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ABL001

Clinical Trial Protocol CABL001E2201

A phase 2, multi-center, open-label, randomized study of oral asciminib added to imatinib versus continued imatinib versus switch to nilotinib in patients with CML-CP who have been previously treated with imatinib and have not achieved deep molecular response

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(e)CRF	(Electronic) Case Report Form
ABL	Abelson proto-oncogene
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
AESI	Adverse Events of Special Interest
Alb	Albumin
ALL	Acute Lymphoblastic Leukemia
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AP	Accelerated Phase
AST	Aspartate Aminotransferase
ASAC	Asciminib single agent cohort
ATC	Anatomical Therapeutic Chemical
ATP	Adenosine Triphosphate-binding
AUC	Area Under the Curve
AUC0-12hours	Area Under the plasma concentration-time Curve from time zero to 12 hours
AUC0-24hours	Area Under the plasma concentration-time Curve from time zero to 24 hours
AUCinf	Area Under the plasma drug concentration-time Curve from time zero to infinity
AUClast	The AUC from time zero to the last measurable concentration sampling time (T_{last}) (mass x time x volume-1)
AUCR	Area Under the Curve Ratio
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
AV	Atrioventricular
BC	Blast Crisis
BCR	Breakpoint Cluster Region
BCR::ABL1	BCR-ABL1 fusion protein
BCR::ABL1	BCR-ABL1 fusion gene
BCRP	Breast Cancer Resistant Protein
BCS	Biopharmaceutical Classification System
BID	Bis In Diem (twice a day)
BLRM	Bayesian Logistic Regression Model
BP	Blast Phase
CABG	Coronary Artery Bypass Graft
CCA	Clonal Chromosomal Abnormalities
CCyR	Complete Cytogenetic Response
CDS	Core Data Sheet (for marketed drugs)
CFR	Code of Federal Regulation
CHR	Complete Hematologic Response
CI	Confidence Interval
Cmax	The maximum (peak) observed plasma drug concentration after oral dose administration (mass x volume-1)
Cmin	Minimum drug plasma (serum/blood) concentration
CML	Chronic Myeloid Leukemia

CML-AP	Chronic Myeloid Leukemia - Accelerated Phase
CML-BC	Chronic Myeloid Leukemia - Blast Crisis
CML-CP	Chronic Myeloid Leukemia - Chronic Phase
CMO&PS	Novartis Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	Central Nervous System
CO	Cross-Over
COA(s)	Clinical Outcome Assessments
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSF	Clinical Service Form
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTIS	Clinical Trial Information System
CTR	Clinical Trial Regulation
Ctrough	Minimal concentration before the next dose is administered
CV	Coefficient of Variation
CYP	Cytochrome P450
DAR	Dose Administration Record
DDI	Drug-Drug Interactions
DHEA	Dehydroepiandrosterone
DILI	Drug-Induced Liver Injury
DLTs	Dose Limiting Toxicities
DMR	Deep Molecular Response
DS&E	Oncology Novartis Drug Safety and Epidemiology Department
DTI	Direct Thrombin inhibitor
EBV	Epstein–Barr virus
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELN	European Leukemia Network
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
eRT	eResearchTechnology
EU	European Union
EudraCT	European Union Drug Regulatoring Authorities Clinical Trials
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First-In-Human
FISH	Fluorescent In-situ hybridization
FMI	Final Market Image
FSH	Follicle-stimulating hormone

GCP	Good Clinical Practice
GGT or γGT	Gamma-glutamyl-transferase
GP	General Population
GUSB	Glucuronidase Beta
HbA1c	Hemoglobin A1c
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B
HCV	Hepatitis C
hERG	Human Ether-a-go-go-related Gene
HIV	Human Immunodeficiency Virus
HSV	Herpes simplex virus
IB	Investigator's Brochure
IC50	Inhibitory Concentration (IC_{50}, the half maximal)
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identification Number
IEC	Independent Ethics Committee
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRIS	International Randomized Study of Interferon and STI571
IRT	Interactive Response Technology
IS	International Scale
ITT	Intent to treat
IUD	Intrauterine device
IUS	Intrauterine system
LC-MS/MS	Liquid chromatography/tandem mass spectrometry
LDL	Low Density Lipoprotein
LFT	Liver function test
LLN	lower limit of normal
LLOQ	Lower limit of quantification
LPLV	Last Patient Last Visit
LSC	leukemic stem cell
MCR or MCyR	Major Cytogenetic Response
MCV	Mean corpuscular volume
mCyR	minor Cytogenetic Response
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial Infarction
MMR	Major Molecular Response
MNT	Micronucleus test
MR	Molecular Response
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging

NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
CCI	CCI [redacted]
nM	nanoMolar
NOAEL	No observed adverse effect level
NTCP	sodium-dependent taurocholate co-transport protein
OATP	Organic anion-transporting polypeptide
OCT	Organic Cation Transporter
OS	Overall Survival
P-gp	Permeability glycoprotein
PAS	Pharmacokinetic analysis set
PBPK	Physiologically-Based Pharmacokinetic
PCR	Polymerase Chain Reaction
PD	pharmacodynamic(s)
Ph+	Ph+ Philadelphia chromosome positive
PK	pharmacokinetic(s)
PRO	Patient Reported Outcome(s)
PT	Prothrombin Time
QD	Quaque Die (once daily)
QLQ	Quality of Life Questionnaire
QMS	Quality Management System
QT	QT interval
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected according to Fridericia's Formula
RNA	Ribonucleic acid
RoW	Rest of the World
RP2D	Recommended phase (Ph) II dose
RT-qPCR	real-time quantitative reverse transcriptase - Polymerase Chain Reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	statistical analysis system
SC	steering committee
sCr	serum creatinine
SD	standard deviation
SOCs	System Organ Classes
SOP	Standard Operating Procedure
STAT5	Signal transducer and activator of transcription 5
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	total bilirubin
TdP	Torsade de Pointe
TFR	Treatment Free Remission
TKI	Tyrosine Kinase Inhibitor
Tlast	Time of last measurement (time)
Tmax	The time to reach maximum (Cmax) plasma drug concentration after oral dose administration (time)

TSQM	Treatment Satisfaction Questionnaire for Medication
UGT	UDP-Glucuronosyltransferase
ULN	upper limit of normal
ULQ	upper limit of quantification
US	United States
UV-LLNA	Ultraviolet radiation - Local Lymph Node Assay
WBC	white blood cell(s)
WHO	World Health Organization
ß-HCG	Beta fraction of human chorionic gonadotropin

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), tissue, urine etc. taken from a study subject or patient
Cycle	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g. q28 days)
DMR	Deep Molecular Response is considered as a response level of at least $MR^{4.0}$ IS (either detectable disease ≤ 0.01% BCR::ABL1 IS or undetectable disease in cDNA with ≥ 10 000 ABL1 (log_{10} 4.0) or ≥ 24 000 GUSB (glucuronidase beta) transcripts)
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product".
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.

Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study.
Subject Number	A unique identifying number assigned to each subject who enrolls in the study
Sustained Minimal Residual Disease	Sustained MRD (Minimal Residual Disease) is based on the last 5 quarterly performed PCR assessments, i.e (1) the first and the last assessments are MR4.5 (log_{10} 4.5 reduction in transcripts), (2) no assessment is worse than MR4, and (3) no more than two assessments are between MR4 and MR4.5
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

Amendment 4 (24-Aug-2023)

Amendment rationale

The study is currently ongoing 84 patients in treatment arms 1– 4 have completed or discontinued the trial, and in the asciminib single agent cohort, 17 patients have been screened and 12/20 patients have been enrolled.

This protocol amendment aims to update concomitant medications that should be used with caution. OATP1B and BCRP substrates have been added to this list. This is based on the results of a PBPK simulation study done as part of post-marketing requirements request per FDA (ABL001 IB Ed.10 – Section 1.4.2).

Based on investigators feedback, the inclusion criterion 3 has been updated to allow enrollment of patients who were treated with imatinib at a dose of 300 mg QD or higher for at least one year and have not achieved DMR. The level of response for entering the trial remains unchanged, BCR::ABL1 levels > 0.01% IS and ≤ 1% IS at the time of randomization.)

Imatinib 400 mg QD is the approved dose for newly diagnosed patients with CML. However, some patients require a lower dosage of imatinib to manage toxicity or impact on quality of life. For patients with BCR::ABL1 levels > 0.01% IS and ≤ 1% IS, stable on a 300 mg QD dose of imatinib, a switch to asciminib provides an opportunity to allow patients to remain on treatment at an optimal dose for longer in order to achieve deep responses. As the BCR::ABL1 levels required at the time of study entry are unchanged, no impact on the efficacy endpoints is expected with this change in the inclusion criteria. BCR::ABL1 levels required at the time of study entry are unchanged, no impact on the efficacy endpoints is expected with this change in the inclusion criteria.

The exploratory biomarker assessments of CCI [redacted] via CCI [redacted] has been removed for patients entering the study in the asciminib single agent cohort. Sample collection and analysis will be completed for patients in treatment arms 1-4 and discontinued there-after due to low number of samples meeting assay eligibility criteria(CCI [redacted] detected in samples analyzed to date.

PK sample log specific for the asciminib single agent cohort is removed to harmonize it over all treatment arms (using the same for all arms).

Updates based on Novartis template version implementation plan and guidance for protocols in the context of the upcoming transition for the European Clinical Trial Directive (EU CTD) 2011/C 172/01 to the European Union Clinical Trial Regulation (EU CTR) 536/2014

Changes to the protocol

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

The following sections have been updated :

- Section 1.1.1.1 Update for the CABL001A2301 is done to reflect current status of the trial along with ABL001 IB Ed. 10 updates.
- Section 4.6 is updated to reflect changes in the protocol template.
- Section 5.1 inclusion criterion~~a~~ 3 is updated based on investigator's feedback. The inclusion criterion number 3 is changed from 3a. to 3b. for reflecting the change in the protocol.
- Section 6.1.1 Study drugs table is updated to reflect updated protocol template.
- Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action : OATP1B, BCRP substrates added as permitted concomitant medication requiring caution.
- Section 7 is updated to remove the optional phone call interview.
- Table 8-1 Assessment Schedule, randomized treatment: asciminib single agent cohort added; subject interview removed; note added that sample collection for CCI [redacted] is only for treatment arms 1-4.
- Section 8.5.2.1 Table 8-10 PK sample log specific for the asciminib single agent cohort is removed to harmonize it over all treatment arms (using the same for all arms).
- Section 8.5.3 and Table 8-11 (named as Table 8-10 in PA4): CCI [redacted] sample collection and exploratory biomarker analysis was limited to treatment arms 1-4.
- 10.1.2 Serious adverse events and 10.1.3 SAE reporting sections are updated to reflect new protocol template.
- 10.1.5 is updated and Table 10-1 is removed to reflect new protocol template and EU-CTR language.
- 13.3 is updated to reflect new protocol template and EU-CTR language.
- 16.3.3 Section Appendix 3 List of concomitant medications which are prohibited or to be used with caution: updated based on revisions in Section 6.2 and current knowledge. OATP1B and BCRP substrates updated as per ABL001 IB Ed.10.

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

IRBs/IECs

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

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

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

Amendment 3 (12-Jul-2022)

Amendment rationale

An interim analysis was performed to gain an early insight into the safety and efficacy of the asciminib add-on combination. The interim analysis was planned to be performed when at least 40 (50%) patients have been randomized and have been followed for their 24 weeks visit assessment or have discontinued treatment. The interim analysis cut-off was on 22-July-2020. The results showed no excess of risk and/or reduced efficacy in the asciminib add-on arms. No change in study conduct were performed based on the benefit/risk balance.

This amendment aims to add an asciminib single agent cohort to assess whether asciminib single agent at the recommended dose of 80 mg QD leads to similar efficacy and safety as observed in the add-on arms of asciminib and imatinib. This additional cohort will help to evaluate if the combination of asciminib with imatinib is needed to increase the likelihood of achieving DMR, or if this can be achieved by asciminib alone. The primary analysis cut-off was on 10-Jan-2022. Eighty-four patients have been randomized in the study. The primary analysis results show activity of asciminib as an add-on therapy to imatinib, assessed by $MR^{4.5}$ rate at Week 48. The $MR^{4.5}$ rate at Week 48 was 19%, 28.6%, 0% and 4.8% in the asciminib 40 mg + imatinib, asciminib 60 mg + imatinib, continued imatinib and switch to nilotinib arm. Asciminib 40 mg QD or 60 mg QD added on to imatinib was well tolerated with no new or worsening events as compared to the known safety profile of single agent asciminib and imatinib.

Data for molecular response with single agent asciminib is available from studies CABL001A2301 (called A2301 henceforth) and CABL001X2101 (called X2101 henceforth) that included heavily pre-treated CML-CP patients with prior treatment with at least 2 or more TKIs. The $MR^{4.5}$ rate in study A2301, in the subgroup of patients treated with asciminib single agent with baseline BCR::ABL1 levels the same as that of patients enrolled in study CABL001E2201 (called E2201 henceforth) (i.e., $> 0.01 \leq 1\%$), was very similar (18.8%, 3 responders among 16 patients) to that seen with the asciminib as add-on to imatinib in study E2201.

The list of concomitant medications permitted to be used with caution and prohibited for the asciminib combination arms has been updated. Based on emerging data from pharmacokinetic studies [Asciminib Investigator Brochure], prohibition for strong CYP3A4/5 inhibitors has been removed and caution statement for asciminib combination arm are added. Additionally, instructions are added for strong CYP3A4 inducers to be used with caution for asciminib single agent and prohibited for the combination arms.

