of the on-treatment period and
- Therapies starting prior to start of randomized study treatment and continuing after the start of randomized study treatment.

These summaries for the on-switched treatment period using the Switch Analysis Set will include:

- Medications starting on or after the start of switched treatment but no later than the end of the on-switched treatment period and
- Medications starting prior to start of switched treatment and continuing after the start of switched treatment.

All concomitant therapies will be listed using the Safety Set. Any concomitant therapies starting and ending prior to the start of randomized study treatment or starting beyond end of the on-treatment period if not switched, or starting beyond end of on-switched treatment period if switched will be flagged in the listing.

The prohibited concomitant medications will be summarized by lowest ATC class and preferred term up to the end of on-treatment and on-switched treatment periods, respectively. Prohibited medications will be concomitant medications that led to the protocol deviation "Use of prohibited concomitant medication".

2.5 Analysis of the primary objective/estimand

In this section, the targeted treatment effect corresponding to the primary objective as well as the primary objective is clarified using the estimand language.

The primary clinical question of interest is: Is the efficacy of asciminib (40 mg bid) superior to bosutinib (500 mg qd) in CML patients in chronic phase, previously treated with 2 or more tyrosine kinase inhibitors, with regards to achieving MMR at 24 weeks while on study treatment and without meeting any treatment failure criteria (defined in section 5.4.4) prior to 24 weeks, regardless of dose modification, dose interruption, or deviation in any intake of concomitant medications.

The primary estimand is described by the following attributes:

Population: CML patients in chronic phase, previously treated with 2 or more tyrosine kinase inhibitors. Further details about the population are provided in Section 5 of the protocol.

Endpoint: Major Molecular Response (MMR) achieved at 24 weeks while on study treatment without meeting any treatment failure criteria (defined in section 5.4.4) prior to 24 weeks. A patient will be counted as having achieved MMR at 24 weeks if he/she meets the MMR criterion (BCR-ABL ratio $\leq$ 0.1%) at 24 weeks while on study treatment unless the patient met any treatment failure criteria (defined in section 5.4.4) prior to 24 weeks.

Intercurrent events:

- Treatment discontinuation (i.e. having performed an EOT visit) prior to 24 weeks due to any reason (e.g. intolerance, treatment failure, death, etc.): non response
- Meeting any treatment failure criteria (defined in section 5.4.4) prior to 24 weeks: non response
- Dose modification, dose interruption, or deviation in any intake of concomitant medications: ignore (treatment policy strategy)

Treatment of interest: the randomized treatment (the investigational treatment asciminib or the control treatment bosutinib) received for at least 24 weeks with or without dose modification, dose interruption or deviation in any intake of concomitant medications. Further details about the investigational treatment and control treatment are provided in Section 6 of the protocol.

Handling of remaining intercurrent events : no other IE foreseen

The summary measure: difference in MMR rate and its 95% confidence interval at week 24 between the two treatment arms.

2.5.1 Primary endpoint/estimand

The primary endpoint is Major Molecular Response (MMR) achieved at 24 weeks while on study treatment without meeting any treatment failure criteria (defined in section 5.4.4) prior to 24 weeks. A patient will be counted as having achieved MMR at 24 weeks if he/she meets the

MMR criterion (BCR-ABL ratio ≤ 0.1%) at 24 weeks while on study treatment unless the patient met any treatment failure criteria (defined in section 5.4.4) prior to 24 weeks.

MMR will be considered as a binary variable with patients achieving MMR grouped as 'responders' and patients not achieving MMR grouped as 'non responders'. Only patients with MMR at 24 weeks are considered responders. In other words, any patient who achieves MMR before 24 weeks, but is no longer in MMR at 24 weeks, will be considered as a non-responder in this primary analysis.

Patients discontinuing treatment (i.e. having performed an EOT visit) prior to 24 weeks due to any reason (e.g. intolerance, treatment failure, death, etc.) and patients meeting any treatment failure criteria (defined in section 5.4.4) prior to 24 weeks will be considered as not having achieved MMR at 24 weeks.

Details of derivation of Polymerase Chain Reaction (PCR) results and calculation of BCR-ABL ratio are presented in Section 5.4.

2.5.2 Statistical hypothesis, model, and method of analysis

The MMR rate at 24 weeks will be calculated based on the FAS and according to the Intent To Treat (ITT) principle. MMR rate and its 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. The 95% confidence interval for the unstratified difference in MMR rate between treatment groups will be provided using the Wald method.

The null hypothesis is that there is no difference between the treatment groups with respect to MMR rate at 24 weeks. The Cochrane-Mantel-Haenszel (CMH) chi-square test, stratified by the randomization stratification factor, i.e. cytogenetic response status (MCyR vs no MCyR) at screening, will be used to compare MMR rate between the two treatment groups, at the two-sided 5% level of significance. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will be presented.

2.5.3 Handling of remaining intercurrent events of primary estimand

No remaining intercurrent events.

2.5.4 Handling of missing values not related to intercurrent event

Patients with missing PCR evaluations at 24 weeks will be considered as non-responders. However, if the 24-week PCR evaluation is missing, but both a PCR evaluation at 16 weeks and a PCR evaluation at 36 weeks indicate MMR, the 24-week assessment is imputed as a 'Response', assuming that MMR is maintained between 16 and 36 weeks.

2.5.5 Sensitivity analyses

The following sensitivity analyses will be performed:

- The CMH chi-square test of MMR rate at 24 weeks will be repeated stratifying by the stratum recorded in the CRF (MCyR vs no MCyR at baseline).
- Due to the COVID-19 (Coronavirus) pandemic, there is a risk that planned hospital visits are cancelled, potentially resulting in missing PCR evaluations. In order to assess the impact of COVID-19 (including potential missing data) on the primary endpoint, the

CMH chi-square test of MMR rate at 24 weeks will be repeated on the FAS excluding the patients with planned 24-week visit (start of study treatment + 161 days) after the start date of COVID-19 epidemic. As per Novartis guidance, the start date, in a given country or region, is being defined as the approximate time point at which, according to the WHO situation reports and the Johns Hopkins database, the number of confirmed COVID-19 infections started to increase significantly (around 100 confirmed cases) and/or governments started to take measures (such as stay-at-home orders) to contain the epidemic, whichever occurred first (China: January 1, 2020; South Korea: February 20, 2020; Japan: February 21, 2020; Italy: February 23, 2020 and Rest of the World: March 1, 2020).

- The CMH chi-square test of MMR rate at 24 weeks will be repeated without the imputation rule used in the main analysis in case of missing PCR evaluations at 24 weeks.

2.5.6 Supplementary analyses

Additional supplemental logistic regression and subgroup analyses are described in Section 2.14.

Assess whether the efficacy of asciminib (40 mg bid) is superior to bosutinib (500 mg qd) in CML patients in chronic phase, without T315I or V299L mutation detected at Week 1 Day 1 visit and previously treated with 2 or more tyrosine kinase inhibitors, with regards to achieving MMR at 24 weeks while on study treatment and without meeting any treatment failure criteria (defined in section 5.4.4) prior to 24 weeks, regardless of dose modification, dose interruption, or deviation in any intake of concomitant medications.

The corresponding estimand attributes are the same as the ones of the primary estimand except that the population excludes patients detected with T315I or V299L at Week 1 Day 1 visit (As per protocol, these patients were discontinued from study treatment when the mutation results became available).

The CMH chi-square test of MMR rate at 24 weeks will be repeated on the FAS excluding patients detected with T315I or V299L at Week 1 Day 1 visit.

2.6 Analysis of the key secondary objective/estimand

The key secondary clinical question of interest is: Is the efficacy of asciminib (40 mg bid) superior to bosutinib (500 mg qd) in CML patients in chronic phase, previously treated with 2 or more tyrosine kinase inhibitors, with regards to achieving MMR at 96 weeks while on study treatment and without meeting any treatment failure criteria (defined in section 5.4.4) prior to 96 weeks, regardless of dose modification, dose interruption, or deviation in any intake of concomitant medications.

The key secondary estimand is described by the following attributes:

Population: CML patients in chronic phase, previously treated with 2 or more tyrosine kinase inhibitors. Further details about the population are provided in Section 5 of the protocol.

Endpoint: Major Molecular Response (MMR) achieved at 96 weeks while being treated without meeting any treatment failure criteria (defined in section 5.4.4) prior to 96 weeks. A patient will be counted as having achieved MMR at 96 weeks if he/she meets the MMR criterion (BCR-

ABL ratio ≤ 0.1%) at 96 weeks while on study treatment unless the patient met any treatment failure criteria (defined in section 5.4.4) prior to 96 weeks.

Intercurrent events:

- Treatment discontinuation (i.e. having performed an EOT visit) prior to 96 weeks due to any reason (e.g. intolerance, treatment failure, death, etc.): non response
- Meeting any treatment failure criteria (defined in section 5.4.4) prior to 96 weeks: non response
- Dose modification, dose interruption, or deviation in any intake of concomitant medications: ignore (treatment policy strategy)

Treatment of interest: the randomized treatment (the investigational treatment asciminib or the control treatment bosutinib) received for at least 96 weeks with or without dose modification, dose interruption or deviation in any intake of concomitant medications. Further details about the investigational treatment and control treatment are provided in Section 6 of the protocol.

Handling of remaining intercurrent events : no other IE foreseen

The summary measure: difference in MMR rate and its 95% confidence interval at week 96 between the two treatment arms

The analysis of the key secondary objective will be performed at the time of the 96-week analysis.

2.6.1 Key secondary endpoint/estimand

The key secondary endpoint is MMR achieved at 96 weeks while on study treatment without meeting any treatment failure criteria (defined in section 5.4.4) prior to 96 weeks. A patient will be counted as having achieved MMR at 96 weeks if he/she meets the MMR criterion (BCR-ABL ratio ≤ 0.1%) at 96 weeks while on study treatment unless the patient met any treatment failure criteria (defined in section 5.4.4) prior to 96 weeks.

