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Asciminib/ABL001

Oncology Clinical Trial Protocol CABL001A2302

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

Document type:	Oncology Clinical Trial Protocol
EUDRACT number:	2020-006057-21
Version number:	01 (Amended Protocol – Clean)
Clinical Trial Phase:	IIIb
Release date:	10-Aug-2022

Clinical Trial Protocol Template Version 3.0 dated 31-Jan-2020

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List of abbreviations

ACA	Additional Chromosomal Abnormalities
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AP/BC	Accelerated Phase / Blast Crisis
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
BCR-ABL1	Breakpoint Cluster Region Tyrosine-protein kinase ABL1
b.i.d.	bis in die/twice a day
BMA	Bone Marrow Aspirate
BUN	Blood Urea Nitrogen
CCyR	Rate of complete cytogenetic response
CMV	Cytomegalovirus
CML-CP	Chronic Myelogenous Leukemia – Chronic Phase
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
dd-PCR	Droplet Digital Polymerase Chain Reaction
DILI	Drug-Induced Liver Injury
EBV	Epstein–Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
ELN	European Leukemia Network
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOT	End Of Trial
ERCP	Endoscopic Retrograde Cholangiopancreatography
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
HBV	Hepatitis B Virus
HbsAg	antigen of the hepatitis B virus
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
HSV	Herpes Simplex Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgM	Immunoglobulins M

IgG	Immunoglobulins G
IMP	Investigational Medical Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IS	International Scale
LFT	Liver function test
LLN	lower limit of normal
MCV	Mean Cell Volume
MDASI-CML	MD Anderson Symptom Inventory – Chronic Myelogenous Leukemia
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMR	Major Molecular Response
MRI	Magnetic Resonance Imaging
MR4	Molecular response 4 log reduction from baseline
MR4.5	Molecular response 4.5 log reduction from baseline
CCI	CCI
OS	Overall Survival
p.o.	oral(ly)
PFS	Progression Free Survival
Ph+	Philadelphia chromosome-positive
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcomes
q.d.	Quaque Die / Once a day
QTcF	QT interval corrected by Fridericia's formula
RNA	Ribonucleic acid
RQ-PCR	Real Time Quantitative Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	standard deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin
TFR	Treatment Free Remission
TKIs	Tyrosine Kinase Inhibitors
TTF	Time to Treatment Failure
TSH	Thyroid Stimulating Hormone
ULN	upper limit of normal
US	United States
WBC	white blood cell(s)
WHO	World Health Organization

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
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 participant
Cohort	A specific group of patients fulfilling certain criteria and generally treated at the same time
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
International scale	Definition of molecular response standardized using the definition of the IRIS study
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, such as e.g. nurse, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned

Remote	Describes any trial activities performed with the participant at a location that is not the investigative site where the investigator will conduct the trial, but is for example the participant's home or another appropriate location
Randomization number	A unique identifier assigned to each randomized participant
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the patients as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 01 (10-Aug-2022)

Amendment rationale

As of 10 August 2022, 111 patients have been screened in the study and 91 patients have been randomized and received treatment. The study is ongoing.

The main purpose of this protocol amendment is to:

Implement UK and Canada local protocols amendment changes within the global protocol

- Add an exclusion criterion for recent participation in an interventional trial and clarify the IMP wash-out period required for study participation
- Include guidance in Table 6-4 regarding dose withholding in patients, who experience 5- to 20-fold ULN transaminase elevations while taking asciminib and dose modifications guidelines for patients having elevated levels at baseline.
- Table 6-5 added regarding Clinical and diagnostic assessments to rule out possible alternative causes of observed LFT abnormalities
- Clarify the guidance regarding dose modification criteria for recurrence of grade 3/4 cytopenia and to elaborate the guidance for follow up of a participant having potential drug-induced liver injury during the study.
- Implement editorial changes throughout the protocol to correct typos and provide clarifications where required.

Information on FDA marketing authorization for asciminib has been added.

These amendment items are considered to contribute to improve readability and accessibility of the protocol.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using red underlined font for insertions. This amendment is considered substantial.

The following sections, tables and figures were changed:

- Section 1.1: inclusion of information concerning FDA approval of asciminib for adult patients with Ph+ CML -CP, previously treated with two or more TKIs. The recommended dose of asciminib is a total daily dose of 80 mg, taken either as 80 mg q.d. or 40 mg BID. The FDA also approved asciminib for adult patients with Ph+ CML in CP with T315I mutation. The recommended dose of asciminib in patients with Ph+ CML in CP with T315I mutation is 200 mg BID.
- Section 2.1: updated wording on investigational treatment
- Section 4.2: clarification regarding blood pressure assessment in supine position only
- Figure 4-1: dose of “40 mg” is specified in the title
- Section 5.2: addition of an exclusion criterion for recent participation in an interventional trial and clarify the IMP wash-out period required for study participation

- Section 5.2: removal of exclusion criteria regarding 'history of active ongoing acute or chronic liver disease' as it was not in sync with inclusion of patients having baseline moderate hepatic impairment (total bilirubin ≤ 3 x ULN)
- Section 5.2: clarification regarding baseline evaluation of Hepatitis B parameters are added. HBV DNA estimations are required only if anti-Hbc is positive. Patients having HbsAg positivity will automatically be excluded, and HBV DNA estimations are not required in such scenario.
- Section 5.2: statement added to contraception criteria based on FDA request regarding female contraception
- Table 6-4: dose withholding guidelines were updated for patients who experience 5- to 20-fold ULN transaminase elevations while taking asciminib. In addition, appropriate dose modifications guidelines in patients having elevated transaminase levels at baseline are added. This change has been implemented in the protocol in response to the MHRA comment to revise the current dosing recommendations for transaminase elevations of 5- to 20-fold ULN in the protocol.
- Section 6.6.4.1: Additional clarifications have been added to the guidance for the follow up of a participant having potential drug-induced liver injury during the study. Compared to the local protocol amendment approved in Canada, a statement related to pediatric patients has been removed. This study being conducted in adult, the statement is considered not relevant.
- Section 8: updates regarding visit numbers two weeks post-dose escalation
- Table 8-1: addition of a row with visit days and appropriate visit windows
- Table 8-1: addition of a row with asciminib drug dispensation
- Table 8-1: updates regarding urine pregnancy test to be performed monthly between visits from week 24 to week 132
- Table 8-1: Mutational analysis by CCI [redacted] at screening/baseline is removed
- Section 8.1: correction regarding the bone marrow aspirate evaluation window prior randomization
- Section 8.4.2: updated to allow local labs to be completed in case of central lab logistical challenges. Noted BCR-ABL1 still required to be completed centrally.
- Section 8.4.4: clarification added in section pregnancy and assessments of fertility regarding contraception
- Section 8.5.1: clarification explaining that completed PRO measures will not be reviewed for AEs by the investigator/study personnel
- Section 8.4.3: addition of sentence below the table clarifying that ECGs are not required to be performed within a specified time frame (post-dose), after the week-2 visit.
- Section 9.1.1: clarification regarding adverse events and re-occurrence of adverse events reference Table 6-4
- Section 10.1.4: addition of a note within SAE reporting section if more stringent, local regulations regarding reporting timelines prevail
- Section 11.3: addition to include the 15 year retention period for study conduct documents after study completion

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. Mutational analysis by CCI [redacted] at screening/baseline is removed.

The change does affect the Informed Consent.

Protocol summary

Protocol number	CABL001A2302
Full Title	A phase IIIb, multi-center, open-label, treatment optimization study of oral asciminib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP) previously treated with 2 or more tyrosine kinase inhibitors
Brief title	Asciminib treatment optimization in ≥ 3rd line CML-CP
Sponsor and Clinical Phase	Novartis Global Medical Affairs, Phase IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of the study is to optimize the treatment of asciminib in patients with chronic myelogenous leukemia in chronic phase (CML-CP) previously treated with 2 or more Tyrosine Kinase Inhibitors (TKIs). Patients for this study will be identified based on warning criteria and resistance definition following European Leukemia Network (ELN) 2020 recommendations. In addition, the study will investigate the use of two different posologies. For this, patients will be randomized to either receive asciminib 40 mg twice a day (b.i.d.) or of 80 mg once a day (q.d.). In patients not achieving MMR at 48 weeks or not maintaining the response after the week 48 assessment up to week 108, asciminib dose may be escalated to 200 mg q.d. if in the investigator's opinion the patient may benefit from the escalation. In addition, there must not be any grade 3 or 4 toxicity while on therapy, or persistent grade 2 toxicity, possibly related to asciminib and unresponsive to optimal management.
Primary Objective(s)	The primary objective of the study is to estimate the major molecular response rate (MMR) of all the patients at week 48 with CML-CP following two or more prior TKI treatments and with no evidence of MMR at baseline.
Secondary Objectives	• To evaluate the safety and tolerability of asciminib in patients with CML-CP following 2 or more prior TKI treatments • To assess the rate of MMR in patients without MMR at baseline and at alternative time points at weeks 12, 24, 36, 72, 96 and 144 • To assess the rate of MMR at week 48 for patients with MMR at baseline • To assess the time to MMR • To assess the rate of early responses of BCR-ABL1 ≤10% and ≤1% at weeks 12, 24, 36 and 48 • To assess the rate of deep molecular responses (MR4 and MR4.5) at weeks 12, 24, 36, 48, 72, 96 and 144 • To assess cytogenetic response (% Ph+ metaphases) at weeks 48 and EOT. • To characterize the impact of additional cytogenetic abnormalities on efficacy • To assess cumulative molecular responses by all-time points • To assess duration of MMR • *To assess sustained deep molecular responses as prerequisite for Treatment Free Remission (TFR)* • To assess rate of progressions (PFS) • To assess overall survival (OS) • To assess time to treatment failure (TTF) • To evaluate patient reported outcomes and quality of life by using MDASI-CML

Study design	The study is an international, multi-center, non-comparative, phase IIIb, treatment optimization study of daily 80 mg asciminib (randomized to either 40 mg b.i.d. or 80 mg q.d.) in patients previously treated with 2 or more TKIs and who are considered failing or in warning as per ELN 2020. In patients not achieving MMR at 48 weeks or losing the response after the week 48 assessment up to week 108, asciminib dose may be escalated to 200 mg q.d. if in the investigator's opinion the patient may benefit from the escalation. In addition, there must not be any grade 3 or 4 toxicity while on therapy, or persistent grade 2 toxicity, possibly related to asciminib and unresponsive to optimal management. Treatment duration is 144 weeks for the individual patient. This is the maximum treatment duration for each patient.
Study population	The trial will enroll a total of approximately 186 patients: • 156 patients with CML-CP not in MMR at baseline who were treated with two or more TKIs and who were either resistant (ELN 2020 warning or failure) or intolerant to the last treatment will be enrolled. For this population, the primary endpoint for MMR at 48 weeks will be assessed. • Up to 30 additional patients intolerant only to their last TKI treatment and in MMR at baseline will also be enrolled. This patient population will not be part of primary endpoint analysis; however, all assessments will be done as with the 156 patients from the population of the primary endpoint analysis.
Key Inclusion criteria	• Signed informed consent must be obtained prior to participation in the study • Male or female patients with a diagnosis of CML-CP ≥ 18 years of age • Treatment with a minimum of 2 or more prior TKIs (i.e. imatinib, nilotinib, dasatinib, bosutinib, radotinib or ponatinib) • Warning or failure (adapted from the 2020 ELN Recommendations) or intolerance to the most recent TKI therapy at the time of screening • Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2 • Adequate end organ function (as per central laboratory tests)
Key Exclusion criteria	• Known presence of the BCR-ABL1 T315I mutation at any time prior to study entry • Known second chronic phase of CML after previous progression to AP/BC • Previous treatment with a hematopoietic stem-cell transplantation • Patient planning to undergo allogeneic hematopoietic stem cell transplantation • Uncontrolled cardiac repolarization abnormality • 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 • History of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis • Testing for Hepatitis B surface antigen (HbsAg) and Hepatitis B core antibody (HBcAb / anti HBc) will be performed at screening. Patients with active Hepatitis B Virus (HBV) infection (hepatitis B surface antigen [HbsAg] positive) will be excluded
Study treatment	The investigational treatment for this study is asciminib (80 mg daily, randomized to either 40 mg b.i.d. or 80mg q.d.). In patients not achieving MMR at 48 weeks or losing the response after the week 48 assessment up to week 108, asciminib dose may be escalated to 200 mg q.d. per investigator decision. Novartis will supply asciminib to the investigational site as 20 mg and 40 mg tablets.
Treatment of interest	Asciminib
Efficacy assessments	• The efficacy of asciminib will be primarily assessed through molecular monitoring by Real Time Quantitative Polymerase Chain Reaction (RQ-PCR) of the BCR-ABL1 transcripts in the peripheral blood, the standard methodology for assessing CML disease activity. RQ-PCR assessments will be performed at each study visit (except at Week 1 Day 1, Week 2 Day 1, Week 4 and Week 8 visits). For patients who escalate

	dose an additional, 2-week post-escalation ECG visit will be performed, there will be no RQ-PCR assessment done for this visit. • At selected visits cytogenetic analyses will be performed locally to assess the number of Philadelphia-positive cells in the bone marrow and additional cytogenetic aberrations. Cytogenetic analysis is a second standard assessment of disease status and response to treatment in CML. • Additional routine assessments of cell counts in peripheral blood will be performed at every visit. Though these are less sensitive than molecular monitoring and cytogenetics, an increase in blast cells may indicate a lack of response and potential sign of disease progression.
Key safety assessments	• Adverse event monitoring • Physical examination • Vital Signs • Hematology and biochemistry (and pregnancy when applicable) • 12-lead Electrocardiogram (ECG)
Other assessments	• Patient Reported Outcomes: MD Anderson Symptom Inventory – Chronic Myelogenous Leukemia (MDASI-CML) • Biomarker assessments (BCR-ABL1 resistance mutation analysis for ATP binding site and myristoyl binding site mutations) • CCI [redacted]
Data analysis	The primary estimand will be analyzed based on the data from the Full Analysis Set (FAS) and according to the Intention-To-Treat (ITT) principle. Exact test for single proportion will be used at the one-sided 2.5% level of significance. The null hypothesis is that the MMR rate at Week 48 is equal to 0.23. The alternative hypothesis is that the rate is greater than 0.23.
Key words	Randomized, non-comparative Phase IIIb CML chronic phase, after failure of or intolerance to 2 or more prior TKI Treatment optimization Asciminib ELN Recommendations 2020 MMR rate at 48 weeks

1 Introduction

1.1 Background

Chronic myeloid leukemia (CML) is a hematologic malignancy characterized by the clonal myeloproliferative expansion of transformed primitive hematopoietic progenitor cells with an incidence of 1 to 2 cases per 100,000 people (Faderl et al 1999). If untreated, the disease progresses from an initial chronic phase with a duration of about 3 to 5 years to an accelerated phase of shorter duration to a fatal blast crisis (Sawyers et al 1999). The hallmark of CML is the occurrence of the Philadelphia (Ph) chromosome, a shortened version of chromosome 22 as a result of a reciprocal translocation t(9;22)(q34;q11) (Nowell et al 1960, Rowley et al 1973). The molecular consequence of the t(9,22) translocation is the creation of the fusion protein BCR-ABL1, a constitutively active cytoplasmic tyrosine kinase with increased signaling activity, that activate multiple signal-transduction cascades affecting the growth and differentiation of hematopoietic cells, allowing them to escape constraints on normal growth and to become leukemic. (Sawyers et al 1999).

The management of Ph+, BCR-ABL1+ CML has undergone a profound evolution from the early use of cytotoxic agents to allogeneic stem cell transplantation and recombinant interferon-alpha and to newer tyrosine-kinase inhibitors (TKI), which represent the standard of care in the treatment of CML (Baccarani et al 2013). TKIs are a class of compounds competitively binding against ATP for the ATP-binding site of ABL1 and thereby inhibiting the ability of ABL1 to phosphorylate and activate proteins downstream. Following the registration of the first TKI imatinib, later referenced as '1st generation TKI' several other compounds have been developed with higher affinity to ABL1 such as the '2nd generation TKIs' nilotinib, dasatinib and bosutinib, and the more recent '3rd generation TKI' ponatinib. Four of the five TKIs: imatinib, nilotinib, dasatinib and bosutinib have been approved by the European Medical Agency and Food Drug Administration for the treatment of newly diagnosed CML. Ponatinib is approved for patients with a rare mutation variant of BCR-ABL1 T315I, which renders the other 4 TKI ineffective, and for patients with CML resistant to two or more TKIs. Although all 2nd gen TKIs eligible for the patient with newly diagnosed CML have been tested against imatinib, their activity has never been tested against each other (Hochhaus et al 2020a). Therefore, no consensus exists over the optimal treatment sequence of the different drugs in lines of treatment, and in case of treatment failure or intolerance of a TKI the next TKI may be chosen depending on the medical history, condition of the patient and treatment objective.