Agents causing QT prolongation or with a "known", risk of Torsades de Pointes (TdP) are no longer prohibited but should be used with caution. Of note there is no need for caution or prohibition for drugs with “possible” or “conditional” risk of TdP and this statement is modified accordingly. Asciminib is not relevantly affected by UGT1A/2B inducers, or BCRP and P-gp

inhibitors, thus there is no longer a limitation to use of these agents for patients being treated with asciminib. No relevant interaction with sensitive substrates of CYP2C8 has been observed. Additionally, the amendment clarifies the exploratory biomarker objective studying the CCI and removes an exploratory objective based on subject qualitative interviews due to logistical issues to implement the process to complete these interviews. The interviews intended to describe concepts important to study patients not captured by standard PRO instruments that could inform future clinical trial designs were removed.

As the TFR study has not been initiated and will not be available for patients completing the study E2201, the option for TFR study as a post-trial access mechanism for patients has been removed.

The content of the local amendment for the USA Amendment 02-US.01 (10-Aug-2020) is superseded by this global amendment 03 as male contraception for the US patients on asciminib was removed based on the latest [Investigator's Brochure] and approved US prescribing information (USPI), where no male contraception is required.

Changes to the protocol

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

The following sections have been updated to include the asciminib single agent cohort:

- Protocol Summary updated based on Protocol Amendment changes
- Section 1.1.1 Introduction to investigational treatment(s) and other study treatment(s): updated for asciminib with current available information from non-clinical studies for phototoxicity and from ongoing clinical studies as reflected in the current [Asciminib Investigator's Brochure]
- Section 1.2 Purpose: added secondary objective to estimate the efficacy of asciminib single agent. Section 2 Objectives and related endpoints:
  - Duration of $MR^{4.5}$ added to secondary objective (to assess additional parameters of the efficacy of asciminib 60 mg /40 mg added to imatinib vs continued imatinib or switch to nilotinib) to assess if patients in the add-on arms have a longer response to treatment
  - Secondary objectives and the corresponding endpoints added for asciminib single agent
  - Duration of $MR^{4.5}$ added to exploratory objective (to describe the efficacy and safety of asciminib 60 mg + imatinib in patients randomized to continued imatinib who cross-over to receive asciminib 60 mg + imatinib) to assess if patients in the add-on arms have a longer response to treatment
  - Exploratory biomarker objective was reworded to add clarity, no changes to assessments
  - Exploratory objective to describe concepts not captured by standard PRO instruments to inform future clinical trial designs was removed due to unavailability of vendor contract
- Section 3 Study design:

  - Asciminib single agent cohort added
  - Four randomized treatment arms were labeled treatment arm 1-4 for clarity
  - End of treatment period added for asciminib single agent cohort
  - End of Study Treatment period added for asciminib single agent cohort, and reworded for clarity
  - Post trial access options were updated to align with clinical development strategy
  - Figure 1-1 was updated to reflect the addition of the asciminib single agent cohort
- Section 4.1.1 Rationale for addition of asciminib single agent cohort section added
- Section 4.2 Rationale for dose/regimen and duration of treatment: asciminib single agent cohort added
- Section 4.5 Risks and benefits: risk-benefit evaluation updated based on new available data
- Section 4.6 Rationale for public health emergency mitigation procedures: section added based on new standard procedures in the event of a public health emergency
- Section 5: Population: asciminib single agent cohort added
- Section 5.2 Exclusion criterion #15: Contraception duration revised to align with USPI; text updated for clarity
  - Criterion from local amendment 02-US.01: male contraception for patients on asciminib removed based on Novartis assessment of the risk for male-mediated embryo/fetal harm through semen transmission according to [*Investigator's Brochure*]
- Section 6.1.3 Treatment arm/group: asciminib single agent cohort added
- Section 6.1.5 Treatment duration: asciminib single agent cohort added
- Section 6.2 Concomitant therapy and prohibited medications updated to align with the latest Investigator Brochure Section 6.3.3 Treatment assignment for asciminib single agent cohort section added
- Table 6-2: Criteria for dose reduction/interruption and re-initiation of asciminib + imatinib: asciminib single agent cohort added. Table updated, the rationale for the change is due to updates to internal NVS guidance on management of LFT derangements and clarification of guidance applicable to patients in the trial
- Table 6-4 Dose reduction guidance for asciminib single agent cohort table added
- Section 6.6.1 Treatment compliance: asciminib single agent cohort added
- Section 6.7.1.1 Handling of study treatment: Reference to public health emergency mitigation procedures added
- Section 6.7.3 Asciminib single agent cohort - Instruction for prescribing and taking study treatment section added
- Section 7 Informed consent procedures text updated for clarity
- Section 8 Visit schedule and assessments: Reference to public health emergency mitigation procedures added
- Table 8-1 Assessment Schedule, randomized treatment: asciminib single agent cohort added; subject interview removed

- Section 8.1.2 Information to be collected on screening failures: asciminib single agent cohort added
- Table 8-3 Blood samples for PCR: asciminib single agent cohort added
- Section 8.4 Safety and Tolerability: Reference to public health emergency mitigation procedures added
- Section 8.4.1 Laboratory evaluations: Reference to public health emergency mitigation procedures added
  - Table 8-7 Central ECG collection plan: asciminib single agent cohort added
  - Section 8.4.3 Pregnancy and assessments of fertility: Reference to public health emergency mitigation procedures added. Definition of post-menopausal and child-bearing potential reworded to add more clarity
  - Section 8.5.1.4 Subject interview: section removed as exploratory objective was removed
  - Section 8.5.2.1 Pharmacokinetic blood collection and handling: asciminib single agent cohort added
  - Section 9.2 Study completion and post-study treatment: Section updated to clarify end of study, Week 96, and final analysis
  - Section 10.1.3 SAE reporting: reporting instructions reworded to cover requirements from authorities
  - Section 12.1 Analysis sets: asciminib single agent cohort added. The analysis of the duration of $MR^{4.5}$ was added to the $MR^{4.5}$ Responder set
  - Section 12.2 Subject demographics and other baseline characteristics: asciminib single agent cohort added
  - Section 12.3 Treatments: asciminib single agent cohort added
- Section 12.5 Analysis of secondary endpoints: secondary endpoint analysis added to align with the objectives. Asciminib single agent secondary endpoint analysis added
  - Section 12.5.1 Efficacy and/or Pharmacodynamic endpoint(s): asciminib single agent added, text updated for clarity
  - Section 12.5.1.1 Rate of $MR^{4.5}$ at 48 weeks: asciminib single agent added, text updated for clarity
  - Section 12.5.1.2 Rate of sustained $MR^{4.5}$ at 96 weeks and section 12.5.1.3. Rate of $MR^{4.5}$ at 96 weeks and section 12.5.1.4 Rate of $MR^{4.5}$ by 48 and 96 weeks: text updated for clarity
  - Section 12.5.1.6 Duration of $MR^{4.5}$: Newly added section to describe the analysis of the duration of $MR^{4.5}$
  - Section 12.5.2 text updated for clarity
  - Section 12.5.3 Pharmacokinetics: asciminib single agent cohort added
  - Table 12-1 Non-compartmental pharmacokinetic parameters: The C_{trough} was removed from the list of pharmacokinetic parameters coming from non-compartmental analysis

as it will be derived from the descriptive stats of the different pre-dose (trough) assessments

- Section 12.7 Interim analyses: clarified that primary analysis was performed in treatment arms 1-4
- Section 12.8 Sample size calculation: updated for asciminib single agent cohort
- Section 13.5 Subject engagement: section added per new protocol template
- Section 15 References: newly cited references added
- Section 16.3 Appendix 3 List of concomitant medications which are prohibited or to be used with caution: updated based on revisions in Section 6.2 and current knowledge.

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

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Amendment 2 (10-Aug-2020)

Amendment rationale

As of 22-Jul-2020, 91 patients have been screened and 62 patients have been randomized in the study. The study is currently ongoing and no analysis has been conducted so far.

Primary purpose of the amendment is:

To allow for modification of study conduct based on interim analysis results in case of observation of an imbalance in the benefit risk profile of one of the investigational arms (asciminib add-on treatment arms), specifically findings related to excessive toxicity without added benefit. The interim analysis is planned to provide early insights into the safety and efficacy parameters to inform the benefit risk assessment of asciminib as an add-on therapy to imatinib. If excessive toxicity without added benefit is observed in one of the investigational arms, discontinuation of that treatment arm will be considered. The decision of discontinuation of an investigational arm in the study will be taken based on the risk benefit balance of the two investigational arms, and in context of the other two treatment options available for the patients in the study, namely, continue on imatinib with no potential improvement of efficacy, or switch to nilotinib with a potential to improve efficacy however with a relatively adverse safety profile as compared to imatinib. The interim analysis is planned to be performed when at least 40 (50%) patients have been randomized and have been followed for their 24 weeks visit assessment or have discontinued treatment.

In addition, dose modification requirements have been updated to further clarify the dose modifications for recurrent Grade 3/4 cytopenias.

- If, after a 1st event of Grade 1/2 cytopenia, recurrent cytopenia of any grade occurs, it is recommended that the study treatment be held until there is resolution to ≤ Grade 2, and thereafter current dose level can be maintained.
- After a 1st event of Grade 3/4 cytopenia, if there is recurrence of Grade 3/4 cytopenia, the dose level should be maintained only if it resolves to ≤ Grade 2 in ≤ 14 days.
- In case of recurrent Grade 3/4 cytopenias of duration >14 days asciminib and imatinib doses are recommended to be reduced by 1 dose level.

Information for CYP3A substrates and inhibitors in the Appendix 3 has been updated in order to reflect updates introduced with protocol amendment 01 based on a most updated PBPK modeling.

Changes to the protocol

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

1. Protocol Summary**:** Study design and Data analysis sections updated in order to match with the updates made in the respective protocol sections.
2. Section 1.1.1.1**- Overview of asciminib**: Narrow therapeutic index specified for substrates of CYP3A4/5, CYP2C8 and CYP2C9.

3. Section 2- **Objectives and endpoints:** Update of the endpoint for exploratory objective CCI [redacted] was removed.
4. Section 3- **Study Design:** Updated for possibility of modification of cross-over arm if signals of toxicity are seen in one or more treatment arms, at the time of interim analysis. If a decision is taken to discontinue asciminib 60 mg + imatinib treatment arm at interim analysis or upon emerging data, cross-over may be changed to asciminib 40 mg + imatinib treatment arm. Figure 3-1 subheading has been amended to match the updates in Section 3.
5. Section 4.4- **Purpose and timing of interim analyses/design adaptations:** Update to allow possibility of modification of study conduct if excessive toxicity without added benefit is observed in one or more treatment arms, at the time of interim analysis.
6. Section 6.5.1**- Dose modification**: Table 6-2 has been updated to clarify recommendations for recurrent cytopenias.
7. Section 8**- Visit schedule and assessments:** Update for CCI [redacted] was removed.
8. Section 12.5.2**- Safety endpoints:** Updated for possibility of change of cross-over treatment based on results of the interim analysis.
9. Section 12.6.2**- Other exploratory endpoints:** Updated for possibility of change of cross-over treatment based on results of the interim analysis.
10. Section 12.7**- Interim Analyses:** Update to allow possibility of study modification if signals of toxicity are seen in one or more treatment arms, at the time of interim analysis.
11. Section 16.3.3- **Concomitant medications to be used with caution for asciminib + imatinib arms**: Information in Appendix 3, Table 16-6 for CYP3A substrates and inhibitors updated in line with information in Section 6.2.

The assessment of the Benefit/Risk concluded the absence of additional risks related to COVID-19.

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

Local version Amendment 02-US.01 (10-Aug-2020) for USA

Additional changes only applicable for the USA:

Amendment rationale

Based on FDA request, requirement for male contraception has been reintroduced in the study.

Changes to the protocol

Section 5.2 Exclusion criterion #15: Male contraception requirements added in exclusion criteria 15. Criteria numbering revised to 15b.

Section 8.4.3 **Pregnancy and assessments of fertility:** added female partners of male to be recorded on Clinical trial pregnancy form and to include guidance for sexually active male. Additionally added, sexually active males on asciminib treatment must use a condom during intercourse while taking the drug and for at least 3 days after stopping treatment and should not father a child in this period.

IRBs/IECs

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

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

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

Amendment 1 (18-Jul-2019)

Amendment rationale

As of 18-Jul-2019, 32 patients were screened and 23 patients were randomized in the study. The study is currently ongoing.