MMR will be considered as a binary variable with patients achieving MMR grouped as ‘responders’ and patients not achieving MMR grouped as ‘non responders’. Only patients with MMR at 96 weeks are considered responders. In other words, any patient who achieves MMR before 96 weeks, but is no longer in MMR at 96 weeks, will be considered as a non-responder in this key secondary analysis.

Patients discontinuing treatment (i.e. having performed an EOT visit) prior to 96 weeks due to any reason (e.g. intolerance, treatment failure, death, etc.) and patients meeting any treatment failure criteria (defined in section 5.4.4) prior to 96 weeks will be considered as not having achieved MMR at 96 weeks.

2.6.2 Statistical hypothesis, model, and method of analysis

The null hypothesis is that there is no difference between the treatment groups with respect to MMR rate at 96 weeks. Following a gatekeeping procedure to control the overall alpha level, only if the primary endpoint is significant, formal statistical testing of the key secondary endpoint with two-sided 5% level of significance will be performed using the CMH chi-square

test, stratified by the randomization stratification factor, i.e. cytogenetic response status (MCyR vs no MCyR) at screening.

MMR rate and its 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. The 95% confidence interval for the difference in MMR rate between treatment groups will be provided using the Wald method. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be presented.

2.6.3 Handling of remaining intercurrent events of primary estimand

No remaining intercurrent events.

2.6.4 Handling of missing values not related to intercurrent event

Patients with missing PCR evaluations at 96 weeks will be considered as non-responders. However, if the 96-week PCR evaluation is missing, but both a PCR evaluation at 84 weeks and a PCR evaluation at 108 weeks indicate MMR, the 96-week assessment is imputed as a 'Response', assuming that MMR is maintained between 84 and 108 weeks.

2.6.5 Sensitivity analysis

- In order to assess the impact of COVID-19 (including potential missing data) on the key secondary endpoint, the CMH chi-square test of MMR rate at 96 weeks will be repeated on the FAS excluding the patients with planned 96-week visit (start of study treatment + 665 days) between the start date of the COVID-19 epidemic (China: January 1, 2020; South Korea: February 20, 2020; Japan: February 21, 2020; Italy: February 23, 2020 and Rest of the World: March 1, 2020) and its end date (to be defined in the future).
- The CMH chi-square test of MMR rate at 96 weeks will be repeated without the imputation rule used in the main analysis in case of missing PCR evaluations at 96 weeks.

2.7 Analysis of secondary efficacy objective(s)

The other secondary efficacy objective is to compare additional parameters (defined below) of the efficacy of asciminib versus bosutinib.

2.7.1 Secondary endpoints

2.7.1.1 Molecular response

MMR rates at all scheduled data collection time points, i.e., the protocol-planned visits except for 24 weeks and 96 weeks which are already covered by primary and key secondary endpoints. Such rates are defined as the proportion of patients with MMR at the respective time points.

MMR rates by all scheduled data collection time points, i.e., the protocol-planned visits. These are cumulative MMR rates by time points and are defined as the proportion of patients who achieve MMR at or before specified visits, i.e. if a patient achieves an MMR but then loses it before or at a specific visit, he/she will still be classed as achieving MMR by that specific time point.

Molecular response category at specific time points, i.e., the protocol-planned visits. Categories of molecular response are defined in Appendix.

Molecular response category by specific time points, i.e., the protocol-planned visits. This is defined as the best (lowest) molecular response category up to the specific time points.

Time to MMR (in weeks) is defined as: (date of first documented MMR - date of randomization + 1)/7.

Duration of MMR is defined for patients in the MMR Responder Set as the time between the date of the first documented MMR and the end date of MMR, i.e. the earliest date of confirmed loss of MMR, progression to accelerated phase (AP)/blast crisis (BC), or CML-related death.

Loss of MMR and progression to accelerated phase (AP)/blast crisis (BC) are defined in Appendix.

For patients for whom none of the events above is reported, the duration will be censored (see Section 2.7.3). The duration of MMR (in weeks) is calculated as: (end date or censoring date of MMR - date of first MMR + 1)/7.

2.7.1.2 Cytogenetic response

At each assessment time point the cytogenetic response status of each patient is classified as complete, partial, major, minor, minimal response and none (a review of a minimum of 20 metaphases is required):

- Complete response (CCyR): 0% Philadelphia chromosome positive (Ph+) metaphases
- Partial response (PCyR): >0 to 35% Ph+ metaphases
- Major response (MCyR = CCyR + PCyR): 0 to 35% Ph+ metaphases
- Minor response (mCyR): >35 to 65% Ph+ metaphases
- Minimal response: >65 to 95% Ph+ metaphases
- None: >95 to 100% Ph+ metaphases.

As per protocol, bone marrow aspirate for cytogenetic analyses will be performed as long as subjects have not achieved MMR. Therefore, in case no bone marrow aspirate was performed but the subject is in MMR at a specific time-point, the subject is considered to have achieved CCyR at that time-point. The date of CCyR is imputed by the date of MMR at the same scheduled time-point.

CCyR rates at all scheduled data collection time points, i.e., the protocol-planned visits. Such rates are defined as the proportion of patients in CCyR at the respective time points among patients in the CCyR Analysis Set, which excludes patients who are in CCyR at baseline.

CCyR rates by all scheduled data collection time points, i.e., the protocol-planned visits. Such rates are defined as the proportion of patients who achieve CCyR at or before the respective time points among patients in the CCyR Analysis Set.

Cytogenetic response category at specific time points, i.e., the protocol-planned visits. At each assessment time point the cytogenetic response status of each patient is classified as complete, partial, major, minor, minimal response and none (a review of a minimum of 20 metaphase is required) as defined in Appendix.

Cytogenetic response category by specific time points, i.e., the protocol-planned visits. This is defined as the best (lowest) cytogenetic response category up to the specific time points.

Time to CCyR (in weeks) is defined for patients as: (date of first documented CCyR - date of randomization + 1)/7.

Duration of CCyR is defined for patients in the CCyR Responder Set as the time between date of first documented CCyR and the end date of CCyR, i.e. the earliest date of loss of CCyR, progression to AP/BC, or CML-related death. Loss of CCyR and progression to AP/BC are defined in Appendix. For patients for whom none of the events above is reported, the duration will be censored (see Section 2.7.3). The duration of CCyR (in weeks) is calculated as: (end date or censoring date of CCyR - date of first CCyR + 1)/7.

2.7.1.3 Other secondary efficacy endpoints

Time to treatment failure (TTF) is defined for patients in FAS as the time from date of randomization to an event of treatment failure. The events that constitute 'treatment failure' are described in the Appendix. They are based on the ELN criteria [Baccarani et al. 2013] defining failure of a second line treatment adapted to include discontinuation of randomized treatment as an event.

TTF (in months) is calculated as: (date of treatment failure or censoring date (see Section 2.7.3) - date of randomization + 1)/30.4375.

Progression-Free-Survival (PFS) is defined for patients in FAS as the time from the date of randomization to the earliest occurrence of documented disease progression to AP/BC or the date of death from any cause (including progressions and deaths observed during the survival follow-up period).

PFS (in months) is calculated as: (date of disease progression/death or censoring date (see Section 2.7.3) - date of randomization + 1)/30.4375.

Overall survival (OS) is defined for patients in FAS as the time from the date of randomization to the date of death (including the survival follow-up period).

OS (in months) is calculated as: (date of death or censoring date (see Section 2.7.3) - date of randomization + 1)/30.4375, regardless whether the patient switched from bosutinib to asciminib.

2.7.2 Statistical hypothesis, model, and method of analysis

No confirmatory statistical testing of non-key secondary efficacy endpoints will be performed, however, nominal p-values will be presented for exploratory purposes (as specified in protocol Section 10.5.2).

MMR rates at and by time points

The FAS will be used for these endpoints. For each time point the MMR rate and the associated 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. The descriptive p-value obtained via CMH chi-square tests stratified by the randomization strata, i.e. MCyR vs no MCyR at screening, will be presented. A 95% confidence

interval for the difference in each MMR rate between treatment groups will be provided using the Wald method. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

A post-hoc analysis of the MMR rate will be performed using the number of subjects with adequate follow-up as the denominator. Subjects will be included in the analysis at a timepoint whenever their time between the date of randomization and the cut-off date is equal or above this timepoint, regardless of whether they discontinued before.

The cumulative incidence of MMR by treatment group will be graphically displayed by an increasing step function. Each curve will increase each time (after randomization) at which a new responder is observed and thus will increase up to the best observed response rate (e.g. up to 50% if half of the patients in the analysis population are able to achieve MMR).

Molecular response at and by time points

Frequency and percentage of all molecular response categories (defined in Appendix) by treatment arm using FAS will be presented for each time point.

For the by-time-points summary, the within-patient best molecular response category up to the specific time points is used to calculate the frequency and percentage.

Time to MMR

The MMR Responder Set will be used. Descriptive statistics (minimum, maximum, median, quartiles, mean, sd) of time to MMR will be provided for the two treatment groups separately.

The FAS will be also used to perform similar Time-to-Event analyses as described below for duration of MMR.

A post-hoc analysis of time to MMR will also be performed considering discontinuation from treatment due to any reason, without prior achievement of MMR as a competing risk.

Time to MMR will be censored at the last molecular assessment (PCR) date on treatment prior to or at the cut-off date, if no events/competing risk occurred before or at the cut-off date or the EOT.

The estimated cumulative incidence rates and 95% confidence intervals at 12, 24, 48, 72 and 96 weeks will be presented for each treatment group. The cumulative incidence curve will be plotted.

Duration of MMR

The MMR Responder Set will be used. The survival distribution of duration of MMR will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals [Brookmeyer and Crowley 1982] of the medians, along with the proportion of patients who are still in MMR at 24, 48, 72 and 96 weeks and the associated 95% confidence intervals, will be presented for each treatment group.

CCyR rates at and by time points

The CCyR Analysis Set will be used for these endpoints.

For each time point the CCyR rate and the associated 95% confidence interval based on the Pearson-Clopper method will be presented by treatment group. The descriptive p-value obtained via CMH chi-square tests stratified by the randomization strata, i.e. MCyR vs no MCyR at screening, will be presented. A 95% confidence interval for the difference in each CCyR rate between treatment groups will be provided using the Wald method. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% confidence interval will also be provided.