These significant advances in the treatment of CML allow patients with good response to treatment to have an almost normal life expectancy or even stop treatment and eventually become treatment-free.

Patients with chronic phase CML and failure of two or more prior treatments however still have a poor prognosis, with treatment failure rates of up to 75% in 3rd line and significantly reduced overall survival (Akard et al 2013).

Patients with intolerance represent a major clinical challenge in particular in later lines of CML treatment (Garg 2009 et al, Giles 2010 et al, Ongoren 2018 et al). Patients with intolerance to two or more prior TKI treatments have a high risk of reoccurrence of the same adverse event, and long-term safety concerns over the use of ATP-site binding TKIs remain

(Steegmann 2016 et al). As a consequence, this population of multiple refractory/resistant or intolerant patients represents still a significant therapeutic challenge with a high medical need for a different treatment approach.

Asciminib is a specific inhibitor of BCR-ABL1 with a different mode of action from all other TKI's currently available on the market or in development (Wylie et al 2017, Hughes et al 2019). Asciminib is the first clinical compound in CML that specifically targets the ABL1 myristate pocket (Specifically Targeting the ABL Myristoyl Pocket STAMP, Cortes et al 2020). It inhibits ABL1 kinase activity by interacting with the myristate binding site and stabilizes the inactive conformation of the enzyme (Manley et al 2018). Because it does not bind to the ATP binding site it maintains activity against kinase domain mutations that would impairs the activity of ATP-competitive drugs (Manley et al 2020). Asciminib is active in patients that have failed two or more prior TKIs, with 48% of patients achieving a major molecular response (MMR) in a heavily pretreated population in the Phase I study CABL001X2101 (Hughes et al 2019). In addition, the selective binding of asciminib is predicted to reduce toxicity (Hughes et al 2019), which is a promising approach for patients where the side effects of previous ATP-competitive TKI treatments did require dose reductions or interruptions and therefore not allow for the durable administration of an efficacious dose.

The ongoing Phase III ASCEMBL (CABL001A2301) study investigates the treatment of asciminib versus bosutinib randomized 2:1 in 233 patients with CML-CP who have failed or are intolerant to prior treatment with at least two ATP-binding site TKIs. The primary objective of the ASCEMBL study is the comparison of the MMR rate at 24 weeks between the two treatments. In the primary analysis, asciminib demonstrated statistically significant superiority and clinically meaningful efficacy when compared to bosutinib with a MMR rate of 25.5% over 13.2% respectively. Median duration of follow-up for all patients was 14.9 months. Treatment discontinuation was 69.7% and 37.6% for bosutinib and asciminib respectively, with lack of efficacy accounting for 31.6% and 21.0% and adverse events accounting for 21.1% and 5.1% of the discontinuation for bosutinib and asciminib, respectively. All-grade AEs occurred in 89.7 % and 96.1% of patients on asciminib and bosutinib, respectively. Grade 3/4 adverse events (AE) occurred in 50.6% of patients treated with asciminib and 60.5% of patients treated with bosutinib. Thrombocytopenia ≥ Grade 3 was the most commonly reported AE on asciminib in 17.3% patients, however only 5 patients (3.2%) discontinued the trial because of this AE. On the basis of these results, the authors concluded that the ASCEMBL results support the use of asciminib as a new treatment option in CML, particularly in patients with resistance/intolerance to ≥2 TKIs (Hochhaus et al 2020c).

The treatment recommendations from the ELN are considered the most widely used therapeutic guidance for CML outside of the US with applications or translations in many country recommendations even outside of Europe (Hochhaus et al 2020a). The ELN recommendations are revised regularly and have been issued in 2006 (Baccarani et al 2006), 2009 (Baccarani et al 2009), 2013 (Baccarani et al 2013) and 2020 (Hochhaus et al 2020a) to reflect the changes in the treatment landscape and to allow for the best possible duration and quality of life for a given patient.

For the ASCEMBL protocol created in 2018 the ELN 2013 recommendations were used to define the failure criteria to the most recent TKI as inclusion criteria (Hochhaus et al 2020c). While the 2013 recommendations still used different sets of criteria to define the response to

1st and 2nd treatment, the 2020 ELN recommendations represent only one set of criteria that is consistent for 1st line and 2nd line treatment. In general, these 2020 treatment milestone define a more ambitious set of response criteria over their 2013 counterpart: in the 2013 ELN recommendations, treatment failure in second-line was defined as: no CHR at 3 months, BCR-ABL1>10% on the International Scale (IS) at 6 months or 12 months. For the 2020 recommendations the milestones for treatment failure have been revised to BCR-ABL1>10% IS at 3 months (if confirmed between 1 and 3 months) and at 6 months, or BCR-ABL1>1% IS at 12 months of therapy. Warning criteria in 2nd line are identified as: BCR-ABL1>10% IS at 3 months, BCR-ABL1>1-10% IS at 6 months and BCR-ABL1>0.1-1% IS at 12 months. As these recommendations represent the profound change of the therapeutic landscape over the last 7 years (Hochhaus et al 2020a) it is considered important to re-evaluate the benefit of asciminib in a 3rd line population if the most recent treatment recommendations for failure and warning in 2nd line are used as inclusion criteria.

The ASCEMBL study investigated the efficacy and safety of a total daily dose of 80 mg asciminib given as one tablet of 40 mg b.i.d. Asciminib is required to be administered under fasting conditions with a food-free period of 2 hour before and 1 hour after the drug intake [Asciminib Investigator Brochure]. Non adherence to TKI therapy in CML has been correlated with poor therapeutic outcomes and is a principal factor contributing to the loss of cytogenetic responses and treatment failures in patients on long-term therapy (Ibrahim et al 2011) In a Finnish assessment, 21% of the CML patients were characterized to have low adherence, while physicians had a tendency to overestimate adherence (Keläle et al 2014). Nilotinib has a similar posology to that of asciminib as used in the ASCEMBL study, with twice daily dosing and the inclusion of a food-free period. In an analysis of 2546 patients in 63 countries. (Geissler et al 2017) showed that the adherence to nilotinib was markedly lower than for imatinib and dasatinib, both of which can be taken on a once daily regimen.

Thus, the posology of asciminib is expected to represent challenges for the optimal compliance for patients and with integration into the daily routine. Changing from a twice daily to once-daily dosage for asciminib may therefore improve the ease of administration, increase the compliance with treatment and thus help to maintain treatment outcomes.

Asciminib has demonstrated activity and tolerability in dosages of up to 200 mg b.i.d. (Hughes et al 2019). Following failure or intolerance of two TKIs, the number of treatment options for patients in 3rd line becomes severely reduced. Moving to another treatment may also bear the risk of additional challenges in the management as the efficacy or tolerability in the next line of treatment may also be inferior. In particular the use of second-generation TKI after failure to 2 TKIs may induce responses, but these are usually not durable except in some CP patients. New treatment options are needed (Garg et al 2009). It is therefore of interest to investigate a dose escalation of asciminib with its novel MoA from the standard dose of 40 mg b.i.d. used in ASCEMBL in patients that do not achieve MMR from 48 weeks of treatment and where there are no side effects at the current dose that would indicate that the risk of the dose increase outweigh a potential benefit.

Asciminib was granted accelerated approval by the US Food Drug Administration on 29-Oct-2021 for adult patients with Ph+ CML -CP, previously treated with two or more TKIs. The recommended dose of asciminib is a total daily dose of 80 mg, taken either as 80 mg q.d. or 40 mg BID. The FDA also approved asciminib for adult patients with Ph+ CML in CP with T315I

mutation. The recommended dose of asciminib in patients with Ph+ CML in CP with T315I mutation is 200 mg BID.

1.2 Purpose

The purpose of the study is to investigate the potential optimization of the treatment with asciminib 80 mg total daily dose in adult patients with chronic myelogenous leukemia in chronic phase (CML-CP) previously treated with 2 or more TKIs.

Patient population:

Patients for this study will be identified based on warning criteria and resistance definition following ELN 2020 recommendations or intolerance on their 2nd TKI (Hochhaus et al 2020a). This is an expanded population compared to the original ASCEMBL study as the inclusion criteria for the ASCEMBL-protocol was based on the ELN treatment recommendations from 2013 (Hochhaus et al 2020c). Applying the newer ELN 2020 criteria will permit patients both with treatment failure as well as with warning signs to be included. This will allow for a population, with less advanced disease and lower risk of progression to enter the trial, which may benefit from a better and longer response to asciminib.

Patients treated with two or more TKI and intolerance to the last TKI treatment represent a clinical challenge as the number of treatment options available to them are limited. For the primary analysis, patients with intolerance will be eligible with BCR-ABL1 $\geq$ 0.1 % (i.e. not in MMR). Additionally, 30 patients who are intolerant to ongoing TKI treatment but in MMR will be allowed to enter the trial.

Simplified posology from b.i.d. to q.d. dosing:

The study will investigate the use of two different dose regimens: All patients will be randomized at baseline to receive 80 mg total daily dose of asciminib either as 40 mg b.i.d. in agreement with the dose investigated in ASCEMBL or as 80 mg q.d. Though the trial will not be powered to compare both treatments, the descriptive data from both treatment groups is expected to provide additional insight into the optimal patient management.

Dose escalation:

Patients treated in later lines of CML often have few remaining therapeutic options. Asciminib has demonstrated activity and tolerability in dosages of up to 200 mg b.i.d. (Hughes et al 2019). With the limited treatment options available it is therefore of interest whether patients not in MMR at 48 weeks or thereafter could benefit from a potential dose escalation. Based on extensive PK modeling, a dose escalation from 40 mg b.i.d. / 80 mg q.d. asciminib to 200 mg q.d. asciminib was chosen for this approach.

Taken together the data will provide valuable guidance for the clinical practice and use of asciminib in patients treated in agreement with most recent treatment recommendations and current clinical practice.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objectives	Endpoint(s)
Primary:	
• To estimate the major molecular response (MMR) rate at week 48 of all patients (40 mg b.i.d. asciminib and 80 mg q.d.) with CML-CP following two or more prior TKI treatments and with no evidence of MMR at baseline.	• Major Molecular Response (MMR) rate at week 48.
Secondary:	
• To evaluate the safety and tolerability of asciminib in patients with CML-CP following two or more prior TKI treatments.	• 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 assess the rate of major molecular responses (MMR) in patients without MMR at baseline, at alternative time points at weeks 12, 24, 36, 72, 96 and 144.	• MMR rate at weeks 12, 24, 36, 72, 96 and 144.
• To assess the rate of molecular responses (MMR) at week 48 for patients with MMR at baseline	• MMR rate at week 48 for patients with MMR at baseline.
• To assess the time to MMR	• Time from the date of randomization to the date of first documented MMR
• To assess the rate of early responses of BCR-ABL1 ≤10% and ≤1% at weeks 12, 24, 36 and 48	• Rate of BCR-ABL1 ≤ 10% and ≤1% at weeks 12, 24, 36 and 48
• To assess the rate of deep molecular responses (MR4 and MR4.5) at weeks 12, 24, 36, 48, 72, 96 and 144.	• Rate of MR4 and MR4.5 at weeks 12, 24, 36, 48, 72, 96 and 144.
• To assess cytogenetic response (% Ph+ metaphases) at weeks 48 and EOT.	• Rate of complete cytogenetic response (CCyR) at weeks 48 and EOT.
• To characterize the impact of additional cytogenetic abnormalities on efficacy	• Additional chromosomal abnormalities and occurrence of high-risk ACAs
• To assess cumulative molecular responses by all-time points.	• Rate of BCR-ABL1 ≤ 10%, BCR-ABL1 ≤1%, MMR, MR4 and MR4.5 by all-time points.
• To assess duration of MMR.	• Duration of MMR.
• To assess sustained deep molecular responses as prerequisite for TFR.	• Duration of MR4 without loss of MMR.
• To assess rate of progression (PFS).	• Time from randomization to death.
• To assess overall survival (OS).	• Time from randomization to treatment failure define as BCR-ABL1 > 1%.
• To assess time to treatment failure (TTF).	• Change in symptom burden and interference from baseline over time according to the MDASI-CML PRO instrument.
• To evaluate patient reported outcomes and quality of life by using QoL scale.	

Exploratory:

- CCI
- CCI
- CCI
- CCI

The selected summary tables for the additional patients intolerant to the last TKI and achieving MMR at baseline is listed in Section 12 and Section 12.5.2.

2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g. premature discontinuation of treatment).

The primary clinical question of interest is: What is the effect of asciminib on MMR in CML patients who were resistant or intolerant to 2 or more prior TKIs?

The primary estimand is described by the following attributes:

1. Population: CML Patients with resistance or intolerance to 2 or more prior TKIs per the 2020 ELN recommendations. Further details about the population are provided in Section 5.
2. Endpoint: MMR rate achieved at week 48 while on study treatment without meeting any treatment failure criteria prior to week 48. A patient will be counted as having achieved MMR at week 48 if he/she meets the MMR criterion (BCR-ABL1 level $\leq$ 0.1%) at week 48 while on study treatment unless the patient met any treatment failure criteria prior to week 48.
3. Treatment of interest: the investigational treatment asciminib received for at least 48 weeks, with or without dose modification, dose interruption or any intake of concomitant medications, or intake of prohibited medications.

Further details about the investigational treatment are provided in Section 6.

4. List of intercurrent events:
   - Treatment discontinuation (i.e. having performed an EOT visit) prior to week 48 due to any reason (e.g. death due to any cause, intolerance, treatment failure, etc.).
   - Dose modification, dose interruption, or any intake of concomitant medications.
   - Intake of prohibited medications Section 6.2.2.
5. The summary measure: MMR rate and its 95% confidence interval at week 48.

Handling of intercurrent events are discussed in Section 12.4.3.

2.2 Secondary estimands

Not applicable.

3 Study design

The study is an international, multi-center, non-comparative, phase IIIb, treatment optimization study of asciminib (randomized 1:1 to either 40 mg b.i.d. or 80 mg q.d.) in adult patients previously treated with 2 or more TKIs. Randomization is only used to have a balance in the allocation of treatment into either asciminib 40 mg b.i.d. or 80 mg q.d.

In patients not achieving MMR at 48 weeks or losing the response after the week 48 assessment up to week 108, asciminib dose may be escalated to 200 mg q.d. if in the investigator's opinion the patient may benefit from the escalation. In addition, there must not be any grade 3 or 4 toxicity while on therapy, or persistent grade 2 toxicity, possibly related to asciminib and unresponsive to optimal management.

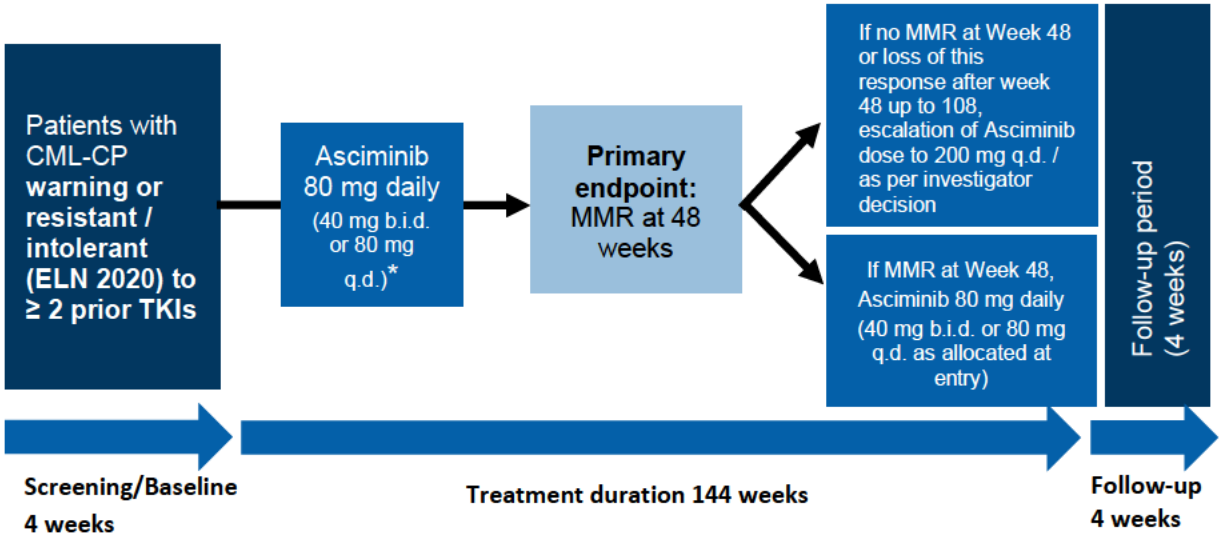
BCR-ABL1 and CCI results are required before increasing asciminib dose, therefore the dose escalation can occur at next scheduled visit upon results review of the prior visit. In patients losing response after the week 48 assessment, the last possible time point to initiate the 200 mg dose will be the week 120 visit to ensure that efficacy and safety of the dose escalation can be sufficiently established during the remaining trial follow up period.