Primary purpose of the amendment is:

Modification of the inclusion criteria #3 regarding imatinib pretreatment duration, from *"at least 24 months"* to *"at least 12 months"* in patients with BCR::ABL1 level between > 0.01% IS and ≤ 1% IS to frontline imatinib. The rationale of this change is based on evolving treatment goals in Chronic Myeloid Leukemia (CML) towards the achievement of faster deep molecular response (DMR) to enable treatment free remission (NCCN 2018, Rea and Cayuela 2017, Mahon 2016). A sustained DMR for at least 2 years is recognized as an essential requirement to attempt discontinuation of Tyrosine Kinase Inhibitor (TKI) therapy in Ph+ CML (NCCN 2018, Baccarani et al 2013, Hochhaus et al 2017). In addition, DMR is associated with improved survival rates and avoidance of disease progression (Cortes 2018, Dulucq and Mahon 2016, Branford 2016, Yeung et al 2015, Hehlmann et al 2014; Etienne et al 2014; Falchi et al 2013). In CML Study IV with frontline imatinib, patients with $MR^{4.5}$ at 4 years had a higher probability of survival at 8 years versus patients with BCR::ABL1 IS of 0.1-1% and no patient who achieved $MR^{4.5}$ had experienced progression to accelerated phase/blast crisis by the data cutoff (Hehlmann et al 2014). A retrospective analysis of patients treated with frontline imatinib found that patients with confirmed $MR^{4.5}$ at any time had a higher event-free survival rate (95.2%) compared to those with Major Molecular Response (MMR), but not $MR^{4.5}$ (64.7%), and those who achieved Complete Cytogenetic Response (CCyR), but not MMR (27.7%) (Etienne et al 2014). Another retrospective study found a lower risk of losing CCyR, progression to Accelerated Phase (AP) or Blast Phase (BP), or death in patients achieving deeper MR (Falchi et al 2013). For patients with BCR::ABL1 level between >0.01% IS and ≤1% IS but no DMR on frontline imatinib for at least 12 months, an early treatment switch provides an opportunity to achieve a faster DMR with a better disease control. This is in line with current treatment guidelines.

The European Leukemia Network (ELN) criteria suggest that (Baccarani et al 2013), patients with BCR::ABL1 levels > 0.1-1% at 12 months are considered to be at a warning level requiring more frequent monitoring. Based on ELN guidelines patients at a warning level may be treated with alternative treatments to improve the level of response (Baccarani et al 2013). Similarly, the ESMO treatment guidelines for CML also consider BCR levels between 0.1-1% at 12 months and beyond to be warning levels and recommend that patients with warning levels may be eligible for potentially better treatments. Additionally, the NCCN CML treatment guidelines recommend a switch of TKI treatment at ≥ 12 months for patients with BCR::ABL1 levels between 0.1-1% and similarly emphasizes that the achievement of response milestones by specific month must be interpreted within the context of clinical and treatment goals (NCCN 2018).

With this change in inclusion criterion, patients with optimal response (BCR::ABL levels > 0.01 and ≤ 0.1% IS) pretreated with at least 12 months on front line imatinib will have the

opportunity to achieve a deeper response and will either continue to receive imatinib, or receive nilotinib, an approved treatment in frontline, or receive asciminib as an add-on to the backbone imatinib treatment.

In view of the evolving understanding of the treatment landscape and to gain an early insight into the safety and efficacy of the asciminib combination, the statistical analysis for the primary objective has been updated to estimate the efficacy of asciminib 40 mg once daily (QD) + imatinib 400 mg QD or asciminib 60 mg QD + imatinib 400 mg QD as against continued imatinib. No formal comparisons between the treatment arms will be performed. Consequently, based on this update in the statistical analysis of the primary objective, the sample size was reassessed using the estimation-precision framework. The sample size of the study has been adjusted from 120 (30 patients per arm) to ~80 (20 patients per arm) patients based on the evaluation of the operating characteristics for the estimation of the efficacy in an exploratory framework while considering clinically relevant effect sizes and emerging clinical data. A sample size of ~80 patients will provide desired precision based on the expected true effect size. With 20 patients enrolled per arm, the lower bound of the two-sided 90% confidence interval of the difference between each asciminib + imatinib arms and the continued imatinib arm will exclude 0 assuming a true 30% difference in the $MR^{4.5}$ rate at 48 weeks.

Further, an interim analysis will be performed in order to gain an early insight into the safety and efficacy of the asciminib add-on combination which will help in planning the future development of the asciminib combination. The interim analysis will be performed when at least 40 (50%) patients have been randomized and have been followed for their 24 weeks visit assessment or have discontinued treatment. The enrollment will continue during this 24 weeks follow-up. The interim analysis will include all randomized patients until the date of data cut-off, and include both efficacy (e.g. BCR::ABL1 assessment overtime, MR4 and $MR^{4.5}$ rate at different time-points) and safety (e.g. Adverse Events and laboratory values) summaries, which will be detailed in the Statistical Analysis Plan for the interim analysis. There will be no change in the study conduct based on this interim analysis and the study will continue as planned after the interim analysis. It is not planned to write an interim CSR based on this interim analysis.

Additionally, the below changes to inclusion and exclusion criteria of the study have been made based on emerging pre-clinical data and feedback received from investigators screening patients for this study:

- Change in prior deep molecular response criteria (inclusion criteria #4) from “must not have achieved deep molecular response (MR^4 IS) at any time during prior imatinib treatment" to " must not have achieved deep molecular response (MR^4 IS) confirmed by 2 consecutive tests at any time during prior imatinib treatment. An isolated, single test result with BCR::ABL1 levels < 0.01 % (MR^4 IS) is allowed, however, it should not have been observed within the 9 months prior to randomization". Additionally, an exclusion criteria (#16) to reinforce this criteria has been added to exclude any patient with “a deep molecular response (MR^4 IS) confirmed by 2 consecutive tests at any time during prior imatinib treatment”. These changes have been made to ensure that patients with unconfirmed, isolated BCR::ABL1 levels of <0.01% are not excluded from the study.

- Patients with history of acute pancreatitis within 1 year prior to randomization or medical history of chronic pancreatitis are already excluded from the study as per exclusion criteria #6. In addition to that, serum lipase requirement for inclusion criteria #5, as a further detail for this criteria, were added. Serum lipase is the preferred test for pancreatitis due to its improved sensitivity, and a threshold concentration of 2-3 x ULN is recommended for the diagnosis of pancreatitis. There are a number of other conditions that can elevate lipase, including TKI pretreatment, thus the screening threshold for lipase is ≤ 1.5 x ULN (CTCAE v4.03 grade 1) as patients with history of acute pancreatitis within 1 year of study and history of chronic pancreatitis are excluded. Amylase is not a specific marker for pancreatitis, as up to 60% of total serum amylase originates from non-pancreatic sources. Its short half-life reduces its value as a diagnostic test in the early clinical course. Lipase has replaced amylase as the biochemical test of choice for acute pancreatitis due to its higher specificity (Basnayake and Ratnam 2015), therefore the requirement of amylase test at screening is not added.
- The requirement for electrolyte levels prior to randomization have been modified (inclusion criteria #6). Increase in potassium of up to 6.0 mmol/L (grade 2) is acceptable at study entry if associated with creatinine clearance within normal limits. Patients with CML often present with hyperkalemia. The release of potassium from platelets is a well-known reason for pseudohyperkalemia in thrombocythemic states including myeloproliferative disorders. (Kim et al 1990). Thus, grade 2 increase of potassium is acceptable in case of normal creatinine clearance as this is not considered to be a risk factor for QTc prolongation. In addition, total calcium (corrected for serum albumin) increase of up to 12.5 mg/dl or 3.1 mmol/L (grade 2) is acceptable prior to randomization if associated with creatinine clearance within normal limits. Grade 1 increase of magnesium is acceptable in case of normal creatinine clearance as this is not considered to be a risk factor for QTc prolongation.
- Based on most updated PBPK modeling predicting a negligible risk for sensitive CYP3A4/5, CYP2C8, or CYP2C9 substrates is predicted. Thus, the prohibition of narrow therapeutic index CYP3A4/5 substrates at study entry has been removed and is no longer an exclusion criterion for the study (exclusion criteria #11 modified). The in vivo potential of asciminib to interact with sensitive CYP3A4/5, CYP2C8 and CYP2C9 substrates is being evaluated. Preliminary results confirm the PBPK predictions with no or weak drug-drug interaction.
- Based on emerging non-clinical data (Asciminib Investigator Brochure edition 6), the exclusion criteria #15 for sexually active males has been updated to remove the requirement of male contraception. In embryofetal development studies with asciminib, fetal malformations (cardiac malformations) and increased visceral and skeletal variants were observed in rats and increased incidence of resorptions indicative of embryofetal mortality and a low incidence of cardiac malformations indicative of dysmorphogenesis were observed in rabbits. Asciminib is not genotoxic. As published in the literature, small molecules can distribute to seminal fluid and the seminal accumulation suggested is semen/plasma ratios up to 11.3 (Klemmt and Scialli 2005). According to the FDA guidance, in general, there is increased concern for reproductive or developmental toxicity in humans for relative exposure ratios (animal: human) that are <10 and decreased concern for exposure ratios >25, (FDA Guidance for Industry 2011). The calculations for the asciminib safety margin were done based on Cmax (plasma) seen in patients at a dose of 200mg BID

(Cmax 6985ng/ml) and the Cmax at the no observed adverse effect level (NOAEL) in the rat and rabbit embryofetal development studies. Hence the safety margins were 482- and 561-fold in rats and rabbits, respectively. In conclusion, for asciminib, as outlined above, the safety margins are well above 25 and therefore no embryo- and feto-toxicity effects can be anticipated via seminal fluid.

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

Changes to the protocol

1. **Section 1: Introduction:** Updates to clinical experience of asciminib based on edition 6 of the Investigator's Brochure (IB) have been made. Section modified to update use of Narrow therapeutic Index CYP3A4/5 substrates, NTI CYP3A4/5 to be used with caution and embryofetal development update. Purpose of study updated to reflect change in requirement of prior imatinib treatment from 24 months to 12 months.
2. **Section 3: Study design:** Updated to reflect change in inclusion criteria and sample size. Figure 1-1 has been replaced.
3. **Section 4.1: Rationale for study design:** Updated statistical details for primary analysis.
4. **Section 4.2: Rationale for Dose/Regimen:** Data error corrected in reporting of DLTs.
5. **Section 4.4: Purpose and timing of interim analyses/design adaptations:** Inclusion of the rationale for the interim analysis.
6. **Section: 4.5: Risk and Benefit:** "Sexually active males" removed.
7. **Section 5: Population:** Number of patients updated to eighty (80) from 120.
8. **Section 5.1- Inclusion Criterion #3:** Duration of prior imatinib treatment changed from 24 months to 12 months.
9. **Section 5.1- Inclusion Criterion #4:** prior DMR changed from "no DMR at any time" to "no DMR achieved confirmed by 2 consecutive tests at any time during prior imatinib treatment. An isolated, single test result with BCR::ABL1 levels < 0.01 % (MR^4 IS) is allowed, however it should not have been observed within the 9 months prior randomization.
10. **Section 5.1- Inclusion Criterion #5:** laboratory criteria for Serum lipase before randomization added.
11. **Section 5.1- Inclusion Criterion #6:** Criteria modified to define laboratory reference range for electrolytes:
    - Potassium increase of up to 6.0 mmol/L is accepted if associated with normal creatinine clearance
    - Total calcium (corrected for serum albumin) increase of up to 12.5 mg/dl or 3.1 mmol/L is acceptable if associated with creatinine clearance within normal limits
    - Magnesium increase up to 3.0 mg/dL or 1.23 mmol/L is acceptable if associated with creatinine clearance within normal limits
    - Criteria for phosphorus were removed
12. **Section 5.2- Exclusion criterion #1:** Footnote to define "confirmed loss of MMR" as in the ELN criteria added

13. **Section 5.2- Exclusion Criterion #7:** reworded to clarify ongoing acute liver disease.
14. **Section 5.2- Exclusion Criterion #9:** Hepatitis screen requirement clarified with additional tests (anti-HBs and HBV-DNA) that can be done if needed.
15. **Section 5.2- Exclusion criterion #11:** Removal of substrates of CYP3A4/5 with narrow therapeutic index as an exclusion, based on most updated PBPK modeling predicting a negligible risk for sensitive CYP3A4/5 substrates.
16. **Section 5.2- Exclusion criterion #15:** Male contraception requirements deleted on the basis of data available from embryofetal development studies.
17. **Section 5.2- Exclusion criterion #16:** new criterion has been added to define DMR criteria on prior imatinib treatment.
18. **Section 6.2- Other treatment (Concomitant Medication and Prohibited Medication) section:** Section on NTI substrates of CYP3A4/5 removed based on a most updated PBPK modeling predicting a negligible risk for sensitive CYP3A4/5 substrates and moved under requiring caution section. Other CYP3A4 substrates (sensitive and moderate CYP3A4 substrates) have been removed from the caution list.
19. **Section 6.5.1- Dose modification**: section has been updated based on Investigator Brochure version 6.
20. **Section 7- Informed Consent Procedure:** update on male contraception.
21. **Section 8-Visit schedule and assessment:** Visit schedule for patients on imatinib and nilotinib already present in Table 8-1 as footnote, reiterated in text.
22. **Section 8.3.2- Bone Marrow analysis and cytogenetics:** "cytogenetics" word has been added as clarification.
23. **Section 8.4.1- Laboratory evaluations:** Local lab CRF and local lab test reporting requirements clarified. Clarification have been made in the table 8.6.
24. **Section 8.4.3- Pregnancy and assessments of fertility:** Clarification added on Crossover treatment CO baseline assessment and update on male contraception.
25. **Section 8.5.1.1- EORTC QLQ-C30 and EORTC QLQ-CML 24:** Clarification for sites where QLQ-CML24 not available due to missing language validation added.
26. **Section 8.5.2.1- Pharmacokinetic blood collection and handling:** Table 8-9 updated with window periods for blood collection log.
27. **Section 9.1.1- Discontinuation of study treatment:** clarification on criteria for treatment failure according to ELN 2013 guidelines.
28. **Section 10.2.1- Liver Safety monitoring:** updated to delete liver CRF. Liver laboratory parameters will be reported on scheduled/unscheduled laboratory CRF.
29. **Section 12.4- Analysis of primary endpoint:** Updated primary endpoint analysis.
30. **Section 12.5.1- Efficacy and/or Pharmacodynamic endpoint(s):** Confidence interval of rate of $MR^{4.5}$changed from 95 to 90%.
31. **Section 12.5.3- Pharmacokinetics section:** Text updated for clarification.
32. **Section 12.7- Interim Analysis:** Inclusion of interim analysis.
33. **Section 12.8- Sample size calculation:** Updated based on updated primary endpoint analysis and addition of interim analysis.
34. **Section 15- References:** Updated with newly added references in protocol.