The cumulative incidence of CCyR by treatment group will be graphically displayed by an increasing step function. Each curve will increase each time (after randomization) at which a new responder is observed and thus will increase up to the best observed response rate (e.g. up to 50% if half of the patients in the analysis population are able to achieve CCyR).

Cytogenetic response at and by time points

Frequency and percentage of all cytogenetic response categories (defined in Section 2.7.1.2) by treatment arm using FAS will be presented for each time point. A shift table comparing baseline and best post-baseline cytogenetic response categories by treatment will also be presented. All assessments of cytogenetic response categories will also be listed by treatment arm.

For the by-time-points summary, the within-patient best cytogenetic response category up to the specific time points is used to calculate the frequency and percentage.

Assessments of bone marrow aspirate at different time points will also be summarized.

Time to CCyR

The CCyR Responder Set will be used. Descriptive statistics (minimum, maximum, median, quartiles, mean, sd) of time to CCyR will be provided for the two treatment groups separately.

The CCyR analysis set will be also used to perform similar Time-to-Event analyses as described below for duration of CCyR.

Duration of CCyR

The CCyR Responder Set will be used. The survival distribution of duration of CCyR will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals [Brookmeyer and Crowley 1982] of the medians, along with the proportion of patients who are still in CCyR at 24, 48, 72 and 96 weeks and the associated 95% confidence intervals, will be presented for each treatment group.

TTF, PFS and OS

For each endpoint the survival distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals [Brookmeyer and Crowley 1982] of the medians, along with the proportion of patients who have not experienced the respective events at 1, 3 and 5 years and the associated 95% confidence intervals, will be presented for each treatment group. The hazard ratio between the two treatments will be calculated, along with its 95% confidence interval, using a stratified Cox model. The descriptive p-value obtained using a stratified log-rank test will be also presented. The stratification will be

based on the randomization stratification factor, i.e. cytogenetic response status (MCyR vs no MCyR) at screening.

2.7.3 Handling of missing values/censoring/discontinuations

MMR rates at specific time points: Patients discontinuing the randomized treatment prior to a specific time point due to any reason or patients without an available assessment at that time point will be considered as non-responders for that time point.

MMR rates by specific time points:

Patients without any documented response for which an evaluable response assessment was never provided will be considered as non-responders for the period of time up to that time point.

Molecular response at specific time points: The category "Missing" will be assigned to

- Ongoing cases, i.e. patients without assessment at the specific time point who have not discontinued study treatment and have not been treated sufficiently long for a specific time point
- Discontinued due to progressive disease/death prior to a specific time point
- Discontinued due to other reasons prior to a specific time point

- **Molecular response category by specific time points**: The category "Missing" will be assigned to patients for whom an evaluable response assessment was never provided.

Time to MMR: For patients in the FAS who have not experienced any MMR, the time will be censored as follows in the Kaplan-Meier analysis:

- If a patient does not achieve the specified response before the cut-off date for the analysis, censoring time will be the last molecular assessment (PCR) date on treatment prior to the cut-off date or the EoT visit, whichever comes first.
- If a patient discontinues study treatment prior to achieving a response for a reason other than disease progression or death, then the patient will be censored at the last molecular assessment (PCR) date on treatment prior to the cut-off date or the EoT visit, whichever comes first.
- If a patient discontinues study treatment prior to achieving a response due to progression or death, then the censoring time will be set to the longest follow-up time in the treatment group, that is, consider the response is impossible to reach.
- In case no on-treatment response assessment was performed, the patient will be censored at day 1.

Duration of MMR: For patients in the MMR responder set who have not experienced any event (loss of MMR, progression to AP/BC, or CML-related death), the duration will be censored at the last molecular assessment (PCR) date on treatment.

CCyR rates at specific time points: Patients discontinuing the randomized treatment prior to a specific time point due to any reason will be considered as non-responders for that time point.

CCyR rates by specific time points: This will be handled similarly as MMR, but with CCyR instead.

Cytogenetic response at specific time points: This will be handled similarly as molecular response category.

Cytogenetic response category by specific time points: This will be handled similarly as molecular response category.

Time to CCyR: For patients in the CCyR analysis set who have not experienced any CCyR, the time will be censored in the same manner as Time to MMR.

Duration of CCyR: For patients in the CCyR responder set who have not experienced any event (loss of CCyR, progression to AP/BC, or CML-related death) the duration will be censored at the last cytogenetic assessment date on treatment or the last PCR evaluation on treatment indicating MMR, whichever is the latest.

TTF: For patients in the FAS who have not reached treatment failure, their TTFs will be censored at the time of their last study assessment (PCR, cytogenetic, hematologic or extramedullary) before the cut-off date.

PFS: For patients who have not experienced an event (disease progression to AP/BC or death from any cause), their PFS times will be censored at the date of last study assessment (PCR, cytogenetic, hematologic or extramedullary) before the cut-off date, regardless of subsequent intake of treatment(s) after randomization.

OS: Patients who are alive at the time of the analysis data cutoff date will be censored at the date of last contact (see Section 2.1.1) before the cut-off date, regardless of subsequent intake of treatment(s) after randomization.

2.8 Safety analyses

All safety analyses will be based on the safety set, except that the summary of safety data during the switched treatment period will be based on the Switch Analysis Set. All listings and tables will be presented by treatment group.

2.8.1 Adverse events (AEs)

AE summaries will include all AEs occurring during the on-treatment period (or the on-switched treatment period). All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome, etc. AEs with start date outside of the on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades or the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sorting order for the preferred term will be based on their frequency in the asciminib arm.

The following adverse event summaries will be produced by treatment arm for the Safety set and Switch Analysis Set: overview of adverse events and deaths, AEs by SOC and PT, summarized by relationship, seriousness, leading to treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy, and leading to fatal outcome. The study treatment-related AEs/SAEs/AEs leading to treatment discontinuation as well as SAE with fatal outcome are summarized for the Safety set and Switch Analysis set.

For posting to ClinTrial.gov and EudraCT, a summary table of on-treatment deaths and serious AEs and another summary table of non serious AEs by treatment, both including occurrences (an occurrence is defined as >1 day between start and prior end date of record of same preferred term) and sorted by SOC and PT, will be presented as well.

In order to account for differences in exposure between the treatment arms, incidence rates of AEs and SAEs will be presented by adjusting for duration of treatment period in patient-years. They will also be reported by time intervals (i.e. period of emergence: the event is assigned to the interval when it first started): 0 to 2 months, > 2 months to 6 months, > 6 months to 12 months, >12 months and more after the start of study treatment.

2.8.1.1 Adverse events of special interest / grouping of AEs

Data analysis of AESIs

An adverse event of special interest (AESI) is a grouping of adverse events that are of scientific and medical concern specific to compound asciminib. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HLGTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. The latest approved version of CRS prior to the respective database lock will be used.

For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during the on-treatment period (or the on-switched treatment period) will be summarized.

Summaries of these AESIs will be provided by treatment arm (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, death, etc.). If sufficient number of events occurred, analysis of time to first occurrence will be applied.

A listing of all grouping levels down to the MedDRA PTs used to define each AESI will be generated.

2.8.2 Deaths

Separate summaries for on-treatment and all deaths *(including post-treatment deaths)* will be produced on the Safety set by treatment arm, system organ class and preferred term.

Similarly, a separate summary for on-switched treatment deaths will be produced on the Switch Analysis Set.

All deaths will be listed, where deaths occurring during the post-treatment, the on-switched treatment or post-switched treatment periods will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

2.8.3 Laboratory data

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. Details of CTCAE grading and imputation rules are presented in Appendix 5.3.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

On analyzing laboratory data, all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date.

The following summaries will be produced on the Safety set separately for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline in the on-treatment period.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

The same summaries will be produced on the Switch Analysis Set for the on-switched treatment period.

The following listings will be produced separately for hematology and biochemistry for the laboratory data:

- Listings of all laboratory data, with CTCAE grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTCAE grade 3 or 4 laboratory toxicities

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis DILI Clinical safety guidelines will be summarized for the criteria defined by single lab parameter. For combination of various parameters, the worst post-baseline values from each single parameter are taken into consideration, i.e. it may not come from the concurrent measurement (i.e. same assessment). :

The following summaries will be produced:

- ALT or AST > 3x upper limit of norm (ULN)
- ALT or AST > 5xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP >= 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

12-lead ECGs including PR, QRS, QT, QTcF and RR intervals will be obtained centrally for each subject during the study. ECG data will be read and interpreted centrally.

The echocardiogram will be performed and evaluated locally to assess the left ventricular ejection fraction (LVEF).

Data handling

The average of the triplicate ECG parameters at each time point will be used in the analyses.

For unscheduled visits, ECGs that are reported on the same day and within 30 minutes apart from each other will be assumed to be sequential ECGs and thus will be used to compute the mean of the ECG parameters.

Unscheduled ECG measurements will not be used in computing the summary statistics for change from Baseline at each post-baseline time point. However, they will be used in the outlier analyses (e.g. QTc > 450 ms, > 480 ms, or > 500 ms at any time point, or an increase from Baseline in QTc > 30 ms or > 60 ms). End of treatment ECG measurements for discontinued patients will be considered as an unscheduled measurement in case it occurs outside a scheduled visit.

Data analysis

The number and percentage of subjects with notable ECG values will be presented by treatment arm for the Safety set and Switched Analysis Set. Notable values are defined below:

- QT, QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- HR

  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

A listing of all ECG assessments will be produced by treatment arm and notable values will be flagged. A separate listing of only the subjects with notable ECG values will also be produced. In each listing the assessments collected during the post-treatment period will be flagged.

Change from baseline ECG parameters by timepoint will also be summarized by treatment.

A listing of all LVEF assessments will be produced by treatment arm. In the listing, the assessments collected outside of on-treatment period will be flagged.

A summary table by treatment arm with descriptive statistics for LVEF at different timepoints (baseline, week 20) and for change from baseline will be presented. A shift table for LVEF categories (≤40%, 41-49%, ≥50%) at baseline versus worst value on treatment will also be presented.