If a dose decrease is required, patients will return to the initial dosing regimen (q.d. or b.i.d.) they were using before the dose increase which was considered tolerable. For this reason, if a patient e.g. escalates from 40 mg b.i.d. to 200 mg q.d., in case of a required dose decrease a use to 80 mg q.d. is not allowed and the patient will continue on 40 mg b.i.d. asciminib.

All patients will be treated for a maximum duration of 144 weeks.

The primary endpoint of the study is MMR rate at 48 weeks. As the ELN 2020 recommendations do not give specific treatment guidance for milestones in 3rd line, the ELN 2020 milestone at twelve months for optimal response in 2nd and 1st line was chosen to define the primary endpoint.

Figure 3-1 Study design



*Treatment assignment to b.i.d. or q.d. (1:1) will be done through Interactive Response Technology (IRT).

At the investigator's direction and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial procedures according to Table 8-1, out of screening and week 1 day 1 visits, performed at a remote location (e.g. tele-visit, local laboratory, other healthcare professional, participants home) in case of temporary inability to perform the procedures on site due to a pandemic such as COVID-19.

Procedures may be performed remotely under the oversight of the Investigator, who retains accountability for the oversight and all efficacy and safety decisions with delegation of tasks to an off-site healthcare professional. The remote procedures may be offered in certain countries and sites as determined by Novartis based on national and local regulations and feasibility.

Off-site healthcare professionals may be provided by a third-party vendor sourced by Novartis. Where a site wishes to use off-site healthcare professionals that are not provided by Novartis this must be agreed with Novartis before use. In addition to procedures performed by the off-site healthcare professional, the on-site staff can perform certain procedures remotely using tele-visits.

If pre-agreed with Novartis and considered by the Investigator in the interest of the participant's health where delivery of Investigational Medical Product (IMP) directly to a participant's secure off-site location (e.g. home) is permitted by national and local governing regulations, dispatch of IMP from the site to the participant will be performed under the accountability of the Investigator.

4 Rationale

4.1 Rationale for study design

The trial presented in this protocol is an open-label, treatment optimization study. Patients will receive asciminib as study treatment continuously for up to 144 weeks or until disease progression, treatment failure or intolerance to treatment. At treatment initiation, asciminib will be provided to all trial patients at a total daily dose of 80 mg. All patients will be randomly assigned 1:1 to 2 groups with 80 mg given either as 40 mg b.i.d. or 80 mg q.d., using IRT to avoid any selection bias. Considering the objective nature of the primary endpoint, an open label study is deemed acceptable.

The ongoing ASCEMBL study is a phase III study, investigating the efficacy of treatment with asciminib versus bosutinib in CML-CP patients with at least 2 prior therapies. In the primary analysis, asciminib (40 mg b.i.d.) demonstrated statistically significant superiority and clinically meaningful efficacy when compared to bosutinib (500 mg q.d.) with a MMR rate at week 24 of 25.5% over 13.2% respectively. Following the release of the initial results, questions remain such as daily dosing schedule and escalation.

Changing from a twice a day (b.i.d.) to once a day (q.d.) dosage for asciminib may improve the ease of administration, increase the compliance with treatment and thus help to maintain treatment outcomes. Though the trial will not be powered to compare both treatments, the descriptive data from both treatment groups is expected to provide additional insight into optimal patient management.

Patients treated in later lines of CML often have few remaining therapeutic options. Considering asciminib has demonstrated activity and tolerability in dosages of up to 200 mg b.i.d. (Hughes et al 2019), it is of interest to investigate whether patients could benefit from a potential asciminib dose escalation. A single step dose escalation to 200 mg q.d. was chosen for this trial as it would allow for a substantial increase in asciminib exposure while at the same time the safety profile can be maintained.

4.1.1 Rationale for choice of background therapy

Not applicable.

4.2 Rationale for dose/regimen and duration of treatment

The primary dose chosen for the trial is total daily dose of 80 mg taken as either 40 mg b.i.d. or 80 mg q.d (1:1 randomization). Following the primary endpoint assessment at week 48, the asciminib dose may be escalated to 200 mg q.d. in patients not achieving or not maintaining MMR at 48 weeks up to 108 weeks per investigator decision.

Based on the results of study CABL001X2101, 40 mg b.i.d. was selected as the recommended dose for patients with CML-CP and was further evaluated as the standard dose in the pivotal registration study ASCEMBL (CABL001A2301). The study population in the ongoing ASCEMBL trial includes 222 patients with CML-CP, and treatment failure according to the ELN 2013 criteria (Baccarani et al 2013), who had prior treatment with 2 or more ATP binding TKIs. The results from this study confirmed that the dose of 40 mg b.i.d. was safe, efficacious and well tolerated (Hochhaus et al 2020c).

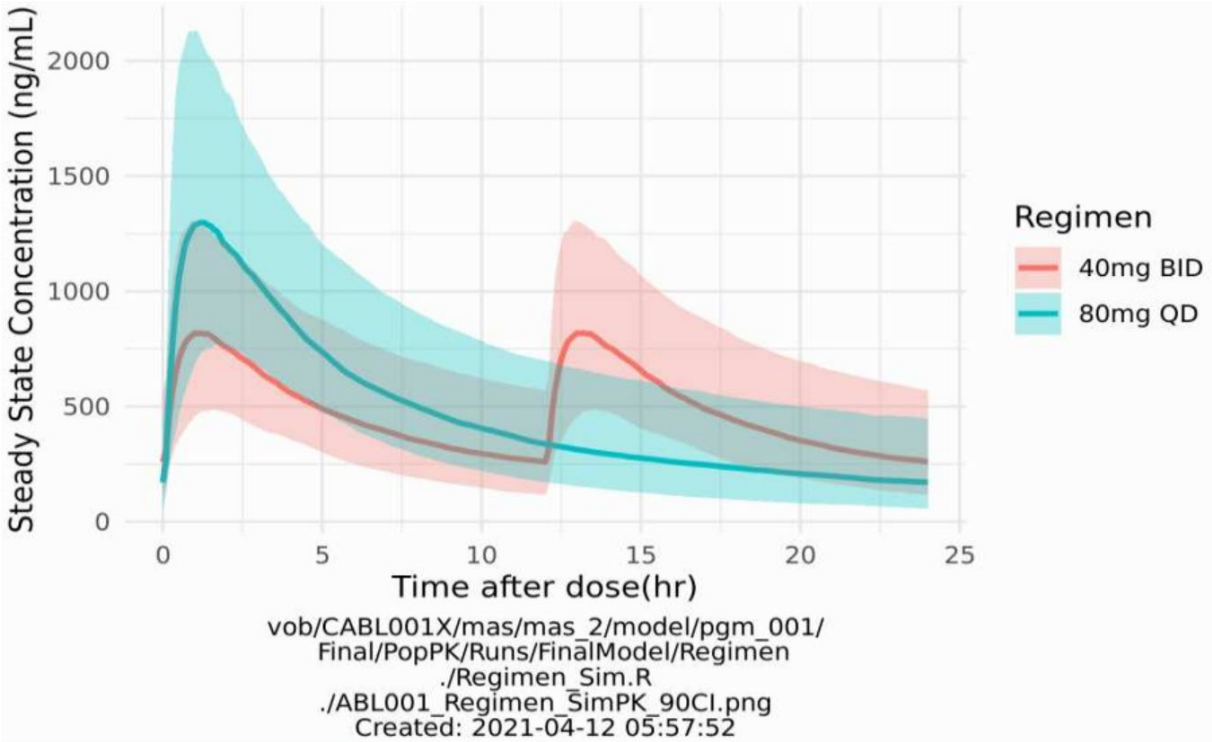
Extensive exposure-efficacy and exposure-safety analyses were performed based on pooled clinical asciminib data.

The exposure-efficacy analysis of %BCR-ABL time course highlighted the existence of a slightly positive exposure-efficacy relationship, which did not translate into meaningful difference in median predicted MMR rates over the complete wide dose range tested (i.e. 20 mg to 400 mg total daily dose), regardless of PK metrics (daily AUC, Cmax and Cmin) used [CCI]. Similar efficacy for asciminib 80 mg q.d. compared to 40 mg b.i.d. in patients were predicted. In agreement with the observed data, the predicted MMR rate at CCI for asciminib 40 mg b.i.d. and 80 mg q.d. was CCI % and CCI %, respectively.

For exposure-safety modelling, a repeated logistic regression model was used to describe the association between the probability of a safety event and PK exposure. Selected relevant safety endpoints included laboratory parameters (amylase, lipase, platelets count, neutrophils, hemoglobin, AST, ALT, total bilirubin, triglycerides and serum creatinine), vital signs (systolic blood pressure and diastolic blood pressure in supine position only) for hypertension, AEs for fatigue and asthenia, Grade ≥ 3 TEAEs and TEAEs leading to dose reductions and/or interruptions. Other safety analyses included time to first dose reduction due to an AE and effect of exposure on serum creatinine (for assessing the potential effect of asciminib on renal transporters). Based on this exposure-safety analysis there is no apparent correlation between the probability of a safety event and increase in exposure when using any PK metrics for 40 mg b.i.d. vs 80 mg q.d. [CCI].

Simulated steady state PK profiles and parameters, using the population estimates for 40 mg b.i.d. and 80 mg q.d. are presented in Figure 4-1 and Table 4-1, respectively. The simulated mean AUC0-24hr values were comparable between the two regimens. Compared to 40 mg b.i.d., Cmax and Cmin were approximately CCI % higher and CCI % lower for 80 mg q.d.

Figure 4-1 Simulated mean steady state PK profiles of asciminib 40 mg b.i.d. and 80 mg q.d.



The shaded area represents the 10th – 90th percentile. The solid line represents the median.
Source: [PopPK Report].

Table 4-1 Summary of simulated PK metrics of 40 mg b.i.d. and 80 mg q.d.

Regimen	Cmin (ng/mL)	Cmax (ng/mL)	AUC0-24hr (ng*hr/mL)
40 mg b.i.d.	302 (60%)	908 (40%)	12638 (43%)
80 mg q.d.	215 (77%)	1463 (40%)	12646 (43%)

Arithmetic mean and %CV are presented
Source: [PopPK Report].

Based on the population PK model there is no difference in clearance between 80 mg q.d. and 40 mg b.i.d.

In summary, based on the available clinical data as well as the extensive exposure-efficacy and efficacy-safety analyses, the risk/benefit ratio of asciminib administered at 80 mg q.d. in patients with CML not harboring the T315I mutation is not different than that of asciminib 40 mg b.i.d.

Treatment duration for the individual patient in this study is anticipated to be 144 weeks. In ASCEMBL (patients with CML-CP and treatment failure according to the ELN 2013 criteria), 37.6% of patients treated with asciminib (40 mg b.i.d.) had discontinued their treatment with 43.4 weeks median duration of exposure for asciminib (Hochhaus et al 2020c). The protocol presented here will be using the 2020 ELN milestones (Hochhaus et al 2020a). Applying the newer ELN 2020 criteria will permit patients both with treatment failure as well as with warning

signs to be included. This will allow for a population, with less advanced disease and lower risk of progression to enter the trial. It is believed that the less resistant patient population may benefit from longer treatment with asciminib. The overall trial duration was therefore selected as 144 weeks while it was 96 weeks in ASCEMBL.

Patients treated in 3rd and later lines of CML often have few remaining therapeutic options with no established standards of care and disease monitoring. (ELN 2020). In this study patients not achieving MMR from 48 to 108 weeks of treatment with asciminib (40 mg b.i.d. or 80 mg q.d.) will be permitted a dose escalation to 200 mg q.d. It is anticipated that this dose of asciminib will lead to a marked increase in exposure that may lead to better efficacy while at the same time remains within the known side effect profile that has been assessed in the CABL001X2101 study up to doses of 200 mg b.i.d.

The protocols of both phase I (CABL001X2101) and phase III (ASCEMBL, CABL001A2301) did not include a planned approach dose escalation in response to a lack of efficacy. Dose escalation was permitted for individual patients at investigators judgement in the phase I (CABL001X2101) study.

A dose of 200 mg q.d. was investigated in the CABL001X2101 protocol for patients with CML-CP and AP (n=12) (CABL001X2101). All patients (n=12) with CML-CP/-AP treated with asciminib 200 mg q.d. single agent had at least one AE regardless of study treatment relationship. Overall, the most frequent AEs by PT reported [≥ 4 patients (33.3%) treated with 200 mg q.d.] were fatigue and headache (50.0%), nausea and diarrhoea (41.7%), amylase increased, hypertension, lipase increased, abdominal pain, constipation, insomnia, depression, hypertriglyceridaemia, myalgia and palpitations (33.3% each). Grade ≥ 3 AEs (regardless of study treatment relationship) were reported in 8 patients (66.7%), with most common being lipase increased (33.3% patients), and hypertension, myocardial infarction and pancreatitis (16.7% each). SAEs suspected to be related to treatment with asciminib were reported in 3 patients (25.0%). These suspected events were angina pectoris, myocardial infarction, pericardial effusion, pancreatitis, and pleural effusion (n=1 each). Overall, one patient discontinued asciminib treatment due to AEs – lipase increased and amylase increased, which were suspected to be related to asciminib treatment. No on-treatment death was reported in cohort taking asciminib 200 mg q.d. single agent for treatment of CML-CP/AP. Though less of patients were exposed to this dosage regimen in CABL001X2101 study, the safety analysis showed that incidence and severity of AEs treated with asciminib 200 mg q.d was comparable with the overall safety profile of asciminib single agent used in treatment of CML-CP/AP.

The exposure-efficacy analysis of %BCR-ABL time course highlighted the existence of a slightly positive exposure-efficacy relationship, hence patients may benefit from such a dose escalation. Asciminib 200 mg q.d. is regarded to be safe and well tolerated, which is also supported by the observed flat exposure-safety relationship across all doses tested (i.e. up to 400 mg total daily dose). To conclude, the risk/benefit ratio is believed to stay positive for asciminib 200 mg q.d. in the patients that fail to achieve MMR from 48 weeks.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable.

4.4 Purpose and timing of interim analyses/design adaptations

There are no formal interim analyses or design adaptation planned for this study. Please refer to Section 10 and Section 12.7 for details on data monitoring and reporting.

4.5 Risks and benefits

Appropriate eligibility criteria, as well as specific dose modification and stopping rules, are included in this protocol.

Patients either failing or being intolerant to previous TKI therapy may have limited sensitivity to the remaining available TKIs or have mutations or comorbidities that prevent the use of specific TKIs. Importantly, with each line of treatment with TKIs, failure rates increase including the risk of progressing to advanced phases of the disease (Cortes et al 2013, Soverini et al 2014 and Soverini et al 2016). Therefore, the ultimate treatment goal is to reach optimal disease control to prevent disease progression in patients with CML-CP.

In two independent clinical studies asciminib has demonstrated to be efficacious in patients pretreated in multiple lines of therapy combined with good tolerability. Results from the phase I study CABL001X2101 showed durable responses with asciminib in a heavily pretreated population who had resistance to or unacceptable side effects from TKIs. In the ASCEMBL study (CABL001A2301) asciminib demonstrated superiority in the molecular response over bosutinib in patients treated with two prior TKI (Hochhaus et al 2020c).