35. **Appendix 16.1 and Table 16.2:** deleted liver CRF. Liver laboratory parameters will be reported on scheduled/unscheduled laboratory CRF.
36. **Appendix 16.3:** Section on NTI substrates of CYP3A4/5 moved under requiring caution.

IRB Section

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

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

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment 1.

Protocol summary

Protocol number	CABL001E2201
Full Title	A Phase 2, multi-center, open-label, randomized study of oral asciminib added to imatinib versus continued imatinib versus switch to nilotinib in patients with CML-CP who have been previously treated with imatinib and have not achieved deep molecular response
Brief title	Study of efficacy and safety of asciminib in combination with imatinib in CML-CP patients
Sponsor and Clinical Phase	Novartis, Study Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The trial is designed to assess the activity of 2 doses of asciminib + imatinib *versus* other two arms (continued imatinib arm and switch to nilotinib arm), assessed by the rate of Molecular Response ($MR^{4.5}$ at 48 weeks as well as additional efficacy parameters, pharmacokinetic (PK), biomarkers, patient reported outcomes (PROs) and safety and tolerability. Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of patients with chronic myeloid leukemia (CML), resulting in an overall survival (OS) that is close to that of the general population and therefore a near normal life expectancy. A new evolving treatment goal in CML treatment is treatment free remission, which requires patients to be in deep molecular response (DMR), considered as a response level of at least $MR^{4.0}$ International Scale (IS). Currently, an option for patients who do not achieve the desired level of molecular response with continued imatinib treatment is to switch to a more potent second generation adenosine triphosphate (ATP)-binding site TKIs. However a high percentage of patients still do not achieve the desired level of response. Asciminib is an allosteric inhibitor of Breakpoint Cluster Region - Abelson proto-oncogene 1 (BCR::ABL1) and due to its distinct mode of action showed pre clinically an additive anti-tumor activity in combination with ATP-binding site TKIs. The addition of asciminib to imatinib is expected to result in more potent inhibition of the ABL kinase domain. It is hypothesized that the addition of asciminib in patients who have not achieved DMR with single agent imatinib will increase their likelihood of achieving this response over time and subsequently allow for consideration of TKI discontinuation. The purpose of this trial is to evaluate the efficacy and safety of the combination of asciminib + imatinib treatment in comparison to continued imatinib in patients who have not achieved MR^4 after at least one year of imatinib first-line treatment. As a secondary endpoint, the difference in efficacy between the combination and nilotinib, a second generation TKI, will be estimated. Results from single agent studies in patients with CML-CP who have been treated with at least 2 prior TKIs have shown activity of single agent asciminib for achievement of DMR in this heavily pretreated population. In study A2301, MR^4 and $MR^{4.5}$ rates of 10.8% and 7.6%, respectively were observed at Week 48 (Mauro et al, 2021). In the subgroup of patients with baseline BCR::ABL1 levels (> 0.01% and ≤1%), the $MR^{4.5}$ rate (18.8%, 3 responders among 16 patients) was similar to that observed in E2201 with asciminib as add-on to imatinib at the primary analysis.

Primary Objective(s)	The primary objective of this study is to assess whether asciminib 40 mg once daily (QD) + imatinib 400 mg QD or asciminib 60 mg QD + imatinib 400 mg QD is more effective than continued imatinib by assessing the $MR^{4.5}$ rates at 48 weeks.
Secondary Objectives	Objective 1: to estimate efficacy of switch to nilotinib assessed by the $MR^{4.5}$ rate at 48 weeks. Objective 2: to estimate difference in efficacy between asciminib 60 mg + imatinib and switch to nilotinib considering the difference in $MR^{4.5}$ rate at 48 weeks. Objective 3: to estimate difference in efficacy between asciminib 40 mg + imatinib and switch to nilotinib considering the difference in $MR^{4.5}$ rate at 48 weeks. Objective 4: to assess additional parameters of the efficacy of asciminib 60 mg or 40 mg added to imatinib *versus* continued imatinib or switch to nilotinib i.e. the rate of $MR^{4.5}$ at 96 weeks, rate of $MR^{4.5}$ by 48 and 96 weeks, sustained $MR^{4.5}$ at 96 weeks, time to $MR^{4.5}$ and duration of $MR^{4.5}$. Objective 5: to characterize the safety and tolerability profile of asciminib 60 mg or 40 mg + imatinib *versus* continued imatinib or switch to nilotinib by comparing the incidence and severity of adverse events (AEs), changes in laboratory values, clinically notable ECG abnormalities and vital signs. Objective 6: to assess the pharmacokinetic profile of asciminib 60 mg or 40 mg and imatinib when administered in combination. Objective 7: to estimate efficacy of asciminib 80 mg QD assessed by the $MR^{4.5}$ rate at 48 weeks, time to $MR^{4.5}$ and duration of $MR^{4.5}$. Objective 8: to characterize the safety and tolerability profile of asciminib 80 mg QD. Objective 9: to assess the pharmacokinetic profile of asciminib 80 mg QD.
Study design	The study is a Phase 2, multi-center, open-label, randomized study of asciminib in two different doses (40 mg or 60 mg) in combination with imatinib 400 mg *versus* continued imatinib *versus* switch to nilotinib in patients with chronic myeloid leukemia in chronic phase (CML-CP) who have been previously treated with imatinib first line therapy for at least one year and have not achieved deep molecular response (DMR). The eligible patients will be randomized 1:1:1:1 to receive asciminib 60 mg QD as add-on therapy to imatinib 400 mg QD, or 40 mg QD as add-on therapy to imatinib 400 mg QD, or to continue imatinib 400 mg QD, or to switch to nilotinib 300 mg twice a day (BID). Patients on the study will continue on the allocated treatment until treatment failure, intolerability, or for up to 96 weeks after the last randomized subject received the first dose of treatment. After the last dose received, every subject will be followed up for safety for 30 days. An interim analysis will be performed when at least 40 (50%) patients have been randomized and have been followed for their 24 weeks visit assessment or have discontinued treatment. At the time of the interim analysis, if excessive toxicity without added benefit is observed in one of the investigational arms, discontinuation of that treatment arm will be considered. The decision to discontinue an investigational arm in the study will be taken based on the risk benefit balance of the two investigational arms, and in context of the other two treatment options available for the patients in the study, namely: continue on imatinib with no potential improvement of efficacy; or switch to nilotinib with a

	potential to improve efficacy however, with a relatively adverse safety profile as compared to imatinib. If a decision is taken to discontinue asciminib 60 mg + imatinib treatment arm at interim analysis, patients ongoing on that treatment arm will be provided an opportunity to continue on the study at a lower dose (asciminib 40 mg + imatinib) if the investigator considers that is in the best interest of the patient. Patients on the imatinib continuation arm who have not achieved $MR^{4.5}$ at 48 weeks may cross-over (CO) to receive the add-on treatment within 4 weeks after week 48 visit. It is planned that these patients cross-over to receive the asciminib 60 mg add-on treatment, as this dose provides higher exposure. Based on the results of the interim analysis or emerging data, cross-over may be changed to the asciminib 40 mg add-on treatment. The cross-over is at the discretion of the investigator and the patient. Apart from a polymerase chain reaction (PCR) result of below $MR^{4.5}$ at Week 48 visit, there are no other entry criteria for the cross-over part. Patients on nilotinib are not allowed to cross-over to receive the add-on treatment. After the primary analysis, the decision was made to add an additional cohort to the study (upon IRB and Health Authority approval) to investigate the efficacy and safety of asciminib 80 mg QD as compared to the add-on and continue on imatinib arms. This cohort will have approximately the same sample size as in treatment arms 1-4 (n = 20). As enrollments are closed in the treatment arms 1-4, all incoming patients will be included in this additional cohort. The patients enrolled in the asciminib single agent cohort will not be allowed to cross-over to another investigational combination arm if they fail to achieve $MR^{4.5}$ at week 48.
Population	Approximately eighty eligible patients with CML-CP will be randomized 1:1:1:1, with a target of 20 patients in each arm (treatment arms 1-4). Approximately n = 20 patients will be included in asciminib 80 mg QD cohort. Male or female patients ≥ 18 years of age will be enrolled.
Key Inclusion criteria	1. Signed informed consent must be obtained prior to participation in the study. 2. Male or female patients ≥ 18 years of age with a confirmed diagnosis of CML-CP 3. b . Minimum of one year (12 calendar months) treatment with imatinib first line for CML-CP (patients have to be on imatinib 300 mg QD or higher). 4. a. BCR::ABL1 levels > 0.01% IS and ≤ 1% IS at the time of randomization as confirmed with a central assessment at screening; patients must not have achieved deep molecular response (MR4 IS) confirmed by 2 consecutive tests at any time during prior imatinib treatment. An isolated, single test result with BCR::ABL1 levels < 0.01 % (MR4 IS) is allowed, however, it should not have been observed within the 9 months prior to randomization. 5. a. Patient must meet the following laboratory values before randomization: • Absolute Neutrophil Count ≥ 1.5 x 10^9 L • Platelets ≥ 75 x 109/L • Hemoglobin ≥ 9 g/dL • Serum creatinine (sCr) < 1.5 mg/dL • Total bilirubin (TBL) ≤ 1.5 x upper limit of normal (ULN) except for patients with Gilbert's syndrome who may only be included with total bilirubin ≤ 3.0 x ULN • Aspartate aminotransaminase (AST) ≤ 3.0 x ULN

	• Alanine aminotransaminase (ALT) ≤ 3.0 x ULN • Alkaline phosphatase (ALP) ≤ 2.5 x ULN • Serum lipase ≤ 1.5 x ULN. For serum lipase > ULN - ≤ 1.5 x ULN, value must be considered not clinically significant and not associated with risk factors for acute pancreatitis 6. a. Patients must have the following laboratory values (≥ lower limit of normal (LLN)) or corrected to within normal limits with supplements prior to randomization: • Potassium (potassium increase of up to 6.0 mmol/L is acceptable 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 if associated with creatinine clearance* within normal limits) • Magnesium (magnesium increase up to 3.0 mg/dL or 1.23 mmol/L if associated with creatinine clearance* within normal limits. *Creatinine clearance as calculated using Cockcroft-Gault formula
Key Exclusion criteria	1. Treatment failure according to ELN 2013 criteria during imatinib treatment. 2. Known second chronic phase of CML after previous progression to accelerated phase/blast crisis (AP/BC). 3. Previous treatment with any TKIs other than imatinib 4. History or current diagnosis of ECG abnormalities indicating significant risk or safety for patients participating in the study such as: • History of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG) within 6 months prior to randomization • Concomitant clinically significant arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree atrioventricular (AV) block without a pacemaker • Resting QTcF ≥ 450 msec (male) or ≥ 460 msec (female) prior to randomization • 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 including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia • Concomitant medications with a "known" risk of Torsades de Pointes per crediblemeds.org that cannot be discontinued or replaced by safe alternative medication • inability to determine the QTcF interval 5. 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, uncontrolled clinically significant hyperlipidemia and high serum amylase). 6. History of acute pancreatitis within 1 year prior to randomization or medical history of chronic pancreatitis; ongoing acute liver disease or history of chronic liver disease.

	7. History of other active malignancy within 3 years prior to randomization with the exception of basal cell skin cancer, indolent prostate cancer and carcinoma in situ treated curatively
Study treatment	• Asciminib (ABL001) 80 mg, 60 mg, 40 mg QD • Imatinib (STI571) 400 mg QD • Nilotinib (AMN107) 300 mg BID
Efficacy assessments	• Peripheral blood for BCR::ABL1 real-time quantitative reverse transcriptase-Polymerase Chain Reaction (RT-qPCR)
Key safety assessments	• Physical examination • Extramedullary involvement • Vital signs • Hematology and biochemistry (and pregnancy when applicable) • ECG • Adverse Events
Other assessments	• Patient Reported Outcomes: EORTC QLQ-C30, EORTC QLQ-CML24, FACIT GP5 and TSQM • PK sampling • Biomarker assessments (characterization of CCI [redacted], CCI [redacted])
Data analysis	The primary efficacy endpoint of the study is the rate of $MR^{4.5}$ at 48 weeks (± assessment window), defined as the proportion of patients still treated with the randomized treatment at 48 weeks and are in $MR^{4.5}$ (BCR::ABL1 ratio of ≤ 0.0032%) at 48 weeks. It will be calculated based on the Full Analysis Set (FAS). The difference in rate of $MR^{4.5}$ between 1) asciminib 60 mg + imatinib *versus* continued imatinib and 2) asciminib 40 mg + imatinib *versus* continued imatinib with its 2-sided 90% confidence interval will be provided using the Wald method. The rate of $MR^{4.5}$ at 48 weeks and its 2-sided 90% confidence interval based on the Clopper-Pearson method will be presented by treatment arm. To estimate the efficacy of asciminib single agent, the rate of MR4.5 at 48 weeks and its 2 sided 90% confidence interval based on the Clopper-Pearson method will be presented. No formal comparison or estimate of the difference with the other treatment arms will be performed for this additional cohort. Interim Analysis: An interim analysis will be performed when at least 40 (50%) patients have been randomized and have been followed for their 24 weeks visit assessment or have discontinued treatment. The interim analysis will include all randomized patients until the date of data cut-off, and include both efficacy (e.g. BCR::ABL1 assessment overtime, MR^4 and $MR^{4.5}$ rate at different time-points) and safety (e.g. Adverse Events and laboratory values) summaries, which will be detailed in the Statistical Analysis Plan for the interim analysis. Based on the results of the interim analysis a benefit risk balance will be assessed for the two add-on treatment arms. It is not planned to write an interim CSR based on this interim analysis. The primary analysis will be performed after all patients in all 4 randomized treatment arms have completed Week 48 or discontinued prior to Week 48. A week 96 analysis will be performed after all patients in all 4 randomized treatment arms have completed Week 96 and/or discontinued study prior to

	Week 96. The final analysis will be performed with all available data from the asciminib single agent cohort at the End of the Study.
Key Words	Chronic Myeloid Leukemia in Chronic Phase (CML-CP), Tyrosine Kinase Inhibitor (TKI), Glivec® (imatinib), Tasigna® (nilotinib), asciminib, Molecular Response

1 Introduction

1.1 Background

CML is a clonal myeloproliferative disorder of transformed, primitive hematopoietic progenitor cells. The hallmark of CML is the Philadelphia (Ph) chromosome found in up to 95% of patients. It results from a reciprocal translocation t(9;22)(q34;q11) which adds a 3' segment of the ABL gene on chromosome 9 to the 5' part of the breakpoint cluster region (BCR) gene on chromosome 22. The resulting fusion gene encodes for a constitutively active tyrosine kinase, the BCR-Abelson (ABL) tyrosine kinase (Faderl et al 1999), which has activity that imparts growth advantage to leukemic cells, increases proliferation and cytokine-independent growth, inhibits apoptosis, and inhibits alternate adhesion pathways (Sawyers 1999, Deininger et al 2000, Van Etten 2004).