2.8.4.2 Cardiovascular risk factor assessment

Prior to randomization and at the end of treatment, for each patient information of the following risk factors is collected: heavy smoking, low physical activity, unhealthy diet, and other. A listing by treatment arm will be presented.

Family medical history of each patient for ischemic heart disease, cardiac arrhythmia, sudden death, high cholesterol, diabetes mellitus, heart defects (congenital heart disease), and heart failure is also collected prior to randomization and at the end of treatment. A listing by treatment arm will be presented.

2.8.4.3 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

The number and percentage of subjects with notable vital sign values (high/low) in systolic blood pressure, diastolic blood pressure, pulse rate, weight and temperature will be presented by treatment arm.

A listing of all vital sign assessments will be produced by treatment arm and notable values will be flagged. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.8.4.4 Liver events

There are separate eCRF pages to collect acetaminophen/paracetamol, autoimmune, drug use 6 months prior to liver event, immunoglobulin, liver function tests, pathology, related imaging, viral serology and potential impact of alcohol use, and an overview eCRF page. Data on the overview eCRF page will be listed by treatment arm. Assessments collected during the post-treatment period will be flagged.

2.8.4.5 Pulmonary function tests

Data of pulmonary function tests will be listed by treatment arm. Assessments collected during the post-treatment period will be flagged.

2.8.5 Additional Analyses

2.8.5.1 ECOG performance status

ECOG performance status collected on treatment will be summarized. Shift tables will be provided comparing baseline with best and worst values during study for each treatment group.

2.9 Pharmacokinetic endpoints

PK parameters

The PK parameters that will be determined are shown in Table 2-7. The PK parameters for asciminib are derived based on the non-compartmental methods using Phoenix WinNonlin® software version 6.4 in patients with full PK sampling in PAS.

Table 2-7 Non-compartmental PK parameters for asciminib in full PK group

AUC0-12h	The area under the plasma concentration-time curve from time zero to 12 hours ($ng*hr*mL^{-1}$)
AUClast	The AUC from time zero to the last measurable plasma concentration sampling time (Tlast) ($ng*hr*mL^{-1}$)
Ctrough	Trough plasma concentration (measured concentration at the end of a dosing interval at steady state [taken directly before next administration])
Cmax	The maximum (peak) observed plasma concentration after dose administration (ng/mL)
Tmax	The time to reach maximum (peak) plasma concentration after dose administration (hr)
Tlast	The time to reach the last measurable plasma concentration after dose administration (hr)
CL/F	The total apparent body clearance of drug from the plasma after oral administration ($L*hr^{-1}$)

Descriptive statistics (n, arithmetic mean, CV% mean, standard deviation (SD), median, geometric mean, CV% geo-mean, minimum and maximum) will be presented by treatment for PAS for all PK parameters defined in Table 2-7 except Tmax, where only n, median, minimum and maximum will be presented.

All individual PK parameters will be listed for patients treated with asciminib and with full PK sampling in the safety set.

PK concentrations

Descriptive statistics (n, m (number of non-zero concentrations), arithmetic mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum) for asciminib concentration will be presented at each scheduled time point for the PAS.

The mean (+/- SD) and geometric mean concentration-time profiles for asciminib over time will be displayed graphically for PAS on the linear and semi-log view (Week 2 Day 1; for patients with full PK sampling only).

The mean (±SD) and median Ctrough values of asciminib over time will be displayed graphically for PAS on the linear scale only (Patients with full and sparse PK sampling).

All individual plasma asciminib concentration data will be listed for patients treated with asciminib in the Safety Set.

Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ, 1 ng/mL) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the

calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing values for any PK data will not be imputed and will be treated as missing.

2.10 PD and PK/PD analyses

The potential relationship between asciminib exposure (e.g. trough concentration) and efficacy, pharmacodynamics (PD) or safety endpoints may be assessed by graphic exploration and/or statistical modeling, as appropriate, including effect of population covariates. Additional exposure-response analyses for ECG may be conducted. The concentration data may be analyzed by a population approach to evaluate the influence of covariates on drug exposure. If applicable, the details of the above-mentioned analyses will be described in a separate analysis plan and reported separately.

The relationship between average trough plasma concentration up to 24 weeks and BCR-ABL ratio IS (%) at 24 weeks will be assessed by graphic exploration.

2.11 Patient-reported outcomes

The FAS will be used for analyzing PRO data unless specified differently. The MDASI CML, PGIC along with EQ-5D-5L will be used to assess patient's disease-related symptoms and health-related quality of life from baseline to EOT; and the WPAI-CML will be used to assess work productivity and activity impairment related to the patient's CML. All tools require patient's direct completion and will be administered utilizing electronic device for data collection at scheduled time points from screening to end of treatment.

The baseline is defined in Section 2.1.1. Patients with an evaluable baseline score and at least one evaluable post-baseline score during the treatment period will be included in the change from baseline analyses. Missing data items in a scale will be handled according to the manual for each instrument. No imputation will be applied if the total or subscale scores are missing at a visit. All measures will assess differences between the treatment arms.

Compliance to the schedule of administration of each PRO questionnaire will be summarized by treatment group, for baseline and scheduled post-baseline assessment time points. The following categories, as collected on the eCRF, will be used to describe whether the questionnaire was completed at a specific time point:

1. yes, fully completed
2. yes, partly completed
3. no

Repeated measures model for continuous scores

To best utilize the repeated assessments of a given PRO score, a repeated measures model for longitudinal data will be used to estimate differences between treatment arms. This repeated measures model will include terms for treatment, the stratification factor (major cytogenetic response status), time, baseline value as main effects, and an interaction term for treatment by time. This analysis will be restricted to patients with an evaluable baseline score and at least

one evaluable post-baseline score. All data collected until end of treatment (including the end of treatment assessment) will be included in the analysis. Note that only data collected under treatment (i.e. while the patient is treated) will be included. The end of treatment assessment will be included if collected within 7 days of the last dose intake.

Time will be considered as a continuous variable expressed in weeks, i.e. considering that the PRO score follow a linear trend.

As a first approach, an unstructured correlation matrix will be used to model the correlation within patients. The structure of the correlation matrix will be investigated and simplified using likelihood ratio tested if appropriate.

2.11.1 MDASI-CML

The M.D. Anderson Symptom Inventory – Chronic Myeloid Leukemia (MDASI-CML) questionnaire is planned to be administered during screening, at weeks 4, 8, 12, 16, 24, 36, 48 and 96 after randomization.

The MDASI-CML is a 26 item self-administered questionnaire for adult CML patients. Twenty of the items measure the severity of disease-related symptoms and are scored from 0 (Not present) to 10 (As bad as you can imagine) and 6 items that measure symptom interference with daily life scored from 0 (Did not interfere) to 10 (Interfered completely).

The severity score will be calculated when a patient scores at least 11 items out of the 20 severity items using the formula: (sum of scores for the items answered) / (number of items answered). If a patient scores fewer than 11 items, the severity score will be missing.

The interference score will be calculated when a patient scores at least 4 items out of the 6 interference items using the formula: (sum of scores for the items answered) / (number of items answered). If a patient scores fewer than 4 items, the interference score will be missing.

For the severity score and interference score, descriptive statistics (n, mean, SD, median, 25th and 75th percentiles) by treatment arm will be provided for the actual scores and changes from baseline scores at each scheduled assessment time point.

Between-treatment differences for the change in severity and interference scores will be evaluated using the above-mentioned repeated measures model.

2.11.2 EQ-5D-5L

EQ-5D-5L is a two-part standardized instrument for measuring health outcomes in a wide range of health conditions and treatments. It consists of a descriptive system and a visual analogue scale (EQ VAS). The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems (or unable to perform the activity). The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'worst imaginable health state'.

The EQ-5D-5L data will be used to calcutae utility values for the economic evaluation of asciminib and bosutinib in a separate analysis.

The EQ-5D-5L questionnaire is planned to be administered during screening, at weeks 4, 8, 12, 16, 24, 36, 48 and 96 after randomization.

Descriptive system

The number and percentage of subjects in the five levels of each EQ-5D demension will be presented by treatment group at each assessment time point.

EQ VAS

The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale from 0, labeled as 'worst imaginable health state', to 100, labeled as 'best imaginable health state'.

For the EQ VAS, descriptive statistics (n, mean, SD, median, 25th and 75th percentiles) by treatment arm will be provided for actual values and for the change from baseline at each assessment time point.

Between-treatment differences for the changes in EQ VAS score will be evaluated using the above-mentioned repeated measures model.

2.11.3 WPAI-CML

The Work Productivity and Activity Impairment Questionnaire – Chronic Myeloid Leukemia (WPAI-CML) questionnaire is planned to be administered during screening, at weeks 4, 12, 24, 48 and 96 after randomization.

The WPAI-CML is a six-item questionnaire which is intended to measure work and activity impairment associated with CML for those who self-identify as currently employed for pay. This questionnaire measures self-reported productivity loss associated with CML during the past seven days. It consists of questions about absence from work due to CML, hours spent at work, the reduction in productivity at work attributed to CML, and the reduction in productivity while performing regular activities. WPAI-CML outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes. Scoring will be done according to WPAI-CML instrument guidance resulting in four scores including: Percent work time missed due to problem; percent impairment while working due to problem; Percent overall work impairment due to problem; and, percent activity impairment due to problem.

Descriptive statistics (n, mean, SD, median, 25th and 75th percentiles) for each of the four derived outcome scores and changes from baseline scores will be presented by treatment arm at each scheduled assessment time point with .

Between-treatment differences for the changes in each of the four outcome scores will be evaluated using the above-mentioned repeated measures model.

2.11.4 PGIC

The Patient Global Impression of Change (PGIC) instrument is planned to be administered during at weeks 4, 8, 12, 16, 24, 36, 48 and 96 after randomization

The PGIC is comprised of a single question intended to measure a patient's perspective of improvement or deterioration over time relative to treatment. The PGIC uses a seven-point scale

where one (1) equals very much improved and seven (7) equals very much worse. Missing values will not be imputed.

The number and percentage of subjects in each of the seven categories for PGIC will be presented by treatment group at each assessment time point.