This phase IIIb study aims to investigate the efficacy and safety of asciminib in an expanded population over the one from ASCEMBL, applying the newer ELN 2020 criteria and allowing patients both with treatment failure as well as with warning signs to be included. This will allow for a population with a less advanced disease and lower risk of progression to enter the trial, who may potentially benefit from a better response to asciminib. In addition, the tolerability of asciminib may allow for a more durable treatment with less side effects and lower risk of treatment discontinuation in this population. Using a second-generation TKI after failure of a prior second generation TKI appears to be of limited value (Hochhaus et al 2020b) and the results are often short-lived. With the demonstrated efficacy from ASCEMBL it appears therefore acceptable to expand the patient population to the ELN criteria 2020 and include patients with warning signs.

Patients who are intolerant to ongoing TKI treatment but in MMR will also be allowed to enter the trial. Management of side effects represent a significant challenge with TKIs, in particular as patients may achieve a normal life expectancy. Data from ASCEMBL (Hochhaus et al 2020c) support a more favorable safety profile of asciminib compared with bosutinib. Patients with long-lasting side effects may therefore benefit from a switch to asciminib and an improved quality of life, while at the same time have little risk of losing the previously attained good response. All patients will also be closely monitored so any loss of molecular response will be detected early.

The patient selection in this protocol is based on the ASCEMBL study, while expanding on the latest finding and results from this trial to reflect the optimum in safety management. Efficacy of the drug is assessed through molecular monitoring in central lab standardized to the international scale. With the exception of the bone marrow assessment required for response

monitoring, the protocol does not include invasive examination. Patient visits are aligned with the safety monitoring requirements as well as with current treatment recommendations and represent a common schedule that is also required in clinical practice outside of the study. It is therefore anticipated, that the protocol will take every precaution to allow for the best possible safety of the patients while at the same time carefully managing the additional burden of the trial to patients.

Patients will be randomized 1:1 into two treatment groups treated with asciminib 40 mg b.i.d or 80 mg q.d. Based on the available clinical data as well as the extensive exposure-efficacy and efficacy-safety analyses, the risk/benefit ratio of asciminib administered at 80 mg q.d. in patients with CML not harboring the T315I mutation is not different than that of asciminib 40 mg b.i.d.

Patients not reaching MMR at 48 weeks or losing the response thereafter will be allowed to escalate the dose to 200 mg. The exposure-efficacy analysis of %BCR-ABL1 time course highlighted the existence of a slightly positive exposure-efficacy relationship, hence patients may benefit from such a dose escalation. Asciminib 200 mg q.d. is regarded to be safe and well tolerated, which is also supported by the observed flat exposure-safety relationship across all doses tested (i.e. up to 400 mg total daily dose). The risk/benefit ratio is believed to stay positive for asciminib 200 mg q.d. in the patients that fail to achieve MMR from 48 weeks.

Women of child-bearing potential must be informed that taking the study treatment 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 requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

There may be unforeseen risk with asciminib, which could be serious. Refer to the latest [Asciminib Investigator's Brochure].

This study carries no requirement for patients to be tested for SARS-CoV-2. Based on the known mechanism of action, asciminib is not expected to negatively impact known immune mechanisms involved in clearing SARS-CoV-2 infection. However, no studies were conducted to assess whether asciminib may possess an additional risk in case of exposure to SARS-CoV-2. Subjects treated with asciminib should be informed there could be unknown side effects that may lead to complications of COVID-19.

There is no known contraindication for the use of an inactivated, viral-vector-, or mRNA-based SARS-CoV-2 vaccine in patients with cancer who receive asciminib therapy. Recognizing that multiple vaccines may have various mechanisms of action with different associated potential risks, locally applicable public health and Health Authority guidance for SARS-CoV-2 vaccine should be followed, and Independent Review Boards (IRB)/Ethics Committees (EC) consulted if needed. For patients in the study, the decision and timing of vaccination against SARS-CoV-2 should be made on a case-by-case basis and at the discretion of the treating physician.

4.6 Rationale for COVID-19 pandemic mitigation procedures

Due to the ongoing COVID-19 pandemic, mitigation procedures may be implemented to ensure participant safety and trial integrity. These are listed in the relevant sections of the protocol. Notification of these mitigation procedures should be discussed with Novartis prior to

implementation of mitigation procedures and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

The trial will enroll a total of approximately 186 patients with CML-CP following treatment with two or more prior TKIs.

One hundred fifty-six (156) patients with CML-CP not in MMR at baseline who have been previously treated with two or more TKIs and who were either resistant (ELN 2020 warning or failure) or intolerant to the last treatment will be enrolled.

Up to 30 additional patients intolerant only to their last TKI treatment and in MMR at baseline will also be enrolled.

The primary endpoint for MMR rate at 48 weeks will be assessed only in patients who are not in MMR at baseline.

The definition of CML-CP will be according to the ELN 2020 criteria (Hochhaus et al 2020a) 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.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Male or female patients with a diagnosis of CML-CP ≥ 18 years of age
3. Patients must meet all 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
4. Prior treatment with a minimum of 2 prior TKIs (i.e. imatinib, nilotinib, dasatinib, bosutinib, radotinib or ponatinib)
5. Warning or failure (adapted from the 2020 ELN Recommendations) or intolerance to the most recent TKI therapy at the time of screening
   - Warning is defined as:
     - Three months after the initiation of treatment: BCR-ABL1 > 10% IS
     - Six months after the initiation of treatment: BCR-ABL1 >1-10% IS
     - Twelve months after the initiation of treatment BCR-ABL1>0,1-1% IS

- At any time after the initiation of therapy BCR-ABL1 >0.1-1% IS, loss of MMR (>0.1% with 5-fold increase of BCR-ABL1 transcripts).

- In addition, patients with failure of treatment according to the ELN 2020 recommendations will be eligible:
  - Three months after the initiation of treatment: BCR-ABL1 > 10% IS if confirmed within 1-3 months
  - Six months after the initiation of treatment: BCR-ABL1 >10% IS
  - Twelve months after the initiation of treatment BCR-ABL1 >1% IS
  - At any time after the initiation of therapy BCR-ABL1 >1% IS, emergence of resistance mutations, high-risk ACA
- 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:
   - Total bilirubin ≤ 3 x ULN; patients with Gilbert's syndrome may only be included if Total bilirubin ≤ 3 x ULN or direct bilirubin ≤1.5 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 ≥ 30 mL/min as calculated using Cockcroft-Gault formula
8. Patients must have the following electrolyte values 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* within normal limits

*calculated using Cockcroft-Gault formula

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

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Known presence of the BCR-ABL1 T315I mutation at any time prior to study entry
2. Known history of 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 of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG) within 6 months prior to starting study treatment
    - 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, permanent pace maker)
    - 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 Torsades de Pointes" (per www.crediblemeds.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
8. Patients with known history of Human Immunodeficiency Virus (HIV).
9. Testing for Hepatitis B surface antigen (HbsAg) and Hepatitis B core antibody (HBcAb / anti HBc) will be performed at screening. Patients with active Hepatitis B Virus (HBV) infection (hepatitis B surface antigen [HbsAg] positive) will be excluded. HBV-DNA testing will also be performed at screening, if anti Hbc is positive. Note: Patients with antecedent but no active HBV (i.e., hepatitis B core antibody [HBcAb] positive, and both HbsAg and HBV-deoxyribonucleic acid negative) are eligible. In these cases, patients may be on anti-HBV prophylaxis and should be monitored for reactivation via monthly HBV-DNA evaluations.
10. Positive test for Hepatitis C Virus (HCV) ribonucleic acid (RNA). Testing for Hepatitis C antibody (HCV Ab) will be performed at screening. HCV-RNA testing will also be performed at screening if HCV Ab are positive.

11. 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)
12. Previous treatment with or known/ suspected hypersensitivity to asciminib or any of its excipients.
13. Pregnant or nursing (lactating) women
14. 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. If local regulations or locally approved prescribing information are more stringent than the protocol required duration of contraception, the longer duration must be followed.

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). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.Use of oral, (estrogen and progesterone), 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 studytreatment.

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms). Women are considered not of child-bearing potential if they are post-menopausal 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.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the Inform Consent Form (ICF).

15. Participation in a prior investigational study within 30 days prior to randomization or within 5-half-lives of the investigational product, whichever is longer.

Exception: The investigator has the discretion to include/exclude a subject in the study, who will be found to have symptoms representative of COVID-19 during the screening phase. Such subjects should be managed as per the country specific guidelines related to COVID-19.

Of note, neutropenia was reported as a common adverse event in CML patients treated with asciminib in ongoing clinical studies. However, lymphopenia was not frequently reported in these patients. In addition, no effects on lymphocytes were observed in rats, dogs or monkeys.

Based on the known mechanism of action, asciminib is not expected to negatively impact known immune mechanisms involved in clearing SARS-CoV-2 infection. However, no studies were conducted to assess whether asciminib may possess an additional risk in case of exposure to SARS-CoV-2. Subjects treated with asciminib should be informed there could be unknown side effects that may lead to complications of COVID-19.

6 Treatment

6.1 Study treatment

The investigational treatment for this study is asciminib (40 mg b.i.d. or 80 mg q.d. as assigned by IRT). Novartis will supply asciminib to the investigational site as 20 mg and 40 mg tablets.

In patients not achieving MMR at 48 weeks or losing the response (confirmed loss of MMR in two consecutive tests) after the week 48 assessment up to week 108, asciminib dose may be escalated to 200 mg q.d. if in the investigator's opinion the patient may benefit from the escalation. In addition, to participate in the dose escalation, there must not be any grade 3 or 4 toxicity while on therapy, or persistent grade 2 toxicity, possibly related to asciminib and unresponsive to optimal management.

Dose escalation may happen at next schedule visit upon receipt of BCR-ABL1 and CCI [redacted].

6.1.1 Dosing regimen

Asciminib

Asciminib will be supplied to the investigational site as 20 mg and 40 mg tablets. Asciminib will be administered orally twice a day (b.i.d.) or once a day (q.d.) as assigned by IRT upon eligibility confirmation, without food, for patients on standard dose of 80 mg daily.

Upon dose escalation to 200 mg, asciminib 40 mg tablets will be administered orally once a day (q.d.).

If a dose decrease from 200 mg q.d. is required, patients will return to the initial dosing regimen (q.d. or b.i.d.) they were using before the dose increase which was considered tolerable. For this reason, if a patient e.g. escalates from 40 mg b.i.d. to 200 mg q.d., in case of a required dose decrease a use to 80 mg q.d. is not allowed and the patient must continue on 40 mg b.i.d. asciminib

Asciminib tablets should be ingested as described in Section 6.3.2.

Study drug

Table 6-1 Investigational drug

Study Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Asciminib (ABL001) 20 mg[a]	Tablet	Oral use	Open-label supply, bottle	Sponsor (global)
Asciminib (ABL001) 40 mg	Tablet	Oral use	Open-label supply, bottle	Sponsor (global)

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

6.1.2 Additional study treatments

No additional treatment beyond investigational drug are included in this trial.

6.1.3 Guidelines for continuation of treatment

See Section 6.6.

6.1.4 Treatment duration

The planned duration of treatment is up to 144 weeks unless patient discontinue from treatment due to unacceptable toxicity, disease progression and/or if treatment is discontinued at the discretion of the investigator or the participant prior to week 144.

At the end of the treatment period, for patients who in the opinion of the investigator are still deriving clinical benefit from asciminib, every effort will be made to continue provision of the drug through alternative options if asciminib is not commercially available. Options includes, but are not limited to, roll over trial or provision of the treatment in a non-trial setting (known as post-study drug supply), in accordance with local laws and regulations.

6.1.4.1 Treatment beyond disease progression

Not applicable.

6.2 Other treatment(s)

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 (refer to Section 6.2.2 and Section 16 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 a weak 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 asciminib is co-administered with anti-platelet pro-drugs such as clopidogrel, ticlopidine and prasugrel, which require metabolic activation by CYP3A4 and CYP2C9. 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.

Drugs that affect gastric pH

Drugs that elevate gastric pH do not affect asciminib absorption. All acid reducing agents are allowed.

6.2.1 Concomitant therapy

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 nondrug 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.

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before starting participant on treatment or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Following drugs should be used with caution:

- CYP3A4/5 substrates with narrow therapeutic index (NTI)
- CYP2C9 substrates with NTI
- Strong CYP3A4 inducers

QT prolonging agents

As far as possible avoid co-administering drugs with a “Known”, “Possible” or “Conditional” risk of Torsades de Pointes (per www.crediblemeds.org/) during the course of the study:

- If during the course of the study, concomitant administration of a drug with “Known risk’ or “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 www.crediblemeds.org/.

6.2.2 Prohibited medication

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.

Rescue medication

Not applicable.

6.3 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 appropriate eCRF.

As per Section 4.6, if the COVID-19 pandemic limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. Delivery of IMP to participants home should be limited to these cases and standard dispensation of IMP at site should resume as soon as patients are able to visit study sites again. The decision on how long a patient can receive IMP delivery at home will be assessed on a case-by-case basis by the Investigator.

The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. In this case, regular phone calls or virtual contacts as outlined in the visit schedule (or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, compliance, investigation of any adverse events, ensuring participants continue to benefit from treatment and discussion of the participant´s health status until the participants can resume visits at the study site.

6.3.1 Handling of study treatment and additional treatment

6.3.1.1 Handling of study treatment

Study treatment must be received by a designated person 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, all study treatment must be stored according to the instructions specified in the [Asciminib Investigator Brochure].

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability is also be maintained under the accountability of the Investigator. If the COVID-19 pandemic limits or prevents on-site study visits, study treatment may be shipped to patient if permitted by local and national regulations. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants will be asked to return all unused study treatment and packaging on a regular basis, and at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all 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.

6.3.1.2 Handling of additional treatment

Not applicable.

6.3.2 Instruction for prescribing and taking study treatment

- 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.
- If the patient on q.d. regimen does not take asciminib within 12 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.
- If the patient on b.i.d. regimen 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 scheduled dose at the prescribed level.

Table 6-2 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Target dose/ Daily dose	Use	Tablet Strength	Number of tablets	Regimen
Asciminib	Tablets for oral use	80 mg	Standard Dose	40 mg	1 tablet of 40 mg	b.i.d.
Asciminib	Tablets for oral use	80 mg	Standard Dose	40 mg	2 tablets of 40 mg	q.d.
Asciminib	Tablets for oral use	40 mg	Dose reduction for standard dose b.i.d.	20 mg	1 tablet of 20 mg	b.i.d.
Asciminib	Tablets for oral use	40 mg	Dose reduction for standard dose q.d.	40 mg	1 tablet of 40 mg	q.d.
Asciminib	Tablets for oral use	200 mg	Dose escalation from standard dose*	40 mg	5 tablet of 40 mg	q.d.
Asciminib	Tablets for oral use	80 mg	Dose reduction from 200mg q.d.**	40 mg	2 tablets of 40 mg	q.d.**

Study treatments	Pharmaceutical form and route of administration	Target dose/ Daily dose	Use	Tablet Strength	Number of tablets	Regimen
Asciminib	Tablets for oral use	80 mg	Dose reduction from 200mg q.d.**	40 mg	1 tablet of 40 mg	b.i.d.**

All kits of study treatment will be recorded via the IRT.

* Dose escalation may only occur based on investigators decision after week 48, from week 60 onwards and up to week 120 based on week 108 data.

** Patients on 200 mg q.d. needing a dose de-escalation will revert to 80 mg total daily dose of asciminib and will follow initial dosing schedule, either q.d. or b.i.d., as initially assigned by IRT.

6.4 Participant numbering, treatment assignment, enrollment

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned within EDC system when the participant is screened and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

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. If the patient fails to be enrolled or start treatment for any reason, (i.e if a patient is screen failed) the reason will be entered into the Screening Disposition page. IRT must be notified by investigator or his/her delegate within 2 days of visit that the patient was enrolled or not.

6.4.2 Treatment assignment

One to one randomization to asciminib 40 mg b.i.d. and asciminib 80 mg q.d. will be performed by IRT for all patients (who were treated with two or more TKIs and who were either resistant or intolerant to the last treatment; and also on the additional patients intolerant only to their last TKI treatment and in MMR at baseline) upon eligibility confirmation. B.i.d. or q.d. dosing allocated at trial start must be maintained for patients who remain at standard dose, or need to de-escalate after increase to 200 mg q.d.

6.4.2.1 Replacement policy

Patients that drop out of the study for any reason after having taken the first tablet of study medication will not be replaced.

6.5 Treatment blinding

Not applicable.