With a constant incidence of 1.2-1.5/100 000 per year the prevalence of CML is steadily increasing (Hochhaus and La Rosée 2013). Clinically, CML progresses through three distinct phases of increasing refractoriness to therapy: chronic phase (CP), accelerated phase (AP), and blast crisis (BC) (Enright H and McGlave 2000). Most patients, however, present in the CP, characterized by splenomegaly and leukocytosis with generally few symptoms.

The gold standard for the treatment of CML was the tyrosine kinase inhibitor (TKI) Glivec® (imatinib), which was introduced in 2001 and revolutionized the CML treatment. Other TKI agents, including nilotinib, dasatinib, ponatinib, bosutinib, are also meanwhile approved for the treatment of CML. Possible options for first-line treatment include imatinib, nilotinib, dasatinib and bosutinib, while imatinib is most widely used in this setting and regarded as standard of care.

Current treatment guidelines recommend continuing therapy with TKI indefinitely in patients with optimal response (Baccarani et al 2013, NCCN 2018). However, in selected CML patients meeting certain criteria, e.g. sustained deep molecular response (sustained DMR), discontinuation of TKI therapy is possible (Hochhaus et al 2017, NCCN 2018, [Tasigna SmPC], [USPI]).

1.1.1 Introduction to investigational treatment(s) and other study treatment(s)

1.1.1.1 Overview of asciminib

Asciminib (ABL001) is a potent, orally bioavailable specific BCR::ABL1 inhibitor with a novel mechanism of action. In contrast to inhibitors such as imatinib, nilotinib and dasatinib that bind within the Adenosine Triphosphate -binding (ATP) site of the ABL kinase domain, asciminib inhibits ABL tyrosine kinase activity by binding to a particular allosteric site on the kinase domain, which has only been identified on ABL1, ABL2 and BCR::ABL1. Consequently, asciminib is specific for the latter three enzymes. Asciminib potently and selectively inhibits the proliferation of cell lines that express BCR::ABL1. By virtue of asciminib not interacting with the ATP-binding site, the drug is active against cells expressing clinically observed ATP-binding TKI resistance mutations. A combination of asciminib with an ATP-site inhibitor, such

as imatinib, has the potential to prevent the emergence of resistance due to point mutation(s) being acquired in one of the binding sites.

As of 30-Jun-2022, asciminib has been approved for treatment of CML pts with resistance or intolerance to previous therapy in Albania, Canada, Japan, Korea, Switzerland, UK, and US.

1.1.1.1.1 Non-clinical experience

In vitro and *in vivo* pharmacology data

Asciminib is an ABL1 inhibitor that binds with high affinity to the allosteric myristate-binding pocket on the kinase SH1 domain and inhibits the ABL1 kinase activity of the BCR::ABL1 fusion protein. Asciminib potently inhibits the proliferation of CML and acute lymphoblastic leukemia (ALL) cell lines that express BCR::ABL1, at doses >1000-fold potent than in cell lines that do not express BCR::ABL1.

Asciminib displays potent anti-tumor activity *in vivo* with a clear pharmacokinetic (PK)/pharmacodynamic (PD)/efficacy relationship [RD-2013-50145]. In a KCL-22 CML-BC cell line mouse subcutaneous xenograft model, tumor regression was observed at doses of 7.5 mg/kg BID and above when asciminib was administered alone. Efficacy in this BCR::ABL1 dependent KCL-22 xenograft model correlated with complete inhibition of the downstream PD marker STAT5 (signal transducer and activator of transcription 5), and the minimal total plasma concentration required to achieve this level of PD suppression was observed to be around 50-100nM.

The KCL-22 xenograft model was also used to assess the activity of asciminib and ATP-site binding TKIs (nilotinib) as single agents and in combination (Wylie et al 2017). In these experiments, when each agent was administered as monotherapy in sequence, initial sensitivity of the tumor was observed to each agent, but relapse occurred in each case. The mutations observed were as expected based on clinical experience (T315I for nilotinib) or modeling (A337V) for asciminib. In contrast, animals treated upfront with the combination of asciminib and nilotinib achieved sustained tumor regression with no evidence of disease relapse during the 68 days of treatment or for > 100 days following discontinuation of treatment. Note that in this KCL-22 model, the cells (derived from a blast crisis CML subject) were grown as a solid tumor rather than as disseminated disease. Also, this model is much more aggressive than chronic phase CML in patients.

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

Safety pharmacology and toxicology

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

Safety pharmacology studies indicate that asciminib is not expected to cause effects on the vital functions of the CNS (Central Nervous System), and the respiratory systems. The half maximal inhibitory concentration (IC_{50}) for asciminib in the hERG (Human Ether-a-go-go-related Gene) patch clamp is 11.4 µM (4498 ng/mL). Despite hERG inhibition occurring *in vitro* at low concentration, this potential did not translate into cardiac rhythm disturbances or QTc (QT

interval corrected for heart rate) prolongation *in vivo* up to exposures 120-fold higher than in patients at the maximum recommended therapeutic dose of 40 mg BID (free drug C_{max} comparisons).

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

Preclinical studies suggested that asciminib might cause phototoxicity and photosensitization. Within the sunlight range (290 to 700 nm), asciminib showed absorption maxima at 312 nm. A photo-inhibition factor (PIF) assay value of 41 was determined in the 3T3 NRU phototoxicity assay. As determined by the results of the phototoxicity assessment (*in vitro* and *in vivo*), phototoxic potential was identified in the mouse UV-LLNA (Ultraviolet radiation - Local Lymph Node Assay) at 200 mg/kg/day. However, at the NOAEL in animal studies, exposure based on Cmax in plasma was 15-fold higher than the exposure in patients at the 40 mg BID. Given the updated data, adult patients enrolled in the single agent asciminib cohort will not need sunlight protection.

In embryofetal development studies with asciminib, fetal malformations (cardiac malformations) and increased visceral and skeletal variants were observed in rats and increased incidence of resorptions indicative of embryofetal mortality and a low incidence of cardiac malformations indicative of dysmorphogenesis were observed in rabbits. Asciminib is not genotoxic. As published in the literature, small molecules can distribute to seminal fluid and the seminal accumulation suggested is semen/plasma ratios up to 11.3 (Klemmt and Scialli 2005). According to the FDA guidance, in general, there is increased concern for reproductive or developmental toxicity in humans for relative exposure ratios (animal: human) that are <10 and decreased concern for exposure ratios >25, (FDA Guidance for Industry 2011). The calculations for the asciminib safety margin were done based on Cmax (plasma) seen in patients at a dose of 200mg BID (Cmax 6985ng/ml) and the Cmax at NOAEL in the rat and rabbit embryofetal development studies. Hence the safety margins were 482 and 561-fold in rats and rabbits, respectively. In conclusion, for asciminib, as outlined above, the safety margins are well above 25 and therefore no embryo- and feto-toxicity effects can be anticipated via seminal fluid.

Repeat dose toxicity studies identified the pancreas, liver, hematopoietic system, adrenal and gastro-intestinal tract as potential target tissues. All findings so far have demonstrated a partial to complete reversibility during a 4-week recovery phase, and can be readily monitored in clinical settings.

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

Non-clinical pharmacokinetics and metabolism

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

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

The metabolite profile of asciminib has been examined *in vitro* using rat, dog, monkey and human hepatocytes. Interspecies differences were observed with direct glucuronidation occurred most readily in human, to a lesser extent in dog and monkey, and was noticeably absent in rat. Nevertheless, the metabolic turnover of asciminib was low to moderate across species. No unique human metabolites were detected in this *in vitro* hepatocytes metabolism study across species.

The metabolite profile of asciminib has also been examined *in vivo* in rats. Following intravenous and oral administration of [^{14}C-ABL001] to intact rats, asciminib was found to be the predominant component of plasma, accounting for ~86%-91% of radioactivity from 0 - 8 hours. Asciminib was excreted primarily in the feces, with ~90% of radioactivity detected in the feces from 0 - 48 h. Renal elimination represented a minor route, with ~2.4% of radioactivity detected in the urine from 0 - 72 h. In the feces, ~58% (intravenous) and ~71% (oral) of the dose was associated with unchanged asciminib, with several oxidative metabolites accounting for the remaining radioactivity. The metabolites formed *in vivo* were consistent with those observed *in vitro*. Similar observations were noted in bile-duct cannulated rats. An absorption, distribution, metabolism, and excretion (ADME) Study was as well conducted in monkey [R1500815] and showed that asciminib is the predominant drug-related component in plasma. All metabolites detected in human plasma were also observed in the ADME monkey Study.

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

Based upon the clinical human ADME data and alignment with the *in vitro* human hepatocyte clearance and enzyme reaction phenotyping studies, the relative contribution of CYP- and UDP-Glucuronosyltransferase (UGT) -mediated asciminib clearance was estimated to be 36.6% and 58.3%, respectively. Multiple enzymes (UGT1A3, UGT1A4, UGT2B7, UGT2B17, CYP3A4/5, CYP2C8, CYP2J2 and CYP2D6) are involved in the metabolism of asciminib. CYP3A4 was estimated to contribute 35% to the total clearance of asciminib in humans, with UGT2B7 contributing 27.9%. The contribution of UGT2B17 and UGT1A3/UGT1A4 to asciminib total clearance was 16.3% and 14.1%, respectively. Other CYP enzymes: CYP2C8, CYP2D6 and CYP2J2 were estimated to contribute to a minor extent (less than 1%). The potential for clinical DDIs with co-medications that inhibit a single UGT enzyme is likely to be low.

Strong inducers or inhibitors of CYP3A4/5 have the potential to alter asciminib concentrations.

Transporter phenotyping studies have identified asciminib to be a substrate of Breast Cancer Resistant Protein (BCRP) (Km ≈ 4 μM) and Permeability glycoprotein (P-gp) (Km could not be estimated due to insufficient saturation of efflux activity). Inhibitors of BCRP and P-gp may increase asciminib concentration and are to be used with caution in this study.

The *in vivo* potential of asciminib to interact with sensitive CYP3A4/5, CYP2C8 and CYP2C9 substrates has been evaluated by PBPK modeling and would indicate a minimal or negligible risk. At the dose of asciminib 80 mg qd (Cmax,ss of ~1270 ng/mL), the PBPK model predicted a AUC ratio of 1.22, 1.11 and 1.08 for the sensitive substrate of CYP3A4 (midazolam), CYP2C8 (repaglinide) and CYP2C9 (S-warfarin), respectively (R1700912)

Therefore, substrates of CYP3A4/5, CYP2C8 and CYP2C9 with narrow therapeutic index should be used with caution.

Based on PBPK asciminib is a weak inhibitor of intestinal P-gp at 40 mg b.i.d., 80 mg q.d. and 200 mg b.i.d.

Further, at doses of 40 mg b.i.d., 80 mg q.d., and 200 mg b.i.d. asciminib weak to moderate increases in OATP1B substrates (e.g., pitavastatin, pravastatin) and BCRP substrates (e.g., sulfasalazine) are expected when administered concomitantly (DMPK-R2270328). At doses of 40 mg b.i.d. and 80 mg q.d. asciminib was predicted to be moderate inhibitor of the dual BCRP and OATP1B substrate rosuvastatin and a strong inhibitor at 200 mg b.i.d.

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

1.1.1.1.2 Clinical experience

As of 15-Jan-2023, asciminib is being investigated in 11 ongoing Novartis sponsored studies in patients with CML- CP/ AP or CML-BC or Ph+ ALL.

The approval of asciminib monotherapy in CML-CP patients with Ph+ CML in CP, previously treated with 2 or more TKIs was based on results from the ongoing first-in-human (FIH) Phase I clinical Study, Study [CABL001X2101] (called X2101 henceforth), and the Phase 3 pivotal Study in 3rd line CML-CP [CABL001A2301] (called A2301 henceforth) .