2.12 Resource utilization

Data relating to resource utilization (described in trial protocol Section 7.2.5) from the FAS will be used for the purpose of economic evaluation, which will be carried out and reported as a separate activity outside the CSR.

The measures of healthcare resource utilization (HCRU) include: hospitalization (H), emergency room (ER) visit, general practitioner (GP) visits, specialist (Sp) visit and urgent care (UC) visit. HCRU will be assessed as follows: frequency and duration of hospitalization from baseline up to end of treatment; frequency of emergency room visits from baseline up to end of treatment; frequency of additional outpatient office visits general practitioner, specialist, and urgent care visits from baseline up to end of treatment. Hospitalization visits will also record the number of days on ward and the type of ward (hospital unit) and the discharge status. At each HCRU collected, the reason for the visit, i.e. related to CML, AE related to CML therapy or other reason, will be collected, in order to quantify the impact of treatment on healthcare resources.

HCRU data by treatment arm will be summarized in the primary analysis CSR and the end of study treatment CSR, with descriptive statistics (n, mean, median, SD, min, max) for quantitative variables, and count and percentage for qualitative variables.

2.13 Biomarkers

As a project standard, Novartis will analyze only biomarkers collected in the clinical database. For exploratory markers, since the studies are not adequately powered to assess specific biomarker-related hypotheses, the goal of these exploratory statistical analyses should be considered as the generation of new scientific hypotheses. No adjustment for multiple comparisons is usually planned for exploratory analyses. Furthermore, additional post hoc exploratory assessments are expected and may be performed.

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue their analysis due to either practical or strategic reasons. Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

If not otherwise specified, the FAS will be used for all biomarker analyses on patients with biomarker data.

Exploratory biomarker objectives

- To characterize mutations in the BCR-ABL1 gene at Week 1 Day 1, upon confirmed loss of molecular response and/or at end of treatment and examine their association with molecular and cytogenetic response for asciminib vs bosutinib

- To understand biology of CML and bone marrow microenvironment on leukemic stem cells (LSCs) eradication, including patients' immunogenicity
- To assess clonal evolution during treatment with asciminib vs. bosutinib
- To evaluate soluble/inflammatory factors that correlate with response to asciminib vs. bosutinib treatment

Only some analyses for the first exploratory biomarker objective about BCR-ABL1 mutation listed above are described here and the results will be included in the respective CSRs. Additional analyses for this and other exploratory biomarker objectives will be described in separate analyses plans, with results reported separately.

List of biomarkers evaluated and the collection time points

The biomarkers evaluated in the study are listed in Table 2-8 below.

Table 2-8 Sample biomarker summary table

Biomarker	Time point	Sample	Method
Immune markers PD-L1 and CD8	Screening and end of treatment	Bone marrow biopsy	Immunohisto-chemistry
Leukemic stem cells characterization	Screening, week 24 and end of treatment	Bone marrow aspirate	Flow cytometry
BCR-ABL1 gene mutation	W1D1 pre-dose and end of treatment. If mutation is present at baseline, then also every 12 weeks after baseline	Peripheral blood	Sanger Sequencing
Low level mutations in BCR-ABL1 gene	W1D1 pre-dose and end of treatment	Peripheral blood	Mass spectrometry and NGS
Circulating cytokines in plasma	W1D1 pre-dose, Week 48 and end of treatment	Peripheral blood	MSD and ELISA
Genetic variant analysis of the UGT2B7 and UGT2B17 gene	W1D1	Peripheral blood	Genechip

General data handling and preprocessing

For bone marrow samples the latest assessment during screening period will be used as the baseline value, while for blood samples the week 1 day 1 (W1D1) pre-dose assessment will be used as the baseline value.

When more than one biomarker data value are available for a subject at any time point, the mean of the replicate values will be used for all statistical analyses.

2.13.1 Somatic mutation biomarker data handling and analysis

Handling of somatic biomarker data

Overall, somatic mutation status (wild type or mutant) will be derived from the mutational status of the interrogated exons for the BCR-ABL1 gene by Sanger Sequencing. These may be non-exclusive and the presence of mutation across more than one exon will be reported in separate categories.

Mutation summary statistics

All somatic mutation data will be reported using counts and percentages by the mutation type in the form of contingency tables with the rows containing the different mutations assayed, and the treatment groups in the columns. All the mutation categories for a gene will also be aggregated into mutant, wild type or missing/unknown groups and counts/percentages will be reported by these three categories as well. A summary table will be presented for baseline mutations and another summary table for post-baseline new mutations (not present at baseline).

All the mutation data will be listed for each subject ordered by treatment group.

Association between biomarkers and clinical outcome

This analysis does not adjust for multiple comparisons and results may have higher false positive rates.

The relationship between Week 1 Day 1 BCR-ABL1 gene mutation data (wild type or mutant) and outcome data (with or without MMR at and by 24 and 96 weeks using FAS, with or without CCyR at and by 24 and 96 weeks using CCyR analysis set) will be explored by reporting contingency tables and by applying a logistic regression including treatment group, Week 1 Day 1 BCR-ABL1 gene mutation and their interaction as covariates. Treatment group will be included in this summary table.

In addition, the same analysis will be performed for

- the relationship between post-baseline new BCR-ABL1 mutation (with or without new mutation) up to 48 weeks and outcome data (with or without MMR at 48 and 96 weeks using FAS, with or without CCyR at 48 and 96 weeks using CCyR analysis set).
- the relationship between post-baseline new BCR-ABL1 mutation (with or without new mutation) up to end of treatment and outcome data (with or without MMR at 96 weeks using FAS, with or without CCyR at 96 weeks using CCyR analysis set).

The odds ratios bewteen treatment groups with 95% confidence intervals will be reported, for each biomarker category and overall. If treatment by biomarker interaction is significant (e.g. when $p < 0.1$), overall odds ratio for treatment will not be reported.

2.14 Other exploratory analyses

MMR rate at 24 weeks

The FAS will be used for the following exploratory analyses:

1. A logistic regression model adjusted for the stratification factor (based on the randomization platform data IRT) will be fit to assess treatment effect. An adjusted odds ratio for the treatment effect with associated 95% confidence intervals will be presented. Mantel-Haenszel estimates of the common odds ratio and the corresponding 95% confidence interval will also be provided.
   Some subjects were mistratified. To assess the impact of this mistratification on the treatment effect assessment, a logistic regression adjusting for major cytogenetic status at baseline based on CRF data will also be run.
2. Based on the subgroups specified in Section 2.2.1, the following analyses will be performed for each subgroup:

   - Proportion of patients with MMR at 24 weeks and its 95% confidence interval based on the Pearson-Clopper method within each treatment group
   - The difference in MMR rate at 24 weeks between treatment groups and the corresponding Wald 95% confidence interval

   Efficacy analyses in subgroups will be purely exploratory and are intended to explore the consistency of treatment effect. Forest plot (n, risk difference, Wald 95% confidence interval) will be produced to graphically depict the treatment effect estimates in different subgroups. No inferential statistics (p-values) will be produced for the subgroups.
   Post-hoc exploration of the treatment effect in different subgroups and assessment of the possible effect of differences in distribution of baseline characteristics were conducted (e.g. distribution of reasons for discontinuation of last prior TKI by gender and treatment, distribution of MCyR status at baseline by reasons for discontinuation of last prior TKI, distribution of mutation status at Week 1 Day 1 by reasons for discontinuation of last prior TKI).
3. A logistic regression model adjusted for the stratification factor (baseline major cytogenetic response status based on randomization data) and other important variables identified by the subgroup analyses above will be fit to assess treatment effect. An adjusted odds ratio for the treatment effect with associated 95% confidence intervals will be presented.
   To assess the impact of mistratifications on the treatment effect assessment, the same analysis will be repeated, adjusting for major cytogenetic status at baseline based on CRF data instead of based on randomization data.

Influence of early molecular response levels on long term molecular response levels

The relationship between MMR status at 24 weeks and MMR status at 48 and 96 weeks will be explored using FAS by reporting contingency tables and by applying a logistic regression including treatment group, MMR status at 24 weeks and their interaction as covariates. Treatment group will be included in this summary table. The odds ratios between treatment groups with 95% confidence intervals will be reported, for each category of MMR status at 24 weeks and overall. If the interaction of treatment by MMR status at 24 weeks is significant (e.g. when $p < 0.1$), overall odds ratio for treatment will not be reported.

Efficacy Analysis on Switch Analysis Set

Efficacy analyses on the Switch Analysis Set will be performed at the time of the 96-week analysis. Unless otherwise specified, endpoints are defined and analyzed similarly as specified in Sections 2.5, 2.6, and 2.7 on Switch Analysis Set, but with baseline, FD, LD, and EoT replaced by baseline_switch, FD_{switch}, LD_{switch}, and S-EoT. The below are the efficacy endpoints to be analyzed:

- MMR rate at and by all protocol-planned visits.
- CCyR rate at and by all protocol-planned visits.
- Time to MMR
- Duration of MMR
- Time to CCyR
- Duration of CCyR
- Time to Treatment Failure

The analysis of time-to-event endpoints will be conducted only if at least 5 events are observed.

2.15 Interim analysis

No formal interim analysis is planned for this trial.

Three to four analyses are planned with the analysis data cut-off dates and the scope of analyses as follows:

- **24-week Primary analysis**: Formal testing of the primary endpoint with full alpha will be performed. Analyses of other efficacy endpoints at and by 24 weeks will also be performed.
- **96-week analysis**: Formal statistical testing of the key secondary endpoint will be performed with $\alpha = 0.05$ (two-sided) only if the primary endpoint (i.e. MMR rate at 24 weeks) is significant. Otherwise, no statistical testing will be performed, and any analysis will be considered exploratory. Analyses of other efficacy endpoints will also be performed.
- **End of study treatment (EOsT) analysis (if required)**: similar to the 96-week analysis without formal statistical testing.

  NOTE: This analysis may be conducted at the same time as 96-week analysis.

- **5-year PFS/OS update analysis**: PFS and OS.