6.6 Dose escalation and dose modification

The standard dose for all patients in this study is asciminib 40 mg b.i.d. or 80 mg q.d. For patients not achieving MMR at 48 weeks or losing the response after the week 48 assessment up to week 108, a dose escalation to 200 mg q.d. may be considered per investigator decision.

6.6.1 Dose escalation guidelines

6.6.1.1 Starting dose

The starting dose for patients will either be asciminib 40 mg b.i.d. or 80 mg q.d. as assigned by IRT upon eligibility confirmation. The q.d. or b.i.d. regimen allocated at randomization must be maintained throughout the study for patients who do not need to escalate dose, or need to de-escalate from 200 mg q.d.

6.6.2 Dose escalation

For patients not in MMR at 48 weeks or losing the response after the week 48 assessments up to week 108, a dose escalation to 200 mg q.d. may be considered for patients on 40 mg b.i.d. or 80 mg q.d., if in the investigator's opinion the patient may benefit from the escalation. In addition, there must not be any grade 3 or 4 toxicity while on therapy, or persistent grade 2 toxicity, possibly related to asciminib and unresponsive to optimal management.

Patients with dose reduction to 40 mg due to side effects may receive a dose escalation to 200 mg daily if the event requiring the dose reduction has disappeared and the patient has been treated at least 3 months on the standard dose of 80 mg.

CCI will be performed in patients not reaching MMR at 48 weeks or patients losing the response after the week 48 assessments up to week 108, and for whom a dose escalation might benefit the patient, to identify potential BCR-ABL mutations that could confer resistance to asciminib. With the limited information on mutations no general treatment recommendations can be given for individual mutations.

Dose escalation may be performed at week 60 for patients not in MMR at week 48. For patients losing the response after week 48 up to week 108, dose escalation may be performed up to week 120 after confirmed loss of MMR in 2 consecutive tests and CCI results are available.

6.6.3 Dose modifications

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

Table 6-3 Dose reduction schedule

***Dose reduction**			
		Starting dose level 0	Dose level – 1
Asciminib	CML-CP	40 mg b.i.d. (total daily dose 80 mg)	20 mg b.i.d. (total daily dose 40 mg)
	CML-CP	80 mg q.d. (total daily dose 80 mg)	40 mg q.d. (total daily dose 40 mg)
	CML-CP	200 mg q.d. (total daily dose 200 mg)	80 mg q.d. or 40 mg b.i.d. (total daily dose 80 mg)**
*Dose reduction should be based on the worst toxicity demonstrated at the last dose. **Patients on 200 mg q.d. needing a dose de-escalation will revert to 80 mg total daily dose of asciminib, according to pre-escalation dosing schedule (q.d. or b.i.d. regimen assigned at enrollment).			
Asciminib dose reduction below total daily dose of 40 mg (20 mg b.i.d. or 40 mg q.d.) is not allowed. 20 mg tablets will be dispensed to patients having 20 mg b.i.d. regimen in the instance of dose reduction.			

These dose modifications, in addition to permanent treatment discontinuations, are summarized in (Table 6-4). Deviations to mandatory dose interruptions and/or reductions are not allowed.

These dose changes must be recorded on the appropriate CRF.

A patient must discontinue treatment with asciminib 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 6-4). 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) last for more than 42 days without recovery to at least a Grade 2, despite asciminib interruption and adequate management (including hematopoietic growth factors), then the patient must be discontinued from study treatment.

Table 6-4 Criteria for dose reduction / interruption / discontinuation and re-initiation of treatment for adverse drug reactions

Dose modifications for asciminib **Please note that if a patient requires a dose interruption of > 28 days for any toxicity, and > 42 days for hematologic toxicity, then the patient should be discontinued from study treatment**	
Worst toxicity **CTCAE Version 5.0**	**Asciminib**
Investigations (hematologic): If a hematologic toxicity (cytopenia grade 3 or 4) lasts for more than 42 days without recovery to at least grade 2, despite asciminib interruption and adequate management (including hematopoietic growth factors), then the patient should be discontinued from study treatment.	
Neutropenia (ANC)	
Grade 1 (ANC < LLN – 1.5 x 10^9/L)	**Recommendation**: Maintain dose level
Grade 2 (ANC < 1.5 – 1.0 x 10^9/L)	**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
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

Dose modifications for asciminib **Please note that if a patient requires a dose interruption of > 28 days for any toxicity, and > 42 days for hematologic toxicity, then the patient should be discontinued from study treatment**	
Worst toxicity **CTCAE Version 5.0**	**Asciminib**
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	**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
Grade 2 (PLT < 75 - 50 x 10^9/L)	**Recommendation**: Maintain dose level
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
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
Recurrence of any cytopenia	**Recommendation:** Hold dose until resolved to grade ≤ 2, then maintain current dose level **For recurrent Grade 3/4 cytopenia, please refer to above guidelines for neutropenia and thrombocytopenia; no further dose reduction is allowed for already reduced dose.**
Non-hematologic adverse reactions except where further specified in individual sections	
Grade 1	**Recommendation**: Maintain dose level
Grade 2	**Recommendation:** Hold dose until resolved to grade ≤ 1, then maintain dose level
Grade 3	**Mandatory:** Hold dose until resolved to grade ≤ 1, then reduce dose ↓ 1 dose level
Grade 4	**Mandatory**: Permanently discontinue patient from treatment
Investigations (renal)	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	**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
Grade 3 (> 3.0 - 6.0 x ULN)	**Mandatory:** Permanently discontinue patient from treatment
Grade 4 (> 6.0 x ULN)	**Mandatory:** Permanently discontinue patient from treatment
Investigations (hepatic)	
Isolated total bilirubin elevation	
> ULN – 1.5 x ULN, if baseline was normal	**Recommendation:** Maintain dose level
> 1.5 - 3.0 x ULN if baseline was normal	**Recommendation:** Maintain dose. Repeat Liver Function Tests (LFT) within 48-72 hours then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN or baseline: 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 (irrespective of the baseline levels) *	**Mandatory:** Hold dose. Repeat LFTs within 48-72 hours then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN or baseline: if resolved in ≤ 14 days, then reduce dose ↓ 1 dose level if resolved in > 14 days, then discontinue patient from treatment.

Dose modifications for asciminib **Please note that if a patient requires a dose interruption of > 28 days for any toxicity, and > 42 days for hematologic toxicity, then the patient should be discontinued from study treatment**	
Worst toxicity **CTCAE Version 5.0**	**Asciminib**
	The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin level has resolved to baseline or has stabilized over 4 weeks
> 10.0 x ULN (irrespective of the baseline levels) *	See footnote**** - otherwise discontinue study treatment The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin level has resolved to baseline or has stabilized over 4 weeks
Isolated AST or Alanine Aminotransferase (ALT) elevation	
If normal at baseline:	
> ULN - 3.0 x ULN	**Recommendation:** Maintain dose level Repeat liver tests within 48- 72 hours, then monitor weekly until recovery to ≤Grade 1 or to baseline
> 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
> 5.0 - 10.0 x ULN	**Mandatory**: Omit 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, resume at prior dose level If resolved in > 14 days, resume with reduced dose ↓ 1 dose level
> 10.0 - 20.0 x ULN	**Mandatory: Omit 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 resume with reduced dose ↓ 1 dose level
> 20.0 x ULN	**Mandatory:** Permanently discontinue
If elevated at baseline:	
> Baseline - 3.0 x Baseline AND ≤ 5 x ULN	Recommendation: Maintain dose level
> 3.0 x Baseline AND > 5.0 x ULN (duration less than 2 weeks)	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 ≤ ULN or baseline
> 3.0 x Baseline AND > 5.0 x ULN (duration more than 2 weeks):	Mandatory: Omit dose. 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 ≤ ULN or baseline. If resolved, resume with reduced ↓ 1 dose level.
> 5.0 x Baseline AND > 8.0 x ULN (irrespective of the duration):	Mandatory: Omit dose. 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 ≤ ULN or baseline. If resolved, resume with reduced ↓ 1 dose level.
> 20.0 x ULN	Permanently discontinue
Combined[c] elevations of AST or ALT and total bilirubin	

Dose modifications for asciminib **Please note that if a patient requires a dose interruption of > 28 days for any toxicity, and > 42 days for hematologic toxicity, then the patient should be discontinued from study treatment**	
Worst toxicity **CTCAE Version 5.0**	**Asciminib**
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 > 3 x baseline OR [AST or ALT > 8.0 x ULN], whichever is lower combined with total bilirubin > 2 x baseline AND > 2.0 x ULN Note: For participants with Gilbert's syndrome, at least 2-fold increase in direct bilirubin	**Mandatory:** Hold dose Repeat liver tests 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. Please refer to Section 6.6.4.1 for additional follow-up evaluations as applicable. If DILI confirmed: permanently discontinue patient from study drug treatment If not DILI – interrupt treatment. Treat identified cause according to institutional guidelines. If resolved, then reduce dose ↓ 1 dose level, if cause is treatment related.
Investigation (metabolic)	
Amylase and/or lipase elevation	
Grade 1: > ULN - 1.5 x ULN	**Recommendation:** Maintain dose level, measure 2x per week
Grade 2: > 1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	**Recommendation:** Maintain dose level, measure 2x per week
Grade 3: > 2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	**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 and with signs or symptoms	**Mandatory:** Permanently discontinue patient from treatment. Obtain appropriate imaging (i.e., MRI, CT scan, or ultrasound) **
Vascular disorders	
Hypertension	
Systolic BP 140-159 mm Hg or Diastolic BP 90-99 mm Hg	**Mandatory:** If recurrent or persistent (>=24 hrs), or if symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg; monotherapy anti-hypertensive treatment indicated; Maintain asciminib dose level, with regular monitoring of blood pressure.
Systolic BP >=160 mm Hg or Diastolic BP >=100 mm Hg	Medical intervention indicated: Initiate antihypertensive therapy (if not currently being treated with antihypertensive). If already taking anti-hypertensive drugs; intensive treatment with increased dose of existing anti-hypertensive/ more than one anti-hypertensive drugs than previously used Hold asciminib dose until resolved to grade ≤ 2, then reduce dose ↓ 1 dose level
CTCAE Grade 4	**Mandatory:** Permanently discontinue patient from treatment
Gastrointestinal	
Pancreatitis	

Dose modifications for asciminib **Please note that if a patient requires a dose interruption of > 28 days for any toxicity, and > 42 days for hematologic toxicity, then the patient should be discontinued from study treatment**	
Worst toxicity **CTCAE Version 5.0**	**Asciminib**
Grade 2 (radiologic findings for pancreatitis as per CTCAE v5.0, 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) **
Grade ≥ 3	**Mandatory:** Permanently discontinue patient from treatment. Obtain appropriate imaging (i.e., MRI, CT scan, or ultrasound)
Diarrhea***	
Grade 1	**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, hold dose until resolved to grade ≤ 1, then reduce dose ↓ 1 dose level
Grade 3	**Recommendation:** Hold dose and discontinue patient from treatment
Grade 4	**Mandatory:** Permanently discontinue patient from treatment
Skin and subcutaneous tissue disorders	
Rash/photosensitivity	
Grade 1	**Recommendation:** Maintain dose level. Consider initiating 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)
Grade 3, despite skin toxicity therapy	**Recommendation:** Hold dose until resolved to grade ≤ 1, then: If resolved in ≤ 7 days, reduce dose ↓ 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), discontinue patient from treatment
Grade 4, despite skin toxicity therapy	**Mandatory:** Permanently discontinue patient from treatment
General disorders and administration site conditions	
Fatigue/Asthenia	
Grade 1 or 2	**Recommendation:** Maintain dose level
Grade 3	**Recommendation:** Hold dose until resolved to grade ≤ 1, then: If resolved in ≤ 7 days, maintain dose level If resolved in > 7 days, reduce dose ↓ 1 dose level
All dose modifications should be based on the worst preceding toxicity. [a] Common Terminology Criteria for Adverse Events (CTCAE Version 5.0). [b] Core LFTs consist of ALT, AST, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (ALP) (fractionated [quantification of isoforms], if ALP > 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.	

Dose modifications for asciminib **Please note that if a patient requires a dose interruption of > 28 days for any toxicity, and > 42 days for hematologic toxicity, then the patient should be discontinued from study treatment**	
Worst toxicity **CTCAE Version 5.0**	**Asciminib**
[d] "Cholestasis" defined as ALP elevation (> 2.0 x ULN and R value < 2) in patients 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 should be performed within 1 week of the first occurrence of any grade ≥ 3 amylase and/or lipase elevation. If asymptomatic grade 3 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study treatment. If asymptomatic grade 2 re-occur at reduce dose, closed monitoring of lipase and amylase will be required. *** Note: Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools, or overt diarrhea. **** Note: An isolated bilirubin elevation is not typical for drug-induced liver injury. Bilirubin can be elevated either as part of a "Hy's law" constellation with a preceding elevation of ALT/AST, or as part of a cholestatic reaction with simultaneous elevation of other cholestatic parameters (ALP, GGT). Isolated bilirubin can be seen in conjunction with drugs that inhibit bilirubin conjugation or excretion, but both scenarios do not typically represent liver injury. Alternative causes of bilirubin elevation should therefore, be ruled out before basing dose modification decisions on bilirubin values alone.	

6.6.3.1 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 to ≤ 480 msec
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 www.crediblemeds.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.

Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 msec.

- After resolution to ≤ 480 msec, consider re-introducing treatment at reduced dose, with increase ECG monitoring for the next treatment
- If QTcF remains ≤ 500 msec after dose reduction, continue planned ECG monitoring during subsequent treatment
- If QTcF recurs > 500 msec after dose reduction, discontinue patient from trial.

6.6.4 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 for 30 days or, until resolution or stabilization of the event. Appropriate clinical specialist 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.

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

Patients with transaminase increase combined with TBL increase may be indicative of potentially severe Drug-induced liver injury (DILI), and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

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

- For patients with normal ALT and AST and TBL value at baseline: AST or ALT > 3.0 x ULN combined with TBL > 2.0 x ULN
- For participant with elevated AST or ALT or TBL value at baseline: [AST or ALT > 3 x baseline] OR ALT or AST > 8.0 x ULN], whichever occurs first, combined with [TBL > 2.0 x baseline AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered, and their role clarified before DILI is assumed as the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any preexisting liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, TBL, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase. If available, testing of Glutamate Dehydrogenase (GLDH) is additionally recommended.

Evaluate status of underling malignancy for an extra-medullary hepatic involvement.

Perform relevant examinations (Ultrasound or MRI, Endoscopic retrograde cholangiopancreatography (ERCP)) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis (is defined as an Alkaline Phosphatase (ALP) elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of the liver-specific ALP isoenzyme 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 clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury. Table 6-5 provides guidance on specific

clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed Liver function test (LFT)abnormalities.

Table 6-5 Clinical and diagnostic assessments to rule out possible alternative causes of observed LFT abnormalities

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti- HCV, HCV Ribonucleic acid (RNA), IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ ischemic hepatopathy	Medical history: acute or chronic congestive, heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	Caeruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

Other causes should also be considered based upon patients' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; cardiovascular disease / ischemic hepatitis – ECG, prior hypotensive episodes; Type 1 diabetes / glycogenic hepatitis).

Obtain PK sample to determine exposure to study treatment and metabolites.

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" i.e. >50% likely, if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates probably caused by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

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", and thus, meet the definition of SAE and should be reported as SAE using the term "potential treatment -induced liver injury". All events should be followed up with the outcome clearly documented.

6.6.4.2 Additional treatment guidance

6.6.5 Treatment compliance

The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

Total daily dose of study treatment administered with start and end date and dosing will be collected on the appropriate 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.

6.6.6 Emergency breaking of assigned treatment code

Not applicable.

7 Informed consent procedure

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

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

As per (Section 4.6), if the covid-19 pandemic challenges the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Heath Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

Information about common side effects already known about the investigational drug can be found in the Asciminib Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also includes:

- A subsection that requires a separate signature for tests that are optional. This section refers to optional participation in the CCI research collaboration that will be conducted in Europe and Russia. Refer to (Section 8.1).
- A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study.
- A subsection that requires a separate signature for the 'Optional consent for activities that may be done outside of the study site' to allow some study activities to be done outside of the study site (for example, at participants home or at another suitable offsite location) due to measures implemented as a result of the COVID-19 pandemic, such as travel restrictions or closures of local hospitals and patient treatment facilities.

- As applicable, Pregnancy Outcomes Reporting Consent for female participants

Women of child bearing potential must be informed that taking the study treatment 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 requirements 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.