Study CABL001A2301

Study A2301 is an ongoing Phase III, multi-center, active-controlled, open-label, randomized study of oral asciminib versus bosutinib in patients with CML-CP, previously treated with at least 2 TKIs. Overall, 233 patients with CML-CP were enrolled in the study of which 157 were randomized to asciminib arm and 76 to bosutinib arm, 89 patients (56.7%) in the asciminib arm and 17 patients (22.4%) in the bosutinib arm are still ongoing on study treatment.

The study met its primary endpoint. The MMR rate at 24 weeks was 25.5% in the asciminib arm compared to 13.2% in the bosutinib arm. The estimated difference in MMR rates of asciminib compared to bosutinib at 24 weeks was clinically meaningful and statistically significant 12.2% (95% CI: 2.19, 22.30, p value: 0.029). At the Week 96 cut-off, the clinical superiority of asciminib versus bosutinib increased compared to the primary analysis, the MMR rate in the asciminib arm 37.58% (95% CI: 29.99, 45.65) compared to 15.79 % (95% CI: 8.43, 25.96) in the bosutinib arm.

As of the Week 96 cut-off (06-Oct-2021), 99 of the 233 patients (42.5%) were continuing the study treatment with 84 patients (53.5%) and 15 patients (19.7%) still ongoing in the asciminib and bosutinib arms, respectively. Treatment discontinuations were reported for 45.9% of the patients in the asciminib arm and for 80.3% in the bosutinib arm. Lack of efficacy (defined according to the response milestones in ELN 2013 recommendations) (24.2% in the asciminib arm and 35.5% in the bosutinib arm) remained the most frequently reported reason for treatment discontinuation. The median duration of exposure to study treatment was 103.1 weeks in the asciminib arm and 30.5 weeks in the bosutinib arm (from start of treatment to last treatment as per data cut-off date).

The frequency of AEs was lower in patients on asciminib (91.0%) as compared to bosutinib (97.4%), despite the considerably longer exposure to treatment on asciminib vs bosutinib noted above. In addition, lower percentage of patients with

- Grade ≥ 3 AEs (56.4% vs 68.4%)
- AEs leading to treatment discontinuation (7.7% vs 26.3%)
- AEs Suspected to be treatment-related: 32.7% vs. 52.6%
- Serious AEs: 17.9% vs. 26.3%
- SAEs Suspected to be treatment-related: 3.2% vs. 13.2%
- AEs leading to dose adjustment and/or interruption: 42.3% vs. 64.5%

were reported in the asciminib group as compared to bosutinib group. The most commonly reported AEs in the asciminib and bosutinib treatment arms (≥ 10% in either arm) included the following: thrombocytopenia (23.1% vs. 14.5%, headache (19.9% vs. 15.8%), neutropenia (19.2% vs. 17.1%), fatigue (14.7% vs. 9.2%), hypertension (13.5% vs. 5.3%), arthralgia (12.8% vs. 3.9%), diarrhea (12.8% vs. 72.4%), nausea (11.5% vs. 46.1%), and nasopharyngitis (10.9% vs. 3.9%), anemia (10.3% vs. 7.9%), abdominal pain (9.0% vs. 15.8%), rash (9.0% vs. 23.7%), vomiting (7.7% vs. 26.3%), aspartate aminotransferase increased (5.8% vs. 21.1%), and alanine aminotransferase increased (4.5% vs. 30.3%).

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

Study CABL001X2101

Study X2101 is an ongoing first in human (FIH) dose escalation study. At the time of the primary analysis (cut-off date on 02-Apr-2020) a total of 317 patients with CML-CP/AP or Ph+ ALL have been treated with asciminib monotherapy with dose levels from 10 mg BID to 280 mg BID and dose levels from 80 mg QD to 200 mg QD. or a combination of imatinib, nilotinib or dasatinib.

Asciminib Single Agent

Safety

As of the cut-off date of 02-Apr-2020, 200 patients with CML-CP/AP have been treated with asciminib single agent with dose levels from 10 mg BID to 200 mg BID and dose levels from 80 mg QD to 200 mg QD. Seventy-seven patients (38.5%) discontinued study treatment. The most frequent primary reason for discontinuation was physician's decision (16.0%). Adverse events leading to treatment discontinuation were reported in 19 patients (9.5%). Overall 88% of the patients experienced at least one adverse event suspected to be study related, 44.5% with Grade 3/4 events. 9% of patients experienced at least one Serious Adverse Event (SAE) suspected to be study related. The three most common AEs reported as suspected to be related to asciminib monotherapy in 200 patients with CML-CP or CML-AP were lipase increased (19.5%), fatigue (17.5%) and thrombocytopenia (16.5%). The most common Grade 3/4 events

as suspected to be related to asciminib monotherapy were lipase increased (11%) thrombocytopenia (9.5%), and neutropenia (8%).

No SAEs related to QT prolongation have been observed with asciminib single agent in CML-CP or /AP. QTcF increase > 60 ms from baseline, and new QTcF > 500 ms, were observed in 2/48 (4.2%) patients with CML-CP harboring the T315I mutation treated with single agent asciminib 200 mg BID. In addition, new QTcF > 500 ms was observed in a patient treated with single agent asciminib 80 mg QD.

Efficacy

As per [Asciminib Investigator's Brochure] preliminary data with a cut-off date of 02-Apr-2020, from the ongoing Phase I FIH Study [CABL001X2101] indicate that asciminib exhibits activity as single-agent in patients with CML who have failed at least two prior TKIs or are intolerant to TKIs as well as patients carrying T315I mutation who have failed at least one prior TKI.

Reviewing the totality of the efficacy, safety, and pharmacokinetic data derived from the [CABL001X2101] Study, 40 mg BID single agent dose was recommended for clinical studies in patientswith CML-CP who do not carry T315I mutations and 200 mg BID dose in CML patients carrying T315I mutation.

Asciminib in combination with imatinib, nilotinib or dasatinib

Safety

Twenty-five patients have been treated with a combination of imatinib 400 mg QD and different asciminib dose levels (40 mg BID/QD, 60 mg QD and 80 mg QD). Twelve patients (48.0%) discontinued study treatment. The most frequent primary reason for discontinuation was physician’s decision due to lack of efficacy (16.0%). Adverse events leading to treatment discontinuation were reported in 2 patients (8.0%).

Nausea (48%), abdominal pain (36%) and diarrhea (32%) were the three most common AEs reported in patientswith CML in CP or AP treated with a combination of asciminib and imatinib (all cohorts) regardless of relationship to study drug. Four of 25 patients (16.0%) with CML-CP/-AP treated with a combination of asciminib and imatinib experienced at least one SAE assessed by the investigator as suspected to be related to the study drug: pancreatitis, hepatitis, decreased neutrophil count and myopathy were reported in 1 patient each.

Liver related AEs were seen in 7 of 25 patients (28%) treated with asciminib in combination with imatinib. G3 AST increased, G3 GGT increased and G4 and SAE hepatitis were seen in 1 patient each (4%).

ECG data shows no reported QT prolongation (increase > 60 msec or new > 500 msec) in any asciminib and imatinib combination groups.

Asciminib has been studied in 26 patients with CML-CP/-AP at dose levels of 20 mg BID or 40 mg BID in combination with nilotinib 300 mg QD. Eleven patients (42.3%) discontinued study treatment. The most frequent primary reason for discontinuation was physician’s decision (26.9%, mainly due to lack of efficacy). Only one patient (3.8%) discontinued study treatment due to adverse events.

Asciminib has been studied in 23 patients with CML-CP/-AP at dose levels of 40 mg BID, 80 mg QD and 160 mg QD in combination with dasatinib 100 mg QD. Six patients (26.1%) discontinued study treatment, 3 (13%) patients each due to physician's decision and adverse events respectively.

Efficacy

As per [Asciminib Investigator's Brochure] preliminary data from the ongoing Phase I FIH Study [CABL001X2101] indicate that asciminib in combination with imatinib or nilotinib or dasatinib exhibits activity in patientswith CML who have failed at least two prior TKIs or are intolerant to TKIs.

Based on totality of data, asciminib 40 mg and 60 mg QD dose has been recommended in combination with imatinib 400 mg QD in CML–CP or -AP patients without T315I mutation.

Overall, based on the experience from the ongoing Phase 1 Study, [CABL001X2101], the safety profile of asciminib is acceptable for continued clinical development.

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

Pharmacokinetics

Asciminib, administered as a twice daily and once daily dosing regimen, was rapidly absorbed with a median time to reach maximum plasma concentration (T_{max}) of 2 to 3 hours, independent of dose. Systemic exposure of asciminib, after oral administration of a single dose and multiple doses, as measured by C_{max} and AUC, increased in an approximately dose proportional manner. Generally, the variability of exposure was low to moderate with inter-subject variability (Coefficient of Variation (CV) percentage) ranging from approximately 25% to 70% for both C_{max} and AUC_{last}. With the twice daily dosing regimen, plasma asciminib accumulated slightly with the accumulation ratios ranging from 1.3 to 2.5, while with the once daily dosing regimen there was almost no accumulation of asciminib (1.1 to 1.4).

The data of the human ADME Study [CABL001A2102] show that the relative contribution of the glucuronidation pathway to the total clearance of asciminib via metabolism is estimated to range from 30% to 61%, whereas the relative contribution of the oxidative pathway is estimated to range from 35% to 63%. CYP3A4 was the main contributor for the clearance of asciminib via the oxidative pathway while UGT2B7 and UGT2B17 were responsible for the clearance of asciminib via the glucuronidation pathway. There was no metabolite detected with mean contribution to plasma radioactivity $AUC_{0\text{-}24\ hours} \geq 10\%$. Asciminib was the predominant drug-related component in plasma at all time points analyzed, ranging from 91.9% to 94.2% of the total radioactivity $AUC_{0\text{-}24\ hours}$ AUC, with an average value of 92.7% (half-life is 14.2 hours).

The effect of food on asciminib PK was characterized in a Phase I Study [CABL001A2101] in healthy volunteers using two former variants of the tablet formulation. Food was found to influence the pharmacokinetics of asciminib and exhibited a negative food effect with the two tablet variants. The overall exposure (AUC) decreased by approximately 30% and 65% when administered with a low-fat and high-fat meal, respectively for both tablet variants.

Study [CABL001A2104] assessed the relative bioavailability between a new asciminib tablet formulation (Final Market Image (FMI) 2.2) intended to be used for commercial use and the

clinical service form (CSF) formulation (capsule). The geometric mean ratios and two-sided 90% confidence intervals of the primary PK parameters Area under the plasma drug concentration-time curve from time zero to infinity (AUC_{inf}), AUC_{last} and C_{max} of asciminib for tablet *versus* capsule comparison were 1.00 (0.909, 1.10), 1.01 (0.911, 1.11) and 0.909 (0.805, 1.03), respectively. Therefore, the two formulations have shown similar bioavailability supporting the switch from capsule to tablet. The food effect on this new tablet formulation was assessed in 24 patientsusing an open-label, randomized and cross-over design [CABL001E2101]. A negative food effect was observed following low and high fat meals. Low-fat and high-fat meals decreased the bioavailability of asciminib by ~30% and ~60%, respectively,

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

Exposure-efficacy relationship

A population PKPD is under development. The preliminary pharmacokinetic model for asciminib single agent is described by a two-compartment model with a dual absorption process (zero order absorption process followed by a first order absorption process).

Based on this population PK model, simulations were conducted and revealed that a dose of 40 mg BID maintains Ctroughs above the threshold trough concentration required for 90% inhibition of pSTAT5 derived from a preclinical PK-PD KCL- 22 mouse xenograft model (IC90: 30 to 121 ng/mL, after correction for protein binding) [Asciminib Investigator's Brochure].

Exposure-safety relationship

The relationship between observed plasma asciminib and change from baseline QT interval corrected using Fridericia's correction (ΔQTcF) was assessed in Study [CABL001X2101] (cut-off 15-Jul-2018) in 217 CML and ALL patients receiving monotherapy in range of doses (from 10 mg to 280 mg BID and 80 mg to 200 mg QD). Using the PK-QTcF model, the estimated mean ΔQTcF at the geometric mean Cmax of the highest evaluated dose of 280 mg BID was 5.30 ms (upper bound 90% CI: 7.10 ms), which is below the regulatory threshold of 10 msec. The relationship between observed plasma asciminib concentration and QTcF showed a small, concentration dependent increase in ΔQTcF, which is not clinically relevant up to the highest evaluated dose of 280 mg BID. No clinically significant effect on ΔQTcF is expected at asciminib dose of 60 mg QD being used in the current study.

1.1.1.2 Overview of imatinib

Amongst other approved indications, imatinib (Glivec®/Gleevec®) is indicated for the treatment of adult and pediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) for whom bone marrow transplantation is not considered as the first line of treatment and for the treatment of adult and pediatric patientswith Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis [please refer to the latest Glivec®/Gleevec® local approved product information].

1.1.1.2.1 Non-clinical overview

Imatinib is not genotoxic but it was found to be teratogenic (Glivec®/Gleevec® local approved product information). The fertility of male and female rats was not affected, although there was evidence of effects on spermatogenesis in rats and dogs. Imatinib was carcinogenic in the rat.