In addition, DMC safety analyses will be conducted. Prior to the database lock for the primary analysis, tables and figures aggregated by treatment arm for safety data review by the DMC or for other reporting activities will be produced by an independent statistician and independent statistical programmers.

3 Sample size calculation

3.1 Primary analysis

To test the null hypothesis that the MMR rate at 24 weeks is equal in the two treatment arms, based on two-sided 5% level of significance and with 90% power, 222 patients will be needed in total (i.e. 148 patients in the asciminib arm and 74 patients in the bosutinib arm based on 2:1 randomization allocation). The calculations were made using the software package PASS (2008).

It is assumed that asciminib leads to a 20% improvement in the MMR rate at 24 weeks over bosutinib from 15% to 35% which corresponds to an odds ratio of 3.05. The assumed bosutinib MMR rate of 15% at 24 weeks is based on previous trials evaluating bosutinib therapy ([Kuoury et al. 2012], [Gambacorti-Passerini et al. 2014], [García-Gutiérrez et al. 2015]).

3.2 Power for analysis of key secondary variables

If the primary analysis of MMR rate at 24 weeks is statistically significant, then the key secondary endpoint MMR rate at 96 weeks will be tested, with the overall alpha controlled at the 5% two-sided level using a gatekeeping strategy.

Table 3-1 below summarizes the treatment effects of the key secondary endpoint which can be detected with 80% and 90% power, based on the specified assumptions regarding the bosutinib effect. The calculations were made using the software package PASS (2008).

Table 3-1 Detectable effect sizes for key secondary endpoint

Endpoint	Anticipated effect with bosutinib	2-sided alpha	Power	Detectable effect size§
MMR rate at 96 weeks	30%*	0.05	90%	≥ 23%
			80%	≥ 20%

*: [Gambacorti-Passerini et al. 2014], Figure 1D.
§: Absolute difference from the anticipated effect with bosutinib.

For MMR rate at 96 weeks, if the anticipated effect with bosutinib is 30%, then the given sample size with 2-sided alpha=0.05 would allow to detect an absolute difference of at least 23% (i.e. MMR rate at 96 weeks with asciminib is at least 53%) for 90% power and of at least 20% (i.e. MMR rate at 96 weeks with asciminib is at least 50%) for 80% power.

4 Change to protocol specified analyses

Pharmacokinetic analysis set: Removal of the condition related to vomiting to consider a concentration evaluable as the occurrence and time of vomiting is not collected in the CRF.

The estimand langage was implemented in sections 2.5 and 2.6. Then, the PPS and analyses based on PPS were removed.

The subgroup considering historical BCR-ABL1 mutations was removed as not considered clinically relevant.

A definition for loss of CHR was provided.

Definition of loss of MMR: removed any reference to confirmation of CHR and CCyR as confirmation of CHR and CCyR was not mandated by protocol and was therefore not performed in practise.

The following analyses were added:

ECOG status, time to event analyses for duration of MMR and CCyR, exposure adjusted AE incidence and yearly AE incidence, COVID-19 related sensitivity analyses.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rules should be used for the imputation of the dose end date for a given study treatment component.

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 2: If the dose end date is completely missing and the EOT page is available:

The EOT completion date should be used.

- All other cases should be considered as a data issue and the statistician should contact the data manager of the study.
- After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

  Use the treatment start date

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE, ConMeds and safety assessment date imputation

The imputations specified in this section are only used for analyses of time to and duration of AEs and concomitant medications.

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	**Rule**
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  o Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

day	• If available month and year = month and year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.
	  o Else set start date = study treatment start date.
	• If available month and year > month and year of study treatment start date then 01MONYYYY
	• If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	**Rule** (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as ‘ongoing’ rather than the end date provided.

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Stratum reported in the CRF

This will be derived from the Bone Marrow Aspirate data recorded in the corresponding eCRF pages at baseline. In some case the baseline sample may be missing or not evaluable (i.e. <20 metaphases).

The following imputation rule will be applied to derive the missing or non evaluable values:

- Major cytogenetic response (MCyR) (0 to 35% Ph+ metaphases) will be assumed if BCR-ABL1 levels ≤10% (IS).

Rationale:

ELN 2013 recommendations are providing treatment milestones with response categories for cytogenetic and molecular response, which we can refer to for the imputation:

6 mo	BCR-ABL1 <1% and/or Ph+ 0	BCR-ABL1 1-10% and/or Ph+ 1-35%	BCR-ABL1 >10% and/or Ph+ >35%

MCyR is roughly corresponding to BCR-ABL1 levels ≤10% (IS) (Ross et al 2009).

5.2 AEs coding/grading

Adverse events are coded using the latest available version of Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria

for CTCAE grading of laboratory parameters (embedded below). The latest available version of the document based on the underlying CTCAE version v4.03 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

EASE LAB - CTC grades in Novartis Or

Imputation Rules

Hematology

Immature cells (promyelocytes, myelocytes, metamyelocytes and blasts) will not be displayed in shift tables and will only be listed.

Immature cells are manually counted only if anomalies are detected during the automatic testing. Therefore, when the automatic testing was performed but no data is transferred for immature cells, this means there was no immature cells and their values can be imputed to 0. Note that there should not be any imputation in case the automatic testing was not performed or the test of immature cells is present with missing value in the database (this would mean the test was to be performed but couldn't).

CTCAE grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of white blood cells (WBC).

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

The following rules will be applied to derive the WBC differential percentages when only differential counts are available for a xxx differential

xxx %value = (xxx count × 100) / WBC count

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mmol/L) = Calcium (mmol/L) +0.02 (40 – [Albumin (g/L)]

For calculation of laboratory CTCAE grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mmol/L) as for calcium.

CTCAE grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

Biochemistry

In order to avoid double reporting of the same information, all available values for BUN and UREA will be reported under the parameter name BUN (mmol/L) in listing using the following conversion rule: UREA (mmol/L)=2.14 BUN (mmol/L) ([Lamb E et al 2012]).

5.4 Efficacy variables

5.4.1 Molecular response

Scaling towards an international standard will be performed for all molecular results using laboratory specific conversion factors. In this process, the raw ratio between BCR-ABL and the control gene ABL is calculated and multiplied by the lab-specific conversion factor ([Branford and Hughes 2006]). Therefore, using the international unit, the BCR-ABL ratio will be presented in %. The MRDx assay using PAXgene^{TM} Blood RNA tubes from MMD laboratory will be used in this study. The lab conversion factor for this assay was 1.1 until 1 June 2020 and 1 thereafter.

The BCR-ABL ratio in IS % is calculated by multiplying the raw BCR-ABL ratio with the lab-specific conversion factor and then by 100:

$$\text{BCR-ABL ratio (in \%)} = (\text{BCR-ABL} / \text{ABL}) * \text{conversion factor} * 100$$

The BCR-ABL ratio in IS% provided by the central laboratory will be use in the analyses. However, to calculate the fold change in BCR-ABL1/ABL used to derive the loss of MMR criteria, in case the BCR-ABL number of copies is reported as a 0 value and the patient doesn't have atypical transcript at baseline, then the value will be replaced by 1, and the BCR-ABL ratio will be calculated.

Molecular response is categorized as follows:

- 10% > BCR-ABL ratio
- 1% < BCR-ABL ratio ≤ 10%
- 0.1% < BCR-ABL ratio ≤ 1%
- 0.01% < BCR-ABL ratio ≤ 0.1%
- 0.0032% < BCR-ABL ratio ≤ 0.01%
- BCR-ABL ratio ≤ 0.0032%

Major molecular response (MMR)

Major molecular response (MMR) is defined as a value of ≤ 0.1% of BCR-ABL ratio on the IS. This endpoint corresponds to a ≥ 3 log reduction in BCR-ABL transcripts from a standardized baseline value for untreated CML patients which was established in the IRIS study (STI5710106). MMR will be considered as a binary variable with patients achieving MMR

grouped as 'responders' and patients not achieving MMR or patients with missing PCR evaluations grouped as 'non-responders'.

Loss of MMR

Loss of MMR is defined as an increase in BCR-ABL1/ABL to > 0.1% by international scale (IS) in association with a ≥ 5-fold rise in BCR-ABL1/ABL from the lowest value achieved up to that time point on study treatment and replicated by a second analysis of the same sample. Loss of MMR must be confirmed by a subsequent sample analysis within 4-6 weeks showing loss of MMR associated with a ≥ 5-fold rise in BCR-ABL1/ABL from the lowest value achieved up to that time point on study treatment.

If there is any assessment in between indicating a BCR-ABL ratio of ≤ 0.1% or a < 5-fold increase in BCR-ABL ratio from the lowest value achieved up to that time point on study treatment, then the initial indication of loss of MMR cannot be confirmed. However, an assessment indicating (unconfirmed) loss of MMR will be considered as confirmed loss of MMR if the patient had loss of CHR or loss of complete cytogenetic response (CCyR) after the achievement of MMR. CML-related death or progression to AP or BC will be considered as confirmed loss of MMR in any case (if they occurred on treatment) (given that the patient achieved prior MMR).

5.4.2 Cytogenetic response

Cytogenetic response will be based on the percentage of Ph+ metaphases in the bone marrow. Cytogenetic evaluations will be considered for response assessment only if the number of metaphases examined is ≥ 20 in each bone marrow sample. As per protocol, fluorescent *in-situ* hybridization (FISH) assessments will not be considered for any evaluation of cytogenetic response during treatment.

Cytogenetic response is categorized as follows (a review of a minimum of 20 metaphases is required):

- Complete response (CCyR): 0% Philadelphia chromosome positive (Ph+) metaphases
- Partial response (PCyR): >0 to 35% Ph+ metaphases
- Major response (MCyR = CCyR + PCyR): 0 to 35% Ph+ metaphases
- Minor response (mCyR): >35 to 65% Ph+ metaphases
- Minimal response: >65 to 95% Ph+ metaphases
- None: >95 to 100% Ph+ metaphases.

If bone marrow aspirate blast percentage is provided as '<X' (i.e. below limit of detection), the numeric value is set to X for summary tables. In the listing '<X' will be presented.

Complete cytogenetic response (CCyR)

CCyR is defined as a value of 0% Ph+ metaphases in bone marrow.