The study includes an optional consent for additional research component which requires a separate signature if the participant agrees to participate as mentioned above. It is required as part of this protocol that the Investigator presents this option to the participants, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these optional studies will in no way affect the participant's ability to participate in the main research study.

The study also includes an optional consent for home-nursing visits "activities that may be done outside of the study site" which requires a separate signature if the participant agrees to participate as mentioned above. If certain clinical trial procedures need to be done off site due to temporary inability to perform on site visit due to COVID-19, participant may be proposed this option, if permitted by local laws and feasible.

The process for obtaining consent should be exactly the same as described above for the main informed consent.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be documented in the participant's source documentation. Patients can be consented for study participation prior to study day -28.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study treatment are to return for the end of treatment visit as soon as possible, and attend the follow-up visits as indicated in the Assessment Schedule.

Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the CRF.

As per Section 4.6, if the COVID-19 pandemic limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption due to the pandemic until it is safe for the participant to visit the site again. Screening visit and week 1 day 1 visits must be done on site.

The “X” in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The “S” in the table denotes the assessments that are only in the participant’s source documentation and do not need to be recorded in the clinical database.

No eCRF will be used as a source document.

(S) is defined as “Source”

(D) is defined as “Data Based”

Study visits from Week 1 Day 1 to Week 2 Day 1 should be completed on the designated date [with an allowed “visit window” of +/- 1 day for Week 1 Day 1 and Week 2 Day 1]

Study visits from Week 4 to Week 12 should be completed every 4 weeks on the designated date [with an allowed “visit window” of +/- 2 day]

Study visits after Week 12 (from Week 24) to EOT should be completed every 12 weeks on the designated date [with an allowed “visit window” of +/- 7 days].

Safety follow-up should be completed 30 days from the last dose of study treatment [with an allowed “visit window” of +/- 7 days].

Visit at weeks 62, 74, 86, 98, 110 or 122 that is two weeks post dose escalation should be completed once after dose escalation on the designated date [with an allowed “visit window” of +/- 1 day].

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.

Table 8-1 Assessment schedule

	Category	Protocol Section	Screening Phase	Treatment Phase										EOT (week 144) /Early Discontinuation	Safety follow-up[13]
Visit name			**Screening/ Baseline**	Week 1 Day 1	Week 2 Day1	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	**Every 12 weeks up to week 132 (w60, w72, w84, w96, w108, w120, w132)**	**Week 62/74/86/98/ 110/122 for patient dose escalating**		
Days (+/- X days)			Day -28 to -1	1 (+/- 1 day)	8 (+/- 1 day)	29 (+/- 2 days)	57 (+/- 2 days)	85 (+/- 2 days)	169 (+/- 7 days)	253 (+/- 7 days)	337 (+/- 7 days)	(+/- 7 days)	(+/- 1 day)	(+/- 7 days)	(+/- 7 days)
Obtain Informed Consent	D		X (Screening window - 28 days)												
IRT															
Eligibility checklist/ registration	S		X												
Randomization	D	6.4.2		X											
Demography	D	8.2	X												
Inclusion/exclusion criteria	D	5.1 – 5.2	X												
Medical History	D	8.2	X												
Disease History	D	8.2	X												
Mutation status	D	8.2	X												
Prior antineoplastic therapy	D	8.2	X												
Prior TKI therapy	D	8.2	X												

	Category	Protocol Section	Screening Phase	Treatment Phase										EOT (week 144) /Early Discontinuation	Safety follow-up[13]
Visit name			**Screening/ Baseline**	Week 1 Day 1	Week 2 Day 1	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	**Every 12 weeks up to week 132 (w60, w72, w84, w96, w108, w120, w132)**	**Week 62/74/86/98/ 110/122 for patient dose escalating**		
Days (+/- X days)			**Day -28 to -1**	1 (+/- 1	8 (+/- 1 day)	29 (+/- 2 days)	57 (+/- 2 days)	85 (+/- 2 days)	169 (+/- 7 days)	253 (+/- 7 days)	337 (+/- 7 days)	(+/- 7 days)	(+/- 1 day)	(+/- 7 days)	(+/- 7 days)
Prior/concomitant medications	D	8.2	X	Continuous											
Physical Examinations	S	8.4	X	X		X	X	X	X	X	X	X		X	
Extra medullary Involvement	D		X												
ECOG Performance status	D	8.4.1	X	X		X	X	X	X	X	X	X		X	
Height	D	8.4	X												
Weight	D	8.4	X	X				X	X	X	X	X		X	
Vital signs[1]	D	8.4	X	X	X	X	X	X	X	X	X	X		X	
Laboratory assessments		8.4.2													
Hematology	D	8.4.2	X	X	X	X	X	X	X	X	X	X		X	
Chemistry[2]	D	8.4.2	X	X	X	X	X	X	X	X	X	X		X	
Coagulation	D	8.4.2	X	As clinically indicated											

	Category	Protocol Section	Screening Phase	Treatment Phase										EOT (week 144) /Early Discontinuation	Safety follow-up[13]
Visit name			**Screening/ Baseline**	Week 1 Day 1	Week 2 Day 1	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	**Every 12 weeks up to week 132 (w60, w72, w84, w96, w108, w120, w132)**	**Week 62/74/86/98/ 110/122 for patient dose escalating**		
Days (+/- X days)			**Day -28 to -1**	1 (+/- 1 day)	8 (+/- 1 day)	29 (+/- 2 days)	57 (+/- 2 days)	85 (+/- 2 days)	169 (+/- 7 days)	253 (+/- 7 days)	337 (+/- 7 days)	(+/- 7 days)	(+/- 1 day)	(+/- 7 days)	(+/- 7 days)
Serum Pregnancy test (if applicable)	D	8.4.4	X											X	
Urine Pregnancy test (if applicable)	S	8.4.4		X		X	X	X	Monthly between visits[3]						
Hepatitis markers	D	8.4.2	X												
Efficacy															
Blood collection for BCR-ABL1 quantification by RQ-PCR	D	8.3.1.1	X					X	X	X	X	X		X	
Bone marrow Aspirate / Cytogenetics - Scheduled	D	8.3.1.2	X (Screening window- 56 days)								X			X[4]	
Biomarker assessments															

	Category	Protocol Section	Screening Phase	Treatment Phase										EOT (week 144) /Early Discontinuation	Safety follow-up[13]
Visit name			Screening/ Baseline	Week 1 Day 1	Week 2 Day 1	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Every 12 weeks up to week 132 (w60, w72, w84, w96, w108, w120, w132)	Week 62/74/86/98/110/122 for patient dose escalating		
Days (+/- X days)			Day -28 to -1	1 (+/- 1 day)	8 (+/- 1 day)	29 (+/- 2 days)	57 (+/- 2 days)	85 (+/- 2 days)	169 (+/- 7 days)	253 (+/- 7 days)	337 (+/- 7 days)	(+/- 7 days)	(+/- 1 day)	(+/- 7 days)	(+/- 7 days)
CCI	D	8.5.3.1	CCI									CCI		CCI	
CCI	D	8.5.3.1									CCI	CCI			
CCI	S	8.5.5		CCI	CCI	CCI									
Cardiac assessments															
Electrocardiogram (ECG)	D	8.4.3	X	X	X	X		X	X		X	X[8]	X[9]	X	
Cardiovascular risk factor assessments (including Family	D	8.4.3.3	X											X	

	Category	Protocol Section	Screening Phase	Treatment Phase										EOT (week 144) / Early Discontinuation	Safety follow-up[13]
Visit name			**Screening/ Baseline**	Week 1 Day 1	Week 2 Day 1	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	**Every 12 weeks up to week 132 (w60, w72, w84, w96, w108, w120, w132)**	**Week 62/74/86/98/110/122 for patient dose escalating**		
Days (+/- X days)			**Day -28 to -1**	1 (+/- 1 day)	8 (+/- 1 day)	29 (+/- 2 days)	57 (+/- 2 days)	85 (+/- 2 days)	169 (+/- 7 days)	253 (+/- 7 days)	337 (+/- 7 days)	(+/- 7 days)	(+/- 1 day)	(+/- 7 days)	(+/- 7 days)
Echocardiogram	D	8.4.3.1	X						X[11]					X	
Adverse events / Serious adverse events	D	10.1.1	Continuous												
Patient Reported Outcomes															
MDASI-CML	D	8.5.1	X			X		X	X		X	X[12]		X	
Asciminib drug dispensation				X		X	X	X	X	X	X	X			
Asciminib drug administration	D	6.3.2		Continuous											
Antineoplastic therapies since discontinuation of study treatment	D													X	X

1. Blood Pressure reading to be taken in the supine position for all visits.
2. Hemoglobin A1c to be collected at screening only.
3. A monthly urine pregnancy test must be performed by all women of child-bearing potential between the three monthly visits at the investigational site. Urine pregnancy tests may be performed at the investigational site or at home. Test results performed at home should be recorded in 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.
4. Only required for Early Discontinuation due to lack of response / loss of response.
5. Same tube will be used for RQ PCR CCI [redacted].
6. For patients who are not in MMR at week 48 and for patients loosing the response after week 48 assessments up to week 108 and who may benefit from a dose escalation, CCI [redacted].
7. Samples to be collected before first dose and 2 to 4 hours post dose.
8. After week 48, the ECG assessments will be done at week 60, week 84, week 108 and week 132 for patients on standard dose (80mg q.d. and 40mg b.i.d.).
9. For patients with dose escalation ECG assessment to be conducted: at dose escalation visit (pre-dose and two hours post-dose), two weeks post-dose escalation, 3 months post-dose escalation, 6 months post-dose escalation, 6 monthly thereafter. Please refer to Section 8.4.3 for more information.
10. Personal and family history of the following conditions: Coronary artery disease, Hyperlipidaemia, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Hypertension, medication taken for hypertension, Myocardial infarction or Cerebrovascular accident will be collected at screening. History of smoking, physical activity and diet will be collected at screening and end of treatment.
11. Week 24 echocardiogram can be performed within a window of +/- 4 weeks of the visit
12. After week 48, PRO assessment will be done every 24 weeks up to week 120 (i.e. these assessments will be completed at week 72, week 96 and week 120).
13. Safety follow-up may be done on site or via phone call with patient. The safety follow-up to be completed 30 days from the last dose of study treatment.

8.1 Screening

Molecular pre-screening

Not applicable.

Screening

Written informed consent must be obtained before any study specific medical procedures are performed.

All screening/baseline assessments (with the exception of cytogenetic assessment of Bone Marrow Aspirate) should occur within 28 days before Week 1 Day 1.

The screening visit window for cytogenetic assessment Bone Marrow Aspirate (BMA) 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 and results from prior bone marrow assessment will be collected. At Week 48, and at end of treatment for patient completing trial for lack of efficacy, a bone marrow aspirate must be collected even if the screening/baseline bone marrow aspirate sample was not collected.

During the screening visit, inclusion and exclusion criteria will be assessed. Screening assessments to confirm eligibility must be performed prior to study enrollment. The results of the central real time quantitative polymerase chain reaction (RQ-PCR) and the local cytogenetic assessment (BMA, performed locally within 56 days of Week 1 Day 1) must be available prior to enrollment and first dose of study treatment. Central mutation analysis will be performed during the course of the study and data not available prior to enrollment.

Screening assessments include: demographics, laboratory baseline assessments (including hematology, chemistry, coagulation, serum pregnancy test and hepatitis markers), physical examination including extramedullary involvement, peripheral blood collection for BCR-ABL1 RQ-PCR, bone marrow aspirate for cytogenetic assessment (if prior bone marrow aspirate evaluation was more than 56 days before Week 1 Day 1) and CCI [redacted]. Other assessments includes performance status, ECG, echocardiogram, height, weight and vital signs, as well as evaluation of all relevant medical history including cardiovascular risk factors, CML disease history including T3151 mutation status, prior TKI therapy and antineoplastic medication. Assessment of prior and concomitant medication must be performed prior to the first dose of study treatment. For details of assessments required during screening please refer to Table 8-1.

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 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 the screening window. 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 and a new patient ID will be assigned. 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 aspirate samples for cytogenetic assessment should be re-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.

8.1.1 Eligibility screening

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

8.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be enrolled for any reason will be considered a screen failure. The reason for not being enrolled will be entered on the 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 10.1.4 for SAE reporting details). If the patient fails to be enrolled, the IRT must be notified within 2 days of the screen fail that the patient was not enrolled. The reason for screen failure should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

Patient demographics and baseline characteristics collected will include the following: age at consent, gender (and childbearing potential for female), race/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.

Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, we need to assess the diversity of the study population as required by Health Authorities.

Physical examination including extramedullary involvement, ECOG performance status, vital signs, ECGs, Echocardiography, 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 local reading of the screening ECG, echocardiograms as well as the central results of the qualitative PCR, RQ-PCR and the local cytogenetic assessment (BMA) within 56 days before Week 1 Day 1 must be available prior to enrollment and first dose of study treatment to evaluate eligibility. Central mutation analysis will be performed during the course of the study and not available prior to enrollment.

8.3 Efficacy

8.3.1 Efficacy assessments

If the COVID-19 pandemic limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls, virtual contacts (e.g. teleconsult) or visits by site staff/home nursing service to the participant´s home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the pandemic or until it is safe for the participant to visit the site again. If participants cannot visit the site for protocol specified assessments and that visit by site staff/home nursing service to the participant's home may not be done, an alternative laboratory (local) collection may be used.

8.3.1.1 Molecular response

Molecular response (MR) will be assessed in all patients.

Levels of BCR-ABL1 transcripts will be determined by real-time quantitative PCR (RQ-PCR) testing of peripheral blood and analyzed centrally. Log reduction in BCR- ABL1 transcripts levels from the standardized baseline value, or the percent ratio of BCR-ABL1 transcripts versus control gene (ABL1) transcripts converted to a reference standard, international scale (IS) (Hughes and Branford 2006), will be calculated for each sample.

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

- Rate of 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/ABL1 % by IS as measured by RQ-PCR, confirmed by duplicate analysis of the same sample,
- Time to MMR defined as the time from the date of enrollment 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.
- Rate of Deep Molecular Responses MR4 and MR4.5 are defined as a ≥4 log or ≥4.5 log reduction in BCR-ABL1 transcripts compared to the standard baseline equivalent to 0.01 % or 0.0032% BCR-ABL1/ABL by IS as measured by RQ-PCR, confirmed by duplicate analysis of the same sample with at least 10,000 or 32,000 ABL1 transcripts, respectively.

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 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. The blood samples will be taken as described in Table 8-1 and Table 8-2.

If at one visit the sample is missing during transit to the central PCR laboratory, or the PCR result is difficult to interpret or sample not analyzable, or if the PCR sample was not collected, a subsequent unscheduled visit sample must be collected within 4 weeks either at the next scheduled visit (week 4 or week 8) or as an unscheduled visit.

Table 8-2 Blood samples (efficacy primary endpoint)

Sample Type	Volume	Visit
Blood for BCR-ABL1 quantification by RQ-PCR	20 mL	Screening/Baseline
	20 mL	Week 12
	20 mL	Week 24
	20 mL	Week 36
	20 mL	Week 48
	20 mL	Every 12 weeks thereafter up to week 132 (w60, w72, w84, w96, w108, w120, w132)
	20 mL	End of Treatment

8.3.1.2 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):

- Major (MCyR) - 0 to 35% Ph+ metaphases
- Complete (CCyR) - 0% Ph+ metaphases
- Partial (PCyR) - >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 48 and at EOT (only required if the patient discontinues from the study early due to lack/loss of response). 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 and local assessment data will be collected.

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.

8.3.1.3 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

8.3.2 Appropriateness of efficacy assessments

Assessing molecular response with RQ-PCR is considered as standard in CML therapy and recommended in treatment guidelines (Hochhaus et al 2020a). In order to review individual responses against the milestones in treatment recommendations and to allow for the comparison of trial results against other data, the molecular responses will be reported as standardized results to International Scale (IS) (Cross et al 2015).

8.4 Safety and tolerability assessments

Safety will be monitored by the assessments described below, in addition to the collection of adverse events at every visit. For details on AE collection and reporting, refer to Section 10. 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.

As per Section 4.6, if the COVID-19 pandemic limits or prevents on-site study visits, regular phone or virtual calls can occur as outlined in the Visit Schedule (or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again. If participants cannot visit the site for protocol specified safety lab assessments or that central laboratory analysis cannot be performed due to COVID-19 pandemic consequences, an alternative laboratory (local) collection site may be used. Assessments of blood pressure, heart rate, weight, ECG and blood collection may also be conducted off-site by healthcare professional visits to the participant's off-site location (please refer to Section 4.6).