In vitro, imatinib was found to be a substrate of CYP3A4/5 and to a smaller extent CYP2C8 and an inhibitor of CYP3A4/5 and CYP2D6 with potential clinical relevance. *In vivo*, a single dose of the potent CYP3A4 inhibitor ketoconazole increased mean maximum concentration (C_{max}) and AUC of imatinib by 26% and 40%, respectively. Co-administration with rifampin, an inducer of CYP3A4, reduced plasma imatinib AUC by approximately 70%. Imatinib increased the C_{max} and AUC of simvastatin by 2- and 3.5-fold, respectively, indicating inhibition of CYP3A4. AUC of the CYP2D6 substrate metoprolol was increased between 17% and 24% by imatinib co-administration.

1.1.1.2.2 Clinical overview

In 2001, imatinib, a BCR::ABL1 tyrosine kinase inhibitor, was approved for the treatment of CML (Cohen et al 2002), and since then more than 100 000 patients received the drug with some patients now on treatment since more than 15 years (Gambacorti-Passerini and Piazza 2015). Results from the Phase 3 International Randomized Study of Interferon and STI571 (IRIS) showed that imatinib at a dose of 400 mg once daily was more active and was associated with fewer side effects than interferon-alfa plus cytarabine in patientswith newly diagnosed CML in chronic phase. At 18 months, the estimated rate of complete cytogenetic response (CCyR) was 76.2% in the imatinib group, as compared with 14.5% in the group that received interferon-alfa plus cytarabine, and the estimated rate of freedom from progression to the accelerated phase or blast crisis of CML was 96.7% *versus* 91.5% (O'Brien et al 2003). In 2017, the final analysis of IRIS Study was published, with a median follow up of 10.9 years. In the imatinib group, the cumulative rate of major cytogenetic response (MCyR) at the end of the trial was 82.8% and among 134patients with cytogenetic assessment at 10 years, 91.8% had CCyR. Among 204 patients who had molecular assessment that could be evaluated at 10 years, 93.1% had major molecular response (MMR) and 63.2% had $M^{R4.5}$. Among the patientsin the imatinib group, the estimated overall survival rate at 10 years was 83% (Hochhaus et al 2017).

Adverse reactions reported by system organ class (>10%) are:

- Blood and lymphatic system disorders: neutropenia, thrombocytopenia, anemia;
- Nervous system disorders: headache;
- Gastrointestinal disorders: nausea, diarrhea, vomiting, dyspepsia and abdominal pain;
- Skin and subcutaneous tissue disorders: periorbital oedema, dermatitis/eczema/rash;
- Musculoskeletal and connective tissue disorders: muscle spasms and cramps, myalgia, arthralgia, bone pain;
- General disorders and administration site conditions: fluid retention and oedema, fatigue;
- Investigations: weight increased.

For further details please refer to the latest Glivec®/Gleevec® local approved product information.

Pharmacokinetics

Imatinib is a biopharmaceutical classification system (BCS) class 1 compound with high absolute bioavailability (98%) that is unaffected by food (Peng et al 2005). Based on an average terminal half-life of 18 hours (range 14 to 25 hours), imatinib exposure is expected to reach steady-state after four continuous daily doses i.e. by day 5 with an accumulation ratio of 1.5- to 2.5-fold at steady state. The rate of absorption of imatinib, when given with a high-fat meal, was minimally reduced (11% decrease in C_{max} and prolongation of T_{max} by 1.5 h), with a small reduction in AUC (7.4%) compared to fasting conditions latest Glivec®/Gleevec® local approved product information. In addition, bioavailability is unaffected by food (Peng et al 2005). The average terminal elimination half-life is approximately 18 hours. *In vitro* metabolism studies indicate that CYP3A4 and to a smaller extent CYP2C8 are the major human P450 enzymes catalyzing the biotransformation of imatinib. The N-desmethyl metabolite CGP74588 was the main metabolite identified in humans, is biologically active and contributes to some extent to the therapeutic effect of imatinib.

In a clinical DDI Study, co-administration of rifampicin, a strong CYP3A4 inducer increased imatinib oral-dose clearance by 3.8-fold, which significantly ($p < 0.05$) decreased mean C_{max} and AUC while co-administration of ketoconazole, a strong CYP3A4 inhibitor increased the average C_{max} and AUC by 26% and 40%, respectively.

Imatinib was also shown to be a competitive inhibitor of marker substrates for CYP2C9, CYP2D6 and CYP3A4/5, with Ki values in human liver microsomes being 27, 7.5 and 7.9 µmol/L, respectively. *In vivo*, the mean exposure to metoprolol, a CYP2D6 substrate, was increased upon imatinib co-administration by 17% in intermediate CYP2D6 metabolizers and by 24% in extensive CYP2D6 metabolizers [CSTI571A2106]. Imatinib increased the C_{max} of the CYP3A4 substrate simvastatin 2-fold and the AUC 3.5-fold as shown [CSTI571A2108]. In a Phase III trial in pulmonary arterial hypertension patients [CQTI571A2301], sildenafil concentrations, both a moderate CYP2C19 and sensitive CYP3A4 substrate were raised by 64% when co-administered with imatinib. Therefore, drugs which are substrates of CYP2C9, CYP2D6 and CYP3A4/5 could have their exposure affected by imatinib.

1.1.1.3 Overview of nilotinib

Nilotinib (Tasigna®) is currently approved for the treatment of adult patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (CP) and accelerated phase (AP) resistant to or intolerant to at least one prior therapy including imatinib and for the treatment of adult patients with newly diagnosed Ph+ CML in CP. Discontinuation of treatment may be considered in eligible Philadelphia chromosome positive (Ph+) CML patients in chronic phase who have been treated with Tasigna at 300 mg twice daily for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy.

Nilotinib is an aminopyrimidine, available as an oral formulation that is an Adenosine triphosphate (ATP)-competitive inhibitor of the protein tyrosine kinase activity of BCR::ABL1, which prevents the activation of BCR::ABL1 dependent mitogenic and anti-apoptotic pathways (e.g. Phosphatidylinositol 3-kinases (PI-3 kinase) and signal transducer and activator of transcription 5 (STAT5)), leading to the death of the BCR::ABL1 phenotype.

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

1.1.1.3.1 Non-clinical experience

In vitro safety pharmacology studies revealed a preclinical signal of potential QT prolongation for nilotinib. Despite these findings no QT interval effects were seen in dogs or monkeys.

The main target organ of toxicity was the liver in dogs and monkeys and to a minor degree in rats and mice. Additional target organs after long term treatment were uterus in rats and skin, growing teeth and thymus in mice.

Nilotinib was embryolethal and produced fetotoxicity in embryo-fetal development studies in rats and rabbits at doses that also produced maternal toxicity. There were no signs of teratogenicity. Nilotinib is transferred into the milk in lactating rats.

Nilotinib is not genotoxic and was not carcinogenic in a rat two year bioassay. In a 26-week Tg.rasH2 mouse model carcinogenicity study skin papillomas/carcinoma occurred at 300 mg/kg/day representing approximately 30 to 40 times (based on AUC) the human exposure at the maximum approved dose 800 mg/day (administered as 400 mg twice a day) while no increase occurred at 100 mg/kg/day (approximately 10 to 20 times human exposure, based on AUC).

In vitro human liver microsomes enzyme inhibition studies revealed that nilotinib could act as an inhibitor of CYP2C8, CYP2C9, CYP2D6, and CYP3A4/5 activity and possibly, but less likely, CYP2C19. Enzyme induction studies indicate that nilotinib can be considered to be an *in vitro* inducer of CYP2B6, CYP2C8, and CYP2C9 activities. Therefore, caution should be exercised when co-administering nilotinib with drugs with narrow therapeutic index that are substrates of these enzymes. Nilotinib is not an effective inhibitor of the human sodium-dependent taurocholate co-transport protein (NTCP). Nilotinib was also found to be a substrate for the P-gp transporter as well as a possible inhibitor of P-gp *in vitro*.

1.1.1.3.2 Clinical experience

The Phase III ENESTnd [CAMN107A2303] - Study assessed the efficacy and safety of nilotinib *versus* imatinib in newly diagnosed Ph+ CML-CP Results showed statistically significant differences in the primary endpoint defined as rate of major molecular response (MMR) at 12 months as well as other secondary endpoints such as CCyR by 12 months and time-to-progression to AP/BC on treatment. These results were confirmed at 24, 36, 48, 60, 72 and 84 months Follow-up, which support superior efficacy of nilotinib over imatinib [Nilotinib Investigator's Brochure].

The most commonly reported (> 5%) all-grade non-hematologic adverse reactions in patients with CML were rash, headache, nausea, pruritus, alopecia, myalgia, dry skin, fatigue, arthralgia,

muscle spasms, vomiting, abdominal pain upper, diarrhea, constipation, peripheral edema, abdominal pain, erythema, dyspepsia and asthenia. Hematologic adverse drug reactions included myelosuppression: thrombocytopenia, neutropenia and anemia. Clinically relevant biochemical abnormalities include hyperglycemia, hyperbilirubinemia, hypophosphatemia, and increases in lipase, ALT, and AST.

Elevations in total cholesterol and low density lipoprotein (LDL) cholesterol have been very commonly observed.

Newly-diagnosed or worsened ischemic vascular or cardiovascular events have occurred in patientstreated with nilotinib. Cardiovascular risk factors should be monitored and managed during nilotinib therapy.

Unchanged nilotinib represents the predominant circulating component in serum. Metabolites do not significantly contribute to the pharmacological activity. Strong inhibitors or inducers of CYP3A4 can significantly alter the pharmacokinetics and systemic exposure of nilotinib in humans, so these drugs should be avoided or nilotinib dose changes should be considered. Hepatic impairment has a modest effect on nilotinib pharmacokinetics; however, impaired renal function is not expected to influence nilotinib pharmacokinetics.

The currently approved dose of nilotinib is 300 mg BID for newly diagnosed Ph+ CMLpatients.

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

1.1.1.4 Potential for drug interaction

There is a potential for drug-drug interaction between imatinib and asciminib.

Effect of imatinib on asciminib

The preliminary clinical data from the first-in human Study [CABL001X2101] suggested an increase in asciminib exposure when co-administered with imatinib. Following administration of asciminib 40 mg BID with imatinib 400 mg QD, the geo mean of the area under the plasma concentration-time curve from time zero to 12 hours ($AUC_{0\text{-}12hours}$) values (coefficient of variation CV percentage, n) of asciminib after first dose on days 1, 8 and 22, respectively were estimated to be 3766 ng.h/mL (16%, n = 5), 8721 ng.h/mL (24%, n = 4) and 8890 (10%, n = 2) compared to 2840 ng.h/mL (57%, n = 27), 5402 ng.h/mL (72%, n = 15) and 5171 ng.h/mL (80%, n = 24), respectively for asciminib alone (~1.3 fold and ~1.7 fold increase on days 1 and after repeated doses, respectively) [Asciminib Investigator's Brochure]. In Study [CABL001X2101], patients were instructed to take asciminib under light meal conditions (i.e. < 400 kcal and 20% fat) when combined with imatinib, and under fasted conditions when administered alone. Asciminib exhibited a negative food effect, with low-fat and high-fat meals decreasing the bioavailability of asciminib by ~30% and 65%, respectively [CABL001A2101]. Hence, the estimate of the DDI magnitude might be reduced in Study [CABL001X2101] as asciminib was to be taken under different food conditions when administered alone or in combination. As a result, taking into account an increase in AUC ratio of asciminib between 1.3 to 1.7 under combination therapy after single and multiple doses, respectively and an additional factor of adjustment on the basis of same food conditions (further increase of around 30%), the DDI might vary between 1.7 and 2.3-fold increase. When integrating the *in vitro* and

in vivo data in a preliminary PBPK model and for a dosing regimen of asciminib doses between 20 and 80 mg QD, the model predictions suggested a 1.21 to 1.70-fold increase in asciminib exposure as measured by AUC under combination with imatinib 400 mg QD after single and multiple doses, respectively. Based on these initial predictions, a drug-drug interaction may be expected, with a weak to moderate increase in asciminib exposure when co-administered with imatinib.

Study [CABL001E2101] confirmed the earlier findings. The study assessed the effect of multiple doses of imatinib on the pharmacokinetics of a single oral dose (low-fat meal) of 40 mg asciminib in healthy patients. The analysis showed that the exposure of asciminib was higher when administered in combination with imatinib compared to when asciminib was administered alone. The asciminib exposure, AUCinf and AUClast was approximately 108% higher and Cmax was 59% higher when administered in combination with imatinib compared to when administered alone. The Tmax was not impacted by the co-administration of imatinib. The effect of imatinib on asciminib may result from the inhibition of several metabolism and transport pathways that are involved in the disposition of asciminib (imatinib is an inhibitor of CYP3A4, UGT and P-gp).

Effect of asciminib on imatinib

Although there is a potential risk for asciminib to alter imatinib pharmacokinetics based on *in vitro* metabolism studies where CYP3A4 appears to be the main enzyme responsible for metabolism of imatinib (Filppula et al 2012), this has not been shown to be of clinical significance based on integration of data from clinical and modeling studies. In healthy patients, ketoconazole, a potent CYP3A4 inhibitor, increased the mean of imatinib C_{max} and AUC by 26% and 40%, respectively, in healthypatients, confirming that imatinib is a CYP3A4 substrate, yet not meeting the criteria of a sensitive substrate [CST5710119]. Asciminib inhibited established marker substrates of CYP3A4/5 *in vitro* in human liver microsomes with IC50 values of 1.5 µM and unbound Ki of approximately 0.348 µM but did not exhibit apparent time-dependent inhibition of CYP3A4/5 at asciminib concentrations of up to 50 µM. The clinical relevance of such interaction is considered limited. The PBPK model predictions did not suggest any clinically relevant DDI for imatinib 400 mg QD when co-administered with BID doses of asciminib up to 40 mg. This is also supported by preliminary human data in Study [CABL001X2101] where there was no apparent change in imatinib steady-state concentration upon co-administration with repeated daily doses of asciminib 40 mg BID [CABL001X2101]. Therefore, the potential for asciminib to affect the pharmacokinetics of imatinib is considered low.