CCyR will be considered as a binary variable with patients achieving CCyR grouped as 'responders' and patients not achieving CCyR, patients with missing cytogenetic evaluations grouped as 'non-responders'.

Loss of CCyR

Loss of CCyR is defined as an increase in the Ph+ bone marrow cells to > 0%.

Loss of CCyR must have led to treatment discontinuation because of lack of efficacy (based on the "End of Treatment Phase Disposition" eCRF or "End of Treatment Disposition" eCRF during the Treatment switch phase with Subject status="lack of efficacy" and Reason of treatment failure = "After start of therapy, loss of CHR, CCyR or PCyR").

In addition, CML-related death or progression to AP or BC will be considered as loss of CCyR in any case (if they occurred on treatment).

Major cytogenetic response (MCyR)

MCyR is defined as a value of 0% to 35% Ph+ metaphases in bone marrow.

MCyR will be considered as a binary variable with patients achieving MCyR grouped as 'responders' and patients not achieving MCyR, patients with missing cytogenetic evaluations grouped as 'non-responders'.

Loss of MCyR is defined as an increase in the Ph+ bone marrow cells to > 35%. For patients with response = PCyR, this would constitute loss of PCyR.

CML-related death or progression to AP or BC will be considered as confirmed loss of MCyR in any case (if they occurred on treatment).

5.4.3 Hematologic response

Loss of CHR

Loss of CHR is defined by meeting any of the following:

- WBC count > 20×10^9/L
- Platelet count ≥ 600×10^9/L
- Appearance of blasts or promyelocytes in peripheral blood
- Appearance of myelocytes + metamyelocytes ≥ 5% in peripheral blood
- Progressive splenomegaly refractory to therapy (i.e. ≥ 5cm below left intercostal margin)

Loss of CHR must have led to treatment discontinuation because of lack of efficacy (based on the "End of Treatment Phase Disposition" eCRF or "End of Treatment Disposition" eCRF during the Treatment switch phase with Subject status="lack of efficacy" and Reason of treatment failure = "After start of therapy, loss of CHR, CCyR or PCyR").

In addition, CML-related death or progression to AP or BC will be considered as loss of CHR in any case (if they occurred on treatment).

Complete hematologic response (CHR)

CHR is defined when all of the following criteria are present at any assessment which is confirmed by another assessment at least after 4 weeks:

- White blood cells (WBC) count < 10×10^9 /L
- Platelet count < 450×10^9 /L

- Basophils < 5%
- No blasts and promyelocytes in peripheral blood
- Myelocytes + metamyelocytes < 5% in peripheral blood
- No evidence of extramedullary disease, including spleen and liver. As extramedullary disease is evaluated less frequently than hematology, the results of these evaluations are carried forward until the next assessment (unless extramedullary disease was not present at the current assessment but present at the next).

The assessment is not considered CHR, if there are any values indicative of CML in AP or BC (i.e. by blasts in bone marrow). The information used for hematological assessment will be obtained from the laboratory, extramedullary and bone marrow data, all merged by patient and date. To accommodate for missing parameters, specific laboratory results may be carried forward up to 14 days such that assessments performed within a two-week period can combined into one complete evaluation of hematological response. A value will be carried forward for no more than up to the subsequent valid assessment of the respective laboratory parameter. If even after applying this carry-forward algorithm, any of the above laboratory parameters is not available at a given assessment date, the response assessment will be considered missing, unless any of the available values (including those carried forward) indicates that there is no response in which case the assessment will be 'No response'.

For confirmation of CHR, both the initial CHR as well as the confirming assessment (at least 4 weeks after the initial assessment) must satisfy all the criteria mentioned above and no assessment in between indicates 'No response'. The terms "confirmed CHR" and "CHR" are used as synonymous given that the definition of CHR mentioned above already includes a requirement for confirmation.

5.4.4 Treatment Failure

The following events will constitute 'treatment failure', and are based on the ELN criteria (Baccarani et al 2013) defining failure of a second line treatment adapted to include discontinuation of randomized treatment as an event:

- No CHR or > 95% Ph+ metaphases at three months after initiation of therapy or thereafter
- BCR-ABL1 ratio > 10% IS and/or > 65% Ph+ metaphases at six months after initiation of therapy or thereafter
- BCR-ABL1 ratio > 10% IS and/or > 35% Ph+ metaphases at 12 months after initiation of therapy or thereafter
- Loss of CHR, CCyR or PCyR at any time after initiation of therapy
- Detection of new BCR-ABL1 mutations which potentially cause resistance to study treatment (T315I and V299L), at any time after initiation of therapy
- Confirmed loss of MMR in 2 consecutive tests
- New clonal chromosome abnormalities in Ph+ cells: CCA/Ph+: at any time after initiation of therapy

- Discontinuation from randomized treatment for any reason* (Note that Reason for treatment discontinuation=”completed” doesn’t indicate a premature treatment discontinuation)

5.4.5 CML progression to accelerated phase (AP) or blast crisis (BC)

For the evaluation of CML progression to AP or BC, the following criteria will be used. Accelerated phase (AP) is defined by any of the following:

- ≥ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate
- ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate
- ≥ 20% basophils in the peripheral blood
- Thrombocytopenia (<100 x 10^9/L) that is unrelated to therapy*

*As thrombocytopenia is a known adverse reaction to CML therapy, platelets <100 × 109/L are only considered as CML-AP if the patient had these values within 30 days of treatment discontinuation due to disease progression. In this case, comments are to be provided on the termination page that thrombocytopenia is indicative of progression to AP and an adverse event (AE) entered with relationship to study treatment = ‘Not suspected’

Blast crisis (BC) is defined by any of the following:

- ≥ 30% blasts in peripheral blood or bone marrow aspirate
- Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma).
  The second bullet criteria can’t be considered in this study as this information was not collected.

5.4.6 CML-related deaths

CML-related death is considered as any death during treatment or follow-up (safety or survival)

- if the principal cause of death is marked as “study indication” in the eCRF by the investigator,
- or if the death occurred subsequent to documented progression to AP/BC and the cause of death is reported as “unknown” or not reported by the investigator.

With respect to the second bullet, as “unknown” cause of death will be coded to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term ‘Death’, this MedDRA coding will be used in the derivation of CML-related death.

5.4.7 Disease progression

The following events are considered disease progression

- CML-related deaths
- Accelerated phase (AP)
- Blast crisis (BC)

5.4.8 Overall survival

This includes all-cause deaths.

5.5 Derivation of response rates and categories

5.5.1 Response rate at a specific time point

The molecular and cytogenetic response evaluations will be summarized by the following mutually exclusive categories which are based on the respective assessment within the time window:

- **Response categories** (sections 5.4.1 and 5.4.2)**:** Patients with an available assessment at that time point (+/- time window) indicating any of the response categories.
- **No response:** Patients with assessment at that time point (+/- time window) indicating 'no response'
- **Missing:** Patients without an evaluable response assessment at that time point (+/- time window). This category is then further split into patients who are ongoing without treatment failure at the beginning of the relevant time window, patients who are ongoing with treatment failure at the beginning of the relevant time window, patients who discontinued due to lack of efficacy, disease progression (PD) or death and patients who discontinued due to other reasons.

5.5.2 Response rate by a specific time point (best response)

In this analysis, patients who had achieved any response at or before the time point will be displayed in their best response category, no matter if they lost the response/discontinued or not. Therefore this response rate represents the best observed response rate up to that specific time point (including the time window).

Patients for whom an evaluable response assessment was never provided will be classified as 'Missing'.

5.6 Statistical models

5.6.1 Primary analysis

The null hypothesis of equality of MMR rate at 24 weeks in the two treatment arms will be tested against two-sided alternative. The statistical hypotheses are:

$$H0: RA_{24wk} = RB_{24wk} \text{ versus } HA: RA_{24wk} \neq RB_{24wk}, \text{ for a two-sided test}$$

where RA_{24wk} is the probability of MMR rate at 24 weeks in asciminib arm and RB_{24wk} is the probability of MMR rate at 24 weeks in bosutinib arm.

The Cochran-Mantel-Haenszel chi-square test X^2_{CMH} (implemented via SAS procedure FREQ with CMH option in the TABLES statement), stratified by the randomization stratification factor, i.e. cytogenetic response status (MCyR vs no MCyR) at screening, will be used to test the difference in response rates between the treatment arms. The p-value corresponding to the CMH test for "general association" will be used which follows a Chi-square distribution with one degree of freedom.

The 95% confidence interval for the unstratified difference in MMR rate at 24 weeks between treatment groups will be provided using the Wald method (implemented via SAS procedure FREQ with RISKDIFF option in the TABLES statement, under the default METHOD=WALD and VAR=SAMPLE). If the 2×2 table is with asciminib in row 1, bosutinib in row 2, MMR in column 1 and No MMR in column 2, then the SAS output will give the estimate of (risk for MMR at 24 weeks in asciminib – risk for MMR at 24 weeks in bosutinib). The corresponding Mantel-Haenszel estimate of common risk difference and 95% confidence interval will also be presented (with RISKDIFF(COMMON) option in the TABLES statement, taking the Mantel-Haenszel estimate from the SAS output table).

If the sampling assumptions for chi-square test is not met (i.e. the expected frequencies should exceed 5 for all of table cells), the exact Cochran-Mantel-Haenszel test will be used (implemented via SAS procedure MULTTEST). The test is performed by running a stratified version of the Cochran-Armitage permutation test [Armitage et al. 1969]. In studies with stratified randomization, the chi-square approximation is considered appropriate for the X^2_{CMH} statistics if the rule of Mantel and Fleiss [Mantel and Fleiss 1980] is satisfied.

Confidence interval for MMR rate within each treatment arm

MMR will be summarized in terms of percentage rates with 95% confidence interval using exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table [Clopper and Pearson 1934]).

5.6.2 Key secondary analysis

The null hypothesis of equality of MMR rate at 96 weeks in the two treatment arms will be tested against two-sided alternative. The statistical hypotheses are:

$$H0: RA_{96wk} = RB_{96wk} \text{ versus } HA: RA_{96wk} \neq RB_{96wk}, \text{ for a two-sided test}$$

where RA_{96wk} is the probability of MMR rate at 96 weeks in asciminib arm and RB_{96wk} is the probability of MMR rate at 96 weeks in bosutinib arm.