Table 8-3 Physical examination, vital sign and height and weight assessments

Assessment	Specification
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 at the visits specified in Table 8-1. Presence of extramedullary leukemic involvement will be checked at the physical examination at screening/baseline. Findings on physical examination consistent with extra- medullary leukemic involvement will be recorded (e.g. liver and spleen size, any other organ involvement).
Vital signs	Vital signs include blood pressure (supine position when ECG is collected), pulse measurement, and body temperature and are performed at the visits as specified in Table 8-1.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg)) will be measured as specified in Table 8-1.

8.4.1 Performance status

ECOG Performance status scale will be used as described in Table 8-4 at the visits specified in Table 8-1.

Table 8-4 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

8.4.2 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 8-1. The time windows granted for laboratory evaluations are identical with the corresponding visit time windows for each visit (see Section 8).

Additional unscheduled blood draws may be performed at the discretion of the investigator at any time during the study. For example, if the PCR sample was lost during transit or result is difficult to analyze, to confirm a loss of response to study treatment or as clinically indicated.

If the COVID-19 pandemic limits or prevents on-site study visits, if pre-agreed with Novartis and considered by the Investigator it is in the interest of the participant's health to perform study procedures remotely, safety samples that can be collected remotely will be collected and analyzed in line with the study laboratory manual. If participants cannot visit the site for protocol specified safety lab assessments or in case of central lab logistical challenges an alternative laboratory (local) collection site may be used. Please note that BCR-ABL1 quantification must be performed centrally. Where samples are collected and analyzed at a local laboratory instead of the central laboratory, Novartis will ensure the results reported for

hematology and chemistry described below are equivalent to central laboratory collection and analysis by collecting the local normal ranges.

Table 8-5 Central clinical laboratory parameters collection plan

Test category	Test Name
Hematology	Hemoglobin, platelets, red blood cells, white blood cells, WBC morphology with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils, promyelocytes, myelocytes, metamyelocytes, blast and other)
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, serum glucose (fasting), Hemoglobin A1c (at screening only), Creatinine clearance (Cockcroft-Gault formula)
Coagulation	International Normalized Ratio (INR), Activated Partial Thromboplastin Time (aPTT)
Hepatitis markers	HbsAg, HbcAb /anti-Hbc, HBV-DNA (if anti-Hbc and HbsAg are positive), HCV Ab, HCV-RNA (if HCV Ab is positive).
Liver assessments (for DILI) (see Section 6.6.4.1)	ALT, AST, albumin, creatinine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase
Pregnancy Test	Serum beta fraction of human chorionic gonadotropin (ß-HCG) testing (at screening and EOT). Urine pregnancy test will be done monthly for women of childbearing potential (will be done locally).

8.4.3 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as described in Table 8-6.

ECG assessment needs are similar for all patients up to week 48.

Patients dose escalating to 200 mg q.d. (as outlined in Section 6.6.2) must have ECG assessments performed:

- on the day of dose escalation (pre-dose and between 2h to 3h post-dose ECGs are required),
- two weeks post-dose escalation,
- at next 2 quarterly visits (at 3 and 6 months post-dose escalation),
- every 6 months thereafter.

Please refer to (Table 8-6) below for more details.

After the subject has rested approximately 5 minutes in a supine position, standard 12- lead ECGs must be obtained in triplicate with a recommended interval of 5 minutes between each ECG reading.

The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs and then blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions. The investigator must calculate QTcF if it is not auto-calculated by the ECG machine.

ECGs will be locally collected and evaluated. Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), subject number, date, and kept in the source documents at the study site.

Table 8-6 Local ECG collection plan

Week	Day	Time
Screening/Baseline	Day -28 to -1	3 serial, 12 lead ECGs
1		3 serial, 12 lead ECGs between 2h to 3h post-dose
2		3 serial, 12 lead ECGs between 2h to 3h post-dose
4		3 serial, 12 lead ECGs
12		3 serial, 12 lead ECGs
24, 48		3 serial, 12 lead ECGs
For patients not dose escalating: Week 60, 84, 108, 132		3 serial, 12 lead ECGs
For patients dose escalating: Dose escalation visit (Week 60 or Week 72, 84, 96, 108, 120)		3 serial, 12 lead ECGs pre-dose and between 2h to 3h post-dose
Two weeks post dose escalation visit (Week 62 or Week 74, 86, 98 110, 122)		3 serial, 12 lead ECGs
Twelve weeks post dose escalation visit (Week 72 or Week 84, 96, 108, 120, and 132).		3 serial, 12 lead ECGs
Twenty-four weeks post dose escalation visit (Week 84 or Week 96, 108, 120, 132 and EOT)		3 serial, 12 lead ECGs
EOT		3 serial, 12 lead ECGs
Unscheduled or Unplanned ECG		3 serial, 12 lead ECGs

Three serial ECGs (in triplicate) should be taken approximately 5 minutes apart. QTc prolongation will be based on the average seen in the scans for each time point. The enrollment of patients will be based on locally assessed QTcF time. The patient may not be dosed if the average of the 3 ECGs confirm a QTcF $\geq$ 450 msec (male) or $\geq$ 460 msec (female).

Dose adjustments in case of QTcF prolongation should be performed per Section 6.6.3.1.

ECGs are not required to be performed within a specified time frame (post-dose), after the week-2 visit.

Additional unscheduled ECGs may be performed 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. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a

review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study.

Clinically significant ECG abnormalities present at screening must 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.

If the COVID-19 pandemic limits or prevents on-site study visits, if pre-agreed with Novartis and considered by the Investigator it is in the interest of the participant's health to perform study procedures remotely and if feasible, study visits ECG can be collected remotely by home nurse at patient home.

8.4.3.1 Cardiac imaging - Echocardiogram

Echocardiograms will be performed to monitor cardiac safety. Assessments are scheduled at screening/baseline, Week 24 (+/- 4 weeks) and end of treatment visit. The echocardiogram will be performed and evaluated locally. Any clinically significant findings will be collected and reported in the database (i.e. reported as adverse events).

8.4.3.2 Cardiac enzymes

Not applicable.

8.4.3.3 Estimation of cardiac risk factors

Personal and family history (consisting of father, mother and siblings) of the following medical conditions is to be taken at the screening visit: Coronary artery disease, Hyperlipidemia, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Hypertension, medication taken or not for hypertension for personal history, Myocardial infarction or Cerebrovascular accident. In addition, history of smoking, low physical activity and unhealthy diet has to be taken at the screening/baseline and at the end of the treatment.

8.4.4 Pregnancy and assessments of fertility

All women of childbearing potential have to complete a serum pregnancy test (Serum ß-HCG) at screening in order to confirm study eligibility and at EOT. Pregnancy testing is not required for patients who are determined to be post-menopausal.

A woman is considered of childbearing potential from menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

Urine pregnancy tests have to be performed every 4 weeks during trial. Test results performed at home should be recorded onto a subject diary and brought to each scheduled visit for the site

to review. Information for urine pregnancy test must be included in the source documentation at the study site as unique source data, this information will not be captured in the CRF. If a test result indicates a pregnancy, the subject 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. Additional pregnancy testing might be performed if requested by local requirements.

8.4.5 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

8.5 Additional assessments

Not applicable.

8.5.1 Patient reported outcomes (PRO)

The MDASI-CML PRO instrument will be used to compare data on the patient's disease-related symptoms and health-related quality of life from baseline to EOT.

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 participant must be given the PRO measure to be completed at the scheduled visit before any clinical assessments are conducted. Participant's refusal to complete all or any part of a PRO measure should be documented in the study data capture system and should not be captured as a protocol deviation.

Participant questionnaires should be completed in the language most familiar to the participant. The participant should be given sufficient space and time to complete the PRO measure.

The site personnel (referring to who could be responsible for administering and checking completions of PRO measure) should check PRO measure for completeness and ask the participant to complete any missing responses. The original questionnaire will be kept with the patient's file as the source document and responses reported in EDC by site personnel.

Patients should be made aware that completed PRO measures are not reviewed for AEs by the investigator/study personnel and if they experience an AE, they should report the event to the investigator/study personnel.

If the COVID-19 pandemic limits or prevents on-site study visits, if pre-agreed with Novartis and considered by the Investigator it is in the interest of the participant's health to perform study procedures remotely and feasible, MDASI-CML PRO can be provided to patient by home nurse. If home nursing is not feasible, MDASI-CML will not be completed.

MDASI-CML

The MD 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 statistical analysis plan.

8.5.2 Pharmacokinetics

Not applicable.

8.5.3 Biomarkers

Exploratory biomarker analysis will be performed to identify the activation and exhaustion of the immune system with the goal of better understanding scientific rationale for potential asciminib combination with immune oncology agents. Exploratory Biomarker analysis will be performed during the conduct of the trial, or after end of study for additional biomarkers assessments if applicable. All biomarkers will be measured using validated immunoassays in the central laboratory or by the sponsor selected service provider.

8.5.3.1 Biomarker assessments in blood samples

Mutational analysis

Mutational analysis is required in case of treatment failure to define or exclude alternative treatment options (e.g. by identifying a T315I mutation).

Characterization of low level mutations in BCR-ABL1 gene

CCI [redacted] will be performed in patients not in MMR at week 48 or patients losing response from week 48 onwards to ensure the results are available to inform the dose escalation decision. The 20mL blood sample collected for BCR-ABL1 quantification will also be used for this test. Assessment will be done upon investigator request if they consider the escalation may benefit the patient. Mutation results as well as confirmed loss of MMR in two consecutive tests for patients with loss of response need to be obtained before dose escalation.

CCI [redacted] The 20mL blood sample that is collected for BCR-ABL1 quantification at the respective visit will also be used for this test.

Table 8-7 Biomarkers samples collection plan

	Volume	*Visit*	*Time point*
Blood samples			
CCI	CCI	CCI	CCI
Sample Type	***Volume***	***Visit***	***Time point***
Blood samples			
CCI	CCI	CCI	

8.5.3.2 Additional biomarker assessments

The described list of biomarkers above may be changed or expanded further, as it is recognized that more relevant or novel biomarkers may be discovered during the conduct of the study. Instructions for collection, preparation and shipment of all biomarker samples can be found in the laboratory manual. Required sample collection information must be entered on the requisition forms.

8.5.3.3 Use of residual biological samples

If the patient agrees, the biomarker samples that remain after analysis is completed (plasma, serum) may be kept for up to 15 years to be used for additional studies related to asciminib, including research to help develop ways to detect, monitor or treat CML. A decision to perform such exploratory biomarker research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as assay availability.

8.5.4 Imaging

Not applicable.

8.5.5 Other Assessments

CCI

Samples and analysis CCI has no impacts on patients' treatments, safety nor patient management. CCI

Table 8-8 Optional biomarker samples collection plan

	Volume	*Visit*	*Time point*
Blood samples			
CCI			

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (earlier than the planned completion of study drug administration) and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment. Refer to Section 6.2.2.
- Any situation in which continued study participation might result in a safety risk to the participant
- In the case of certain adverse events and re-occurrence of adverse events (see Table 6-4)
- Major Protocol Deviation, or 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 should be discontinued from the study treatment. The ELN criteria 2020 do not make provisions for treatment failure in 3rd line however they define that a level of BCR-ABL1 > 1% IS and failure to achieve CCyR is not sufficient for optimal survival. The following events will constitute 'treatment failure':
  - BCR-ABL1 >1% IS at 48 weeks after initiation of therapy or no complete cytogenetic response at 48 weeks.

  - Patients fulfilling treatment failure criteria above but without alternative treatment options may however be continued on study drug if in the investigators opinion they are obtaining benefit from the drug. Patients with BCR-ABL 1 greater than 10% after 48 weeks of treatment or patients with signs of progression to AP and BC must however be discontinued.
- Patients with newly emerging T315I mutation and lack or loss of response. While asciminib has known activity against CML with additional T315I mutation, the recommended dose of 200 mg BID for the treatment of T315I is not in use in the study. In case a patient demonstrates a new T315I mutation on asciminib, patients should not continue in the study.
- In the event of disease progression, the patient must be discontinued from the study treatment. The following events are considered disease progression.
  - 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)
  - 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
  - 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).

Any value of AP or BC within the first 4 weeks of study treatment is not defined as progression to AP/BC within the study unless the subject discontinues study treatment due to progression.

If discontinuation from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

Participants who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in the Assessment Schedule (refer to Section 8).

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

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 participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.3 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision (e.g. Each participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them). Completion of the study will be when the last participant has completed end of study follow up.

All enrolled and/or treated participants should have a safety follow-up visit or call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.4. Documentation of attempts to contact the participant should be recorded in the source documentation.

At the end of the treatment period, for patients who in the opinion of the investigator are still deriving clinical benefit from asciminib, every effort will be made to continue provision of the drug through alternative options if asciminib is not commercially available. Options includes, but are not limited to, roll over trial or provision of the treatment in a non-trial setting (known as post-study drug supply), in accordance with local laws and regulations. Safety will be monitored and reported to Health Authorities per regulatory requirements.

9.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination may be:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendation from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment. The end of treatment visit for discontinued or withdrawn patients should be scheduled and performed as described in Table 8-1. 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 participant's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments such as PRO.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. Its outcome (i.e. recovery status or whether it was fatal)

If the event worsens the event should be reported a second time in the CRF 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 CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

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

Progression of malignancy (including loss of response, progression to accelerated phase or blast crisis and death due to disease progression) should not be reported as a serious adverse event, except if the investigator considers that progression of malignancy is related to study treatment.

Adverse events separate from the progression of malignancy (i.e. deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - 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 participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 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. Selected AESIs are discussed in detail in the [Asciminib Investigators Brochure].

10.1.4 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the patient has stopped study treatment, must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the eSAE Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than 24 hours from the investigator receiving the follow-up information. (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

The following SAE reporting timeframes/ conditions apply:

1. Treated patients: SAEs collected between time patient has provided informed consent until 30 days after the patient has discontinued or stopped study treatment, irrespective of investigator's assessment of causality
2. Patients who are screened but have not received any study treatment: ALL SAEs occurring after the patient has provided informed consent must be reported to Novartis until the time the patient is deemed a Screen Failure and/ or dropped-out the study due any reason.

Any SAEs experienced after the 30-day period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations. 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 study treatment, a 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 study treatment 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 EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

10.1.5 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be

given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent 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 and reported on a Clinical Trial Pregnancy Form and reported by the investigator to the 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 asciminib any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

Follow-up of the newborn should be according to the following schedule:

- Tracking of pregnancy cases occurs until Expected Delivery Date (EDD) for all prospective pregnancy cases
- EDD +1 month (mandatory for all cases). Requesting the pregnancy outcome and other clinically relevant pregnancy data or changes in data.
- EDD +2 month (mandatory if no answer is obtained after request at EDD+1 month). A reminder letter for the outcome.
- The follow up at EDD +3 months is mandatory for all cases of live birth. Information on the status of the baby 3 months after delivery and information on any development issue or abnormality that would not be seen at birth must be collected.
- The follow up at EDD +12 months is mandatory for all cases of live birth. Information on the status of the baby 12 months after delivery and information on any development issue or abnormality that would not be seen at birth must be collected.

10.1.6 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the study treatment CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE.

Table 10-1 Guidance for capturing the study treatment errors

Treatment error type	Document in Study Treatment CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

HBV reactivation can occur in chronic carriers of HBV infection (HBsAg-positive, undetectable or low HBV DNA, and normal ALT) who are not on HBV therapy, or in individuals who have serologic evidence of a resolved prior HBV infection (i.e., HBsAg-negative and anti-HBc–positive). While HBsAg-negative, anti-HBc–positive patients are at lower risk of HBV reactivation compared with HBsAg-positive patients, risk of HBV reactivation should be monitored.

10.3 Committees

10.3.1 Steering Committee

The Steering Committee (SC) will be established comprising investigators with international expertise in the CML field participating in the trial, a patient advocate and Novartis representatives from the Clinical Trial Team. Details will be described in further detail in the SC charter.

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. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

11 Data Collection and Database management

11.1 Data collection

Data not requiring a separate written record will be defined in the protocol and the Assessment Schedule (Table 8-1) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source. All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated investigator staff will enter the data required by the protocol into the 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, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

The MDASI-CML Questionnaire Data Collection:

The MDASI-CML questionnaire data will be completed using paper PRO. The data will be entered by the subjects at the site or at home if the visit is conducted during home nursing. The designated site personnel will transcribe the responses from paper PRO to eCRF.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated Contract Research Organization (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 World Health Organization (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.

Dates of screening(s), enrollment, screen failures and treatment as well as study completion, as well as data about all study treatment (s) dispensed to the participant and will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and 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. Continuous remote monitoring of each site's data may be

performed by a centralized Novartis/Clinical Research Associate organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant 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 on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period.

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

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.

Except where categorically stated, all analyses, including the primary analysis will be conducted on **all** participant data (excluding the additional patients who were intolerant to the last TKI and achieved MMR at baseline). The purpose of having two randomized groups is not for comparison, but to provide data on different dosing regimen. The cut-off date for the end of study treatment analysis is defined as 30 days after the end of study treatment period 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 Clinical Study Report (CSR).

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The patient population for the study includes patients resistant or intolerant to 2 or more prior TKI treatments without MMR at baseline, and an additional group of patients who were intolerant to the last TKI and were in MMR at baseline.

The Analysis Sets are stated as follows:

The Full Analysis Set (FAS) comprises all participants to whom study treatment has been assigned and who received at least one dose of study treatment except the additional patients who were intolerant to the last TKI and were in MMR at baseline.

The Full Analysis Set 2 (FAS 2) comprises only the additional patients who were intolerant to the last TKI and were in MMR at baseline and to whom study treatment has been assigned and received at least one dose of study treatment.

The Safety Set (SAF) includes all participants who received at least one dose of study treatment except the additional patients who were intolerant to the last TKI and were in MMR at baseline.

The Safety Set 2 (SAF 2) includes only the additional patients who were intolerant to the last TKI and achieved were in MMR at baseline and who received at least one dose of study treatment.

Unless otherwise stated, the analysis sets will be applied as below:

- For the patients resistant or intolerant to 2 or more prior TKI treatments without MMR at inclusion to the trial
  - The FAS will be used for demographics and baseline characteristics (except disease characteristics) and all efficacy analyses including PROs
  - The SAF will be used for baseline disease characteristics, exposure and all safety analyses
- For the additional patients who were intolerant to the last TKI and were in MMR at baseline
  - The FAS 2 will be used for demographics and baseline characteristics (except disease characteristics) and selected efficacy analyses including PROs
  - The SAF 2 will be used for baseline disease characteristics, exposure and selected safety analyses

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively.

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 by system organ class and preferred term.

12.3 Treatments

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, as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) 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 and all dosing data will be listed.

Analyses of patients with dose escalation will be specified in the SAP.

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

The additional patients who were intolerant to the last TKI and were in MMR already at baseline will be assessed for the duration of exposure in days to asciminib, as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using SAF 2.

12.4 Analysis supporting primary objectives

12.4.1 Definition of primary endpoint

The primary endpoint of the study is Major Molecular Response (MMR) rate achieved at week 48 while on study treatment (asciminib 40 mg b.i.d. and asciminib 80 mg q.d.). A patient will be counted as having achieved MMR at week 48 if he/she meets the MMR criterion (BCR-ABL1 $\leq$ 0.1% IS) at week 48 while on study treatment.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary estimand will be analyzed based on the data from the FAS and according to the Intention-To-Treat (ITT) principle. Exact test for single proportion will be used at the one-sided 2.5% level of significance.

The null hypothesis is that the MMR rate at Week 48 is equal to 0.23. The alternative hypothesis is that the rate is greater than 0.23.

H_0: π=0.23 vs. H_1: π >0.23

where π is the major molecular response (BCR-ABL1 $\leq$0.1% IS) rate at Week 48. MMR rate and its 95% confidence interval based on the Pearson-Clopper method will also be presented.

The null hypothesis will be rejected when the lower bound of the two-sided 95% CI is above 23%.

Summary statistics of MMR at week 48 will also be presented by randomized groups.

12.4.3 Handling of intercurrent events of primary estimand

The primary estimand is described by the following attributes:

1. The target population comprises CML Patients with resistance or intolerance to 2 or more prior TKI per the 2020 ELN recommendations.

2. Endpoint: Major Molecular Response (MMR) rate achieved at week 48 while on study treatment without meeting any treatment failure criteria prior to week 48. A patient will be counted as having achieved MMR at week 48 if he/she meets the MMR criterion (BCR-ABL1 $\leq$ 0.1% IS) at week 48 while on study treatment unless the patient met any treatment failure criteria prior to week 48.
3. Treatment of interest: the investigational treatment asciminib received for at least 48 weeks, with or without dose modification, dose interruption or any intake of concomitant medications, or intake of prohibited medications.
4. The intercurrent events are the events occurring after first dose of study drug that may impact the treatment effect. The intercurrent events of interest are:
   a. Treatment discontinuation (i.e. having performed an EOT visit) prior to week 48 due to any reason (e.g. death from any cause, intolerance, treatment failure, other reasons)
   b. Dose modification or dose interruption, or any intake of concomitant medications
   c. Intake of prohibited medications (Section 6.2.2)
5. The summary measure is the MMR rate and its 95% confidence interval at week 48.

Handling of the intercurrent events.

The approach of accounting for intercurrent events is as follows:

- **For the intercurrent events 4a:** The composite strategy will be applied for treatment discontinuation due to death from any cause, intolerance, and treatment failure. Define treatment discontinuation due to death from any cause, intolerance, and treatment failure as non-responders. The hypothetical strategy will be applied for treatment discontinuation due to other reasons (lost to follow up, withdrawal of consent, investigator decision etc.). The interest focuses on the treatment effect if patients stay on treatment for 48 weeks, if possible.
- **For the intercurrent events 4b:** The treatment policy strategy will be applied. Meaning, the actual values of the variable (BCR-ABL1 % IS) will be used, regardless of whether the intercurrent event has occurred.
- **For the intercurrent events 4c:** The hypothetical strategy will be applied for the intake of any prohibited medication. The interest focuses on the treatment effect if patients had not taken prohibited medications prior to week 48.

12.4.4 Handling of missing values not related to intercurrent event

Patients with missing PCR evaluations at 48 weeks will be considered as non-responders. However, if the 48-week PCR evaluation is missing, but both a PCR evaluation at 36 weeks and a PCR evaluation at 60 weeks indicate MMR, the 48-week assessment is imputed as a 'Response', assuming that MMR is maintained between 36 and 60 weeks.

12.4.5 Sensitivity analyses

The hypothetical strategy of handling intercurrent events in Section 12.4.4 is based on missing completely at random (MCAR) assumption. To explore the robustness of analysis, sensitivity analyses exploring different assumptions will be performed. The details will be provided in SAP.

In addition, due to the COVID-19 (Coronavirus) pandemic, there is a risk that planned visits are cancelled, potentially resulting in missing PCR evaluations. The impact of COVID-19 (including potential missing data or having clinic visits replaced by home nursing staff visit to the participant´s home) on the primary endpoint will also be analyzed if sufficient (to be detailed in SAP) number of patients are affected.

12.4.6 Supplementary analysis

Subgroup analyses of the primary efficacy endpoint to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics may be conducted on the following subgroups, if there are enough patients in each category:

- Gender: Male and Female
- Race: Asian, Caucasian, or others
- Age at baseline (≥18-< 65 years, ≥ 65 years, ≥ 75 years)
- Reason for discontinuation of the last prior TKI: Warning or failure (i.e. lack of efficacy) or intolerance (i.e. adverse event, lack of tolerability) to the most recent TKI therapy at the time of screening

Note: Only one reason for discontinuation is allowed for each prior therapy.

- Number of prior TKI therapies: 2, 3 or ≥4
- Cytogenetic response status at baseline
- Prior TKI treatment
- Prior ponatinib: Yes or No
- Mutation status at baseline: Wild type or mutant

Other subgroup as appropriate, may be analyzed and described in Statistical Analysis Plan (SAP).

12.5 Analysis supporting secondary objectives

The secondary objectives in this study are as follows:

- To evaluate the safety and tolerability of asciminib in patients with CML-CP following two or more prior TKI treatments.
- To assess the rate of MMR in patients with no evidence of MMR at baseline, at alternative time points at weeks 12, 24, 36, 72, 96 and 144.
- To assess the rate of MMR at week 48 for patients with MMR at baseline
- To assess the time to MMR
- To assess the rate of early responses of BCR-ABL1 ≤10% and ≤1% IS at weeks 12, 24, 36 and 48
- To assess the rate of deep molecular responses (MR4 and MR4.5) at weeks 12, 24, 36, 48, 72, 96 and 144.
- To assess cytogenetic response (% Ph+ metaphases) at weeks 48 and EOT.
- To characterize the impact of additional cytogenetic abnormalities on efficacy
- To assess cumulative molecular responses by all-time points.

- To assess duration of MMR.
- To assess sustained deep molecular responses as prerequisite for TFR.
- To assess rate of progression (PFS).
- To assess overall survival (OS).
- To assess time to treatment failure (TTF).
- To evaluate patient reported outcomes and quality of life by using QoL scales.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Unless otherwise stated the FAS will be used for the analysis of all secondary efficacy endpoints.

No statistical testing of secondary efficacy endpoints will be performed.

- Molecular Response MMR rate at weeks 12, 24, 36, 72, 96 and 144
- MMR rate at week 48 for patients with MMR at baseline
- Rate of MR4 and MR4.5 at weeks 12, 24, 36, 48, 72, 96 and 144
- Rate of BCR-ABL1 ≤10% and ≤1% at Weeks 12, 24, 36 and 48
- Rate of BCR-ABL1 ≤ 10%, BCR-ABL1 ≤1%, MMR, MR4 and MR4.5 by all-time points

For each endpoint above, the rate and the associated 95% confidence interval based on the Pearson-Clopper method will be presented.

Additional chromosomal abnormalities and occurrence of high-risk ACAs will be analyzed.

The details will be provided in SAP.

Duration of MMR is defined in Section 8.3.1.1 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. 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.

Duration of MR4 without loss of MMR will be analyzed in a similar fashion to the analysis of duration of MMR.

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).

The additional patients who were intolerant to the last TKI and were in MMR already at baseline will be assessed for the duration of MMR using FAS 2.

Time to MMR is defined in Section 8.3.1.1 and calculated as: date of first documented MMR - date of randomization +1. Descriptive statistics (minimum, maximum, median, quartiles, mean, SD) of time to MMR will be provided.

Cytogenetic Response

Patients in FAS will be categorized with counts and percentages provided for cytogenetic response at week 48 and EOT. Shift tables will also be employed to examine the changes in cytogenetic response category from baseline.

CCyR rates at Weeks 48 and EOT and the associated 95% confidence intervals based on the Pearson-Clopper method will be presented.

Treatment failure, disease progression and survival

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 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. 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.

Time to treatment failure (TTF) is defined as the time from date of randomization to an event of treatment failure define as BCR-ABL1 > 1% IS. The following events will constitute 'treatment failure', and are based on the ELN criteria 2020 defining failure of a second line treatment adapted to include discontinuation of randomized treatment as an event:

- Twelve months (48 weeks) after the initiation of treatment BCR-ABL1 >1% IS
- Emergence of resistance mutations, high-risk ACA

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.

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.

12.5.2 Safety endpoints

For all safety analyses, the safety set (SAF) will be used, except where stated otherwise.

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 addition, a separate summary for death including on treatment and post treatment deaths will be provided. 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).

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

1. Pre-treatment period: from day of participant's informed consent to the day before first dose of study medication
2. On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication

3. Post-treatment period: starting at day 31 after last dose of study medication.

Adverse events

All the summary tables for adverse events (AEs) and deaths will be tabulated by randomized groups.

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the *treatment-emergent* AEs. All information obtained on adverse events will be displayed by primary system organ class, preferred term and maximum severity.

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

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose adjustment.

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.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

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. Selected AESIs are discussed in detail in the [Asciminib Investigator's Brochure].

The following will also be summarized both for a) **all** patients using combined sets (SAF and SAF 2), and for b) SAF 2 only:

- All deaths
- Serious adverse events and adverse events of special interest
- Adverse events lead to treatment discontinuation
- Grade 3 and 4 adverse events

Vital signs

All vital signs data will be summarized by visit/time.

12-lead 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 locally.

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.

All ECG data will be summarized by visit/time.

Clinical laboratory evaluations

All laboratory data will be summarized by visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5. 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 version 5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

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

- Listing of all laboratory data with values flagged to show the corresponding CTCAE version 5.0 if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE version 5.0

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE version 5.0 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE version 5.0:

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

12.5.3 Biomarkers

Biomarkers will not be part of the secondary endpoints and will be evaluated exploratory only.

12.5.4 Patient reported outcomes

The patient reported outcomes objectives are to compare the impact of treatment on patient reported outcomes (PRO) including CML-specific symptoms and health related patient quality

of life from baseline through end of treatment in all patients by using FAS except stated otherwise.

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 additional patients who were intolerant to the last TKI and were in MMR already at baseline will be assessed for the change in PRO from baseline by using FAS 2.

12.6 Analysis of exploratory endpoints

Exploratory biomarker analysis

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 (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:

- CCI [redacted]

The exploratory biomarker analyses rely on biomarkers expressed in blood samples collected before and during treatment. These analyses also rely on the association between biomarkers and applicable clinical response data.

- List and summarize the information by time point for blood biomarkers
- Assess the potential relationship between clinical outcomes and baseline biomarker data (blood)
- Examine the longitudinal changes of blood biomarkers
- Examine the potential relationship between clinical outcomes and changes from baseline for blood biomarkers
- Explore the relationship between BCR-ABL1 mutations at baseline and efficacy outcomes for the primary endpoint. 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 levels.

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.

Optional exploratory biomarker analysis.

The main aim of this optional exploratory biomarker analysis is to predict which patients will be responders at 48 weeks (in MMR) using single cell CCI by mass cytometry. A formal power calculation has not been conducted however, based on previous experience, 80 patients is deemed sufficient.

The optional exploratory biomarker analysis will be reported in a separate exploratory biomarker report that will be done by CCI and provided upon request. This report will be independent from the biomarker analysis describe above and from the study CSR. Publications that may be done from this research will be provided to sites who contributed.

12.7 Interim analyses

No formal interim analysis is planned for this trial. The following analyses are planned as detailed below.

- 48-week primary analysis: Formal testing of the primary endpoint will be performed. Analyses of other efficacy endpoints at and by week 48 will also be performed.
- 96-week analysis: Analyses of efficacy endpoints at and by week 96 will be performed.
- End of study treatment analysis similar to the 96-week analysis.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

A sample size of 156 patients (randomized to either asciminib 40 mg b.i.d. or 80 mg q.d.) will have 80% power to reject the null proportion of 23% (upper limit of 95% exact binomial CI of the MMR rate at Week 48 in Bosutinib arm in ASCEMBL: see below) at 0.025 one-sided level of significance if the true rate (under alternative hypothesis) is 33% (considering a clinically meaningful difference of 10% or more) using exact test for single proportion (nQuery 7).

[The MMR rate (95% CI) at Week 48 in Bosutinib arm of ASCEMBL trial (at primary analysis) was 11.1 % (4.2% – 22.6%; 54 patients were eligible for this sample size computation].

An additional 30 patients (randomized to either asciminib 40 mg b.i.d. or 80 mg q.d.) intolerant only to last TKI and in MMR at baseline will also be analyzed.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable

local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. 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/Sponsor monitors, auditors, Novartis/Sponsor Quality Assurance representatives, designated agents of Novartis/Sponsor, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis/Sponsor immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal Standard of Practices, and are performed according to written Novartis processes.

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis/Sponsor.

- Thank You letter
- Plain language trial summary - after CSR publication

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an 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 and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

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 prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant 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.

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16 Appendices

16.1 List of concomitant medications for patients on asciminib

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 6.2.2 for patients on asciminib.

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 Food and Drug Administration (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). This list is not comprehensive and is only meant to be used as a guide. Please contact the medical monitor with any questions.

Table 16-1 Concomitant medications to be used with caution for patients on asciminib

Category	Drug Names
Strong inducers of CYP3A4	carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort (Hypericum perforatum)
Narrow Therapeutic index substrates of CYP2C9	phenytoin, warfarin (also sensitive)
Narrow Therapeutic index substrates of CYP3A	alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus, terfanadine,
Torsade de Pointes (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,