The same approaches as for the primary endpoint (Section 5.5.1) will be applied here for the Cochran-Mantel-Haenszel chi-square test X^2_{CMH}, the 95% Wald confidence interval for the difference in MMR rate at 96 weeks between treatment groups, the Mantel-Haenszel estimate of common risk difference with 95% confidence interval, and the confidence interval for MMR rate within each treatment arm.

Multiplicity adjustment

Formal statistical testing of the key secondary endpoint will be performed with $\alpha = 0.05$ (two-sided) only if the primary endpoint is significant by means of a gatekeeping procedure to control the overall alpha level.

5.6.3 Other analyses

Mantel-Haenszel common odds ratio

To obtain Mantel-Haenszel estimates of the common odds ratio and the corresponding 95% confidence interval in exploratory analyses, it requires SAS procedure FREQ with CMH and RELRISK options in the TABLES statement.

Logistic Regression

Odds ratio will be used as a measure of association between treatment and response in exploratory analyses (Section 2.14). The odds ratio will be derived from the logistic regression model (implemented using SAS procedure LOGISTIC, with treatment specified as an explanatory variable in the CLASS statement) which allows for including not only the stratification factor but also for adjustments for other covariates (both categorical and continuous). The odds ratio will be presented with 95% Wald confidence limits.

In cases where an exact test has been used to compare response rates, the odds ratio should be determined using exact logistic regression, and the odds ratio presented with exact 95% confidence limits. In these cases, SAS PROC LOGISTIC with EXACTONLY option will be used.

Kaplan-Meier estimates

An estimate of the survival function in each treatment group will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

Hazard ratio

Hazard ratio will be estimated by fitting the Cox proportional hazards model using SAS procedure PHREG (with TIES=EXACT option in the MODEL statement).

A stratified unadjusted Cox model will be, i.e. the MODEL statement will include the treatment group variable as the only covariate and the STRATA statement will include stratification variable(s). Hazard ratio with two-sided 95% confidence interval will be based on Wald test.

Cumulative incidence

The cumulative incidence proportion (CIP) will be estimated using SAS procedure LIFETEST or PHREG with EVENTCODE=Code for event of interest (e.g. MMR) as option in the MODEL statement, whereas code=0 for censored subjects and any other code (e.g. code=2) for subjects who dropped out due to a competing risk. The estimated CIP at the defined time points will be presented with 95% CI together with number of subjects with events, number of subjects with competing risks, and number of subjects censored.

5.6.4 Calculation of exposure-adjusted incidence rate

To adjust for different durations of exposure across treatment arms, the incidence rate per 100 patient-years of exposure (exposure-adjusted incidence rates of adverse events) will be calculated.

The IR/100 pyr is defined as numerator/denominator, where

- Numerator = number of patients with the adverse events of interest (not the number of events; one patient may have more than one event).
- Denominator = patient-years = total time at risk in years = among all patients in the population, sum of the duration of exposure (in days) until the first onset of the event of interest, if the patient experienced the event, or until the date of last dose if the patient did not experience the event / 365.25.

The patient-years (i.e. total time at risk in years) will be calculated as the sum of times at risk in days over all patients in the population / 365.25.

The time at risk for a patient in days will be calculated as follows:

- If the patient experienced the event of interest, the time at risk for this patient is the duration of exposure from the first dose of treatment until the first onset of the event.
- For patients without an event of interest, the time at risk is the total duration of exposure during core study, as applicable.

6 Reference

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NOVARTIS

Clinical Development

ABL001/asciminib

CABL001A2301

A phase 3, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors

Statistical Analysis Plan (SAP) – Summary of changes

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
25-Aug-2017	Prior to DB lock for primary analysis	Creation of final version	N/A - First version	NA
26-Mar-2020	Prior to DB lock for primary analysis	Implementation of protocol amendments 2 and 3.	ABL001 has been replaced by International Nonproprietary Name (INN) asciminib.	Throughout the SAP amendment
			Introduction of the switch to asciminib option for patients experiencing treatment failure on bosutinib treatment	Section 1.1, Figure 1-1 Sections 2.1, 2.3 Analyses added throughout the document
			Update of the definition of end of study treatment	Section 1.1
			Added a potential End-of-Study-Treatment analysis different from the 96-week analysis	
			Addition/removal of secondary safety objectives and exploratory efficacy objectives	Table 1-1
		Additional analyses, clarification	Clarification on which data are included in the analyses, which assessments are considered for safety and efficacy analyses	Section 2.1
			Addition of the treatment arms and definition of the date of end of study treatment Removal of windows defined for ECGs, LVEF and PK assessments as they are not needed.	Section 2.1.1
			As per Health Authorities	Section 2.3.1

	request, addition of the breakdown per different time points of the number (%) of patients who discontinued the study treatment phase and of the primary reason for study treatment phase discontinuation	
	PAS: Removal of the condition related to vomiting to consider a concentration evaluable as the occurrence and time of vomiting is not collected in the CRF.	Section 2.2
	Addition of a subgroup "Stratum reported in the CRF" for the analysis by subgroup of the primary endpoint (to take into account the mistratification cases)	Section 2.2.1
	Removal of the subgroup "with or without historical BCR-ABL1 mutation by local lab" as this is not considered clinically relevant	
	Additional analyses of prior TKI and non TKI antineoplastic therapies	Section 2.4.2
	Implementation of the estimand language for the primary and key secondary objectives	Sections 2.5 and 2.6
	Addition of a sensitivity analysis of the primary estimand stratifying by the stratum recorded in the CRF to take into account that many stratification errors occurred	Section 2.5.5
	Addition of Time-to-event analyses for time to MMR and time to CCyR	Section 2.7.2

			Added how time is censored for time to MMR/CCyR, clarification on how to handle missing BMA assessments due to MMR being achieved	Section 2.7.3
			Added analyses AEs and SAEs incidence rates by adjusting for exposure and by reporting by time intervals to account for potential difference in exposure between the treatment arms	Section 2.8.1
			Clarified handling of unscheduled ECG measurements in the analyses	Section 2.8.4.1
4-June-2020	Prior to DB lock for primary analysis	Creation of amendment 2.0	Clarified baseline for mutations	Section 2.1.1
			Clarified EOT is mapped to defined time points	
			Modified age subgroup, added Line of therapy subgroup and moved Without T315I/V299L to Supplementary analysis (All patients with T315I/V299L mutations identified at the Week 1 Day 1 visit are discontinued from study treatment when the mutation results become available). Clarified Mutation subgroup doesn't include T315I/V299L mutations.	Section 2.2.1
			Modified age categories	Section 2.3
			Added COVID-19 related PDs analysis	Section 2.3.1
			Added definitions of time on treatment, duration of exposure in patient-years and average daily dose	Section 2.4.1

	Additional analyses of prior TKI therapy	Section 2.4.2
	Added summary of concomitant therapies for on-switched treatment period.	Sections 2.5.5, 2.6.5
	Added COVID-19 sensitivity analyses for the primary and key secondary endpoints	Section 2.5.6
	Added a supplementary analysis to the primary endpoint (Patients without T315I/V299L mutations at Week 1 Day 1 visit)	Section 2.9
	Added new graph for Ctrough values of asciminib	Section 4
	Updated the list of changes to the protocol specified analyses	Section 5.3
	Added imputation rules for immature cells	
	Removed imputation rules for corrected calcium as corrected calcium is collected	
	Clarified all available values for BUN and UREA will be reported under the parameter name BUN in listing to avoid double reporting of same information	
	Definition of loss of MMR: Removed reference to confirmation of loss of CHR/CCyR	Section 5.4.1
	Loss of CHR: clarified "Progressive splenomegaly refractory to therapy" is ≥ 5cm below left intercostal margin"	Section 5.4.3
	Implemented change to definition of treatment failure (Protocol amendment 3)	Section 5.4.4

			Clarified what "Thrombocytopenia (<100 x 109/L) that is unrelated to therapy" is.	Section 5.4.5
			Added derivation of response rates and categories section	Section 5.5.
7-Aug-2020	Prior to DB lock for primary analysis	Creation of amendment 3.0 after FDA type C teleconference on 28 July 020	As agreed with FDA, added sensitivity analyses of the primary and key secondary endpoints without the imputation rule used in the main analyses in case of missing PCR evaluations at 24/96 weeks.	Section 2.5.5
			Per FDA request, added another subgroup of interest: BCR-ABL ratio at baseline ≥ 1% or <1%.	Section 2.2.1
			Added calculation rules for duration of interrruption.	Section 2.4.1
			Added derivation rule for corrected calcium using the reported total calcium value and albumin.	Section 5.3
			Aligned the definition of loss of CCyR with the definition of loss of CHR by adding the requirement that loss of CCyR (Ph+ bone marrow cells to > 0%) must have led to treatment discontinuation because of lack of efficacy.	Section 5.4.2
14-Oct-2020	Post DB lock for primary analysis	Creation of addendum 1.0 to include post-hoc analyses added after FIR results review	Added that protocol deviations during the treatment switch period will be reported separately and clarified .	Section 2.3.1
			Clarified how to identify prohibited concomitant medications.	Section 2.4.2
			Added an analysis of time to MMR considering	Sections 2.7.2 and 5.6.3

	discontinuation from treatment due to any reason, without prior achievement of MMR as a competing risk.	
	Added an analysis of the MMR rate using the number of subjects with adequate follow-up as the denominator, i.e. for each time point (week x), only patients randomized at least x weeks prior to the cut-off date will be considered.	
	Added that post-hoc exploration of the treatment effect in different subgroups and assessment of the possible effect of differences in distribution of baseline characteristics were conducted (e.g. distribution of reasons for discontinuation of last prior TKI by gender and treatment, distribution of MCyR status at baseline by reasons for discontinuation of last prior TKI, distribution of mutation status at Week 1 Day 1 by reasons for discontinuation of last prior TKI).	Section 2.14