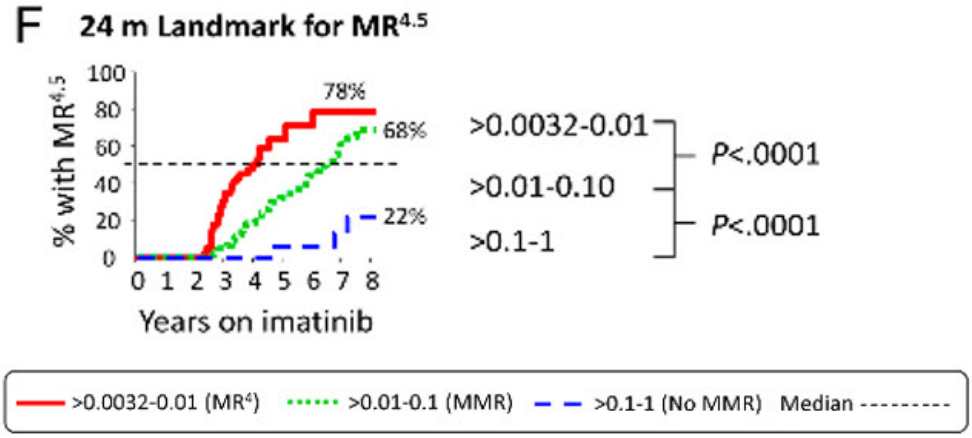
1.2 Purpose

TKIs have revolutionized the treatment of patients with CML, resulting in an overall survival (OS) that is close to that of the general population and therefore a near normal life expectancy. This has consequently drawn emphasis towards the need to improve patient's quality of life, in line with that of the general population. Current treatment guidelines are therefore moving towards discontinuation of treatment in the context of "treatment free remission" (TFR). DMR is a prerequisite for TFR and is therefore emerging as a new treatment goal for CML patients

in chronic phase (NCCN 2018, Rea and Cayuela 2017, Mahon 2016). A sustained DMR for at least 2 years is recognized as one of the essential requirements to attempt discontinuation of TKI therapy in Ph+ CML-CP (NCCN 2018, Baccarani et al 2013, Hochhaus et al 2017). In addition, DMR is associated with improved survival rates and avoidance of disease progression (Cortes 2018, Dulucq and Mahon 2016, Branford 2016, Yeung et al 2015, Hehlmann et al 2014; Etienne et al 2014; Falchi et al 2013). In CML Study IV with frontline imatinib, patients with $MR^{4.5}$ at 4 years had a higher probability of survival at 8 years versus patients with BCR::ABL1 IS of 0.1–1% and no patient who achieved $MR^{4.5}$ in that analysis progressed to accelerated phase/blast crisis by the data cutoff (Hehlmann et al 2014). In a retrospective analysis of patients treated with frontline imatinib, (Etienne et al 2014) reported that confirmed CMR (defined in that study as $MR^{4.5}$) at any time had higher event-free survival (95.2%) versus those with MMR, but not CMR (64.7%), and those who achieved CCyR, but not MMR (27.7%). In another retrospective study by (Falchi et al 2013), a lower risk of losing CCyR, progression to AP or BP, or death in patients with deeper MR was reported. Furthermore, the timing of switch from first line to 2^{nd} line treatment in CML in the context of achieving a faster and deeper molecular response, is also being explored across various studies. Study TIDEL-II studied the effect of early switching from imatinib to nilotinib. Of the 210 patients enrolled in the study, switch to nilotinib occurred in 55 patients for failing to achieve molecular response targets (19, 16 and 20 at 3, 6 and 12 months, respectively). Of the 153 patients in MMR at 24 months, 42 (27%) were reported to have achieved MMR after switch to nilotinib. Of the 71 patients in $MR^{4.5}$ at 24 months, 22 (31%) achieved $MR^{4.5}$ after switch to nilotinib. The study demonstrated improved outcomes when patients were switched from imatinib to nilotinib for non-achievement of BCR::ABL 1 level milestones as per the ELN criteria, at month 3, 6 and 12 (Yeung et al 2015).

The majority of newly diagnosed CML-CP patients is treated with imatinib, but only a proportion of these patients is able to achieve DMR with imatinib treatment. In ENESTnd [CAMN107A2303], the cumulative rates of $MR^{4.5}$ were 23% after 4 years and 33% after 6 years of imatinib treatment (Larson et al 2014). Landmark analysis (Branford et al 2015) performed elsewhere have shown that patientswho have not reached BCR::ABL1 levels of MR^{4} following 24 months of imatinib treatment have low likelihood of achieving DMR with continued treatment; thus these patients would possibly benefit from additional therapy (Figure 1-1).

Figure 1-1 Cumulative incidence of MR$^{4.5}$ according to response level at 24 months of imatinib treatment



Currently, an option for patients who do not achieve the desired level of molecular response with continued imatinib treatment is to switch to a more potent second generation TKI. Results from ENESTcmr [CAMN107A2405] show that, after switching from imatinib to nilotinib, nearly half of the patients without MR$^{4.5}$ at baseline will still not achieve this level of response even after 4 years of switch. Furthermore, second generation TKIs harbor a distinct toxicity profiles as compared to imatinib, and therefore can pose tolerability concerns, especially for patients who have associated co-morbidities. Hence, there is an unmet need for active and safer regimens for the aforementioned patients (Branford et al 2015).

Asciminib is an allosteric inhibitor of BCR::ABL1 which targets the autoregulatory myristoyl binding pocket compared to the catalytic TKIs. Due to its distinct pharmacological profile and as shown by preclinical pharmacological studies demonstrating an additive anti-tumor activity, a combination of asciminib and an ATP-binding site TKI has the potential to achieve a DMR in a higher proportion of CML patients as compared to single agent TKI therapy. Additionally, targeting the ABL kinase domain at two distinct locations through the combination can theoretically prevent the emergence of single point mutation-associated treatment resistance. The value of non-overlapping resistance profiles was evident in mouse models where durable treatment-free regressions were observed with upfront administration of a nilotinib-asciminib combination (Wylie et al 2017). Furthermore, a study conducted by Saunders et al. showed that *in vitro* kinase inhibition achieved with asciminib in combination with imatinib, nilotinib or dasatinib is greater than that achieved with TKIs alone, even at concentrations 1000-fold lower than the average peak plasma concentration on asciminib 40 mg BID (currently investigated monotherapy dose), suggesting that simultaneous targeting of the myristate and ATP binding pockets may be more effective than targeting either side alone. Especially, patients with high IC_{50}, who would be predicted to respond poorly to imatinib, could have dramatically increased kinase inhibition with the addition of low doses of asciminib (Saunders 2016).

The addition of asciminib to imatinib is expected to result in more potent inhibition of the ABL kinase domain enhancing clinical efficacy. It is hypothesized that the addition of asciminib in patients who have not achieved DMR with single agent imatinib will increase their likelihood

of achieving this response over time and may allow TKI discontinuation in the context of TFR. The purpose of this trial is to evaluate the efficacy and safety of asciminib added on to imatinib treatment in comparison to continued imatinib in patients who have not achieved MR^4 after at least one year of imatinib first-line treatment. As a secondary endpoint, the difference in efficacy between the combination and nilotinib, a second generation TKI, will be estimated.

This amendment aims to add an asciminib single agent cohort to assess whether asciminib single agent at the recommended dose of 80mg QD leads to similar efficacy and safety as observed in the add-on arms of asciminib and imatinib. This additional cohort will help to evaluate if the combination of asciminib with imatinib is needed to increase the likelihood of achieving DMR, or if this can be achieved by asciminib alone. The primary analysis results show activity of asciminib as an add-on therapy to imatinib, assessed by MR4.5 rate at Week 48. The MR 4.5 rate at Week 48 was 19%, 28.6%, 0% and 4.8% in the asciminib 40 mg + imatinib, asciminib 60 mg + imatinib, continued imatinib and switch to nilotinib arm (Mauro et al, 2021). Results from other single agent studies in patients with CML-CP who have been treated with at least 2 prior TKIs have shown activity of single agent asciminib for achievement of DMR in this heavily pretreated population. In Study A2301, MR4 and MR4.5 rates of 10.8% and 7.6%, respectively were observed at Week 48. In the subgroup of patients with baseline BCR::ABL1 levels ($> 0.01\%$ and $\leq 1\%$), the MR4.5 rate (18.8%, 3 responders among 16 patients) was similar to that observed in E2201 with the asciminib as add on to imatinib at the primary analysis (data on file).

2 Objectives and endpoints

Objectives and related endpoints are described in Table 2-1.

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess whether asciminib 40 mg QD + imatinib or asciminib 60 mg QD + imatinib is more effective than continued imatinib	• Molecular Response (MR)$^{4.5}$ rate at 48 weeks
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• - To estimate efficacy of switch to nilotinib - To estimate difference in efficacy between asciminib 60 mg + imatinib and switch to nilotinib - To estimate difference in efficacy between asciminib 40 mg + imatinib and switch to nilotinib	• - Molecular Response (MR)$^{4.5}$ rate at 48 weeks - Difference in rate of $MR^{4.5}$ at 48 weeks
• To assess additional parameters of the efficacy of - asciminib 60 mg added to imatinib vs continued imatinib or switch to nilotinib - asciminib 40 mg added to imatinib vs continued imatinib or switch to nilotinib	• - Rate of $MR^{4.5}$ at 96 weeks - Rate of $MR^{4.5}$ by 48 and 96 weeks - Sustained $MR^{4.5}$ at 96 weeks - Time to $MR^{4.5}$ - Duration of $MR^{4.5}$
• To characterize the safety and tolerability profile of asciminib 60 mg or 40 mg + imatinib vs continued imatinib or switch to nilotinib	• Incidence and severity of adverse events, changes in laboratory values, clinically notable ECG abnormalities and vital signs

Objective(s)	Endpoint(s)
• To assess the pharmacokinetic profile of asciminib 60 mg or 40 mg and imatinib when administered in combination	• Plasma concentrations of asciminib and imatinib when administered in combination. PK parameters include but are not limited to C_{max}, T_{max}, C_{min}, AUC_{last} and AUC_{tau}
• To estimate efficacy of asciminib 80 mg QD	• -Molecular Response (MR)[4.5] rate at 48 weeks -Time to MR[4.5] -Duration of MR[4.5]
• To characterize the safety and tolerability profile of asciminib 80 mg QD	• Incidence and severity of adverse events, changes in laboratory values, clinically notable ECG abnormalities and vital signs
• To assess the pharmacokinetic profile of asciminib 80 mg QD.	• Plasma concentrations of asciminib. PK parameters include but are not limited to C_{max}, T_{max}, C_{min}, AUC_{last} and AUC_{tau}
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
• To describe the efficacy and safety of asciminib 60 mg + imatinib in patients randomized to continued imatinib who crossover to receive asciminib 60 mg + imatinib	• - Efficacy endpoints such as time to MR[4.5] and duration of MR[4.5] - Safety endpoints such as incidence and severity of adverse events, changes in laboratory values, clinically notable ECG abnormalities and vital signs
• To assess the proportion of patients eligible for TFR at end of the study	• Patients, with sustained MRD* (Minimal Residual Disease) at the end of the study (i.e. 96 weeks after the first dose of study drug of the last randomized subject) * Please refer to glossary for the MRD definition
• To explore relevant CCI [redacted] , as well as CCI [redacted]	• Analysis of CCI [redacted]
• To explore CCI [redacted]	• CCI [redacted]
• To evaluate CCI [redacted]	• CCI [redacted]
• To explore the impact of treatment on patient reported outcomes (PROs) including CML-specific symptom assessment (disease and treatment), treatment satisfaction and overall impact of side effects of treatment from baseline	• Overall Scores and individual domains for EORTC QLQ-C30 plus CML24, FACIT GP5 and TSQM questionnaire

3 Study design

The study is a Phase 2, multi-center, open-label, randomized study of asciminib + imatinib *versus* continued imatinib *versus* switch to nilotinib in patients with CML-CP who have been previously treated with imatinib first line therapy for at least one year (12 calendar months) and have not achieved DMR.

The trial is designed to assess the activity of 2 doses of asciminib + imatinib QD *versus* imatinib continuation, and to estimate the difference compared to switch to nilotinib, assessed by the rate of $MR^{4.5}$ at 48 weeks as well as additional efficacy parameters, PK, biomarkers, PROs and safety and tolerability. Additionally, the study will estimate safety and efficacy of single agent asciminib.

Approximately eighty eligible patients will be randomized in a 1:1:1:1 ratio to receive study treatment in the below arms:

Treatment arm 1: asciminib 40 mg QD as add-on therapy to imatinib 400 mg QD, or

Treatment arm 2: asciminib 60 mg QD as add-on therapy to imatinib 400 mg QD, or

Treatment arm 3: to continue imatinib 400 mg QD, or

Treatment arm 4: to switch to nilotinib 300 mg BID

The asciminib single agent cohort will be conducted as an open label cohort. Approximately 20 eligible patients will be enrolled to receive asciminib 80 mg QD.

In Treatment arms 1-4, patients on the study will continue on the allocated treatment until treatment failure, intolerability, or for up to 96 weeks after the last randomized subject received the first dose of treatment . After the last dose received every subject will be followed up for safety for 30 days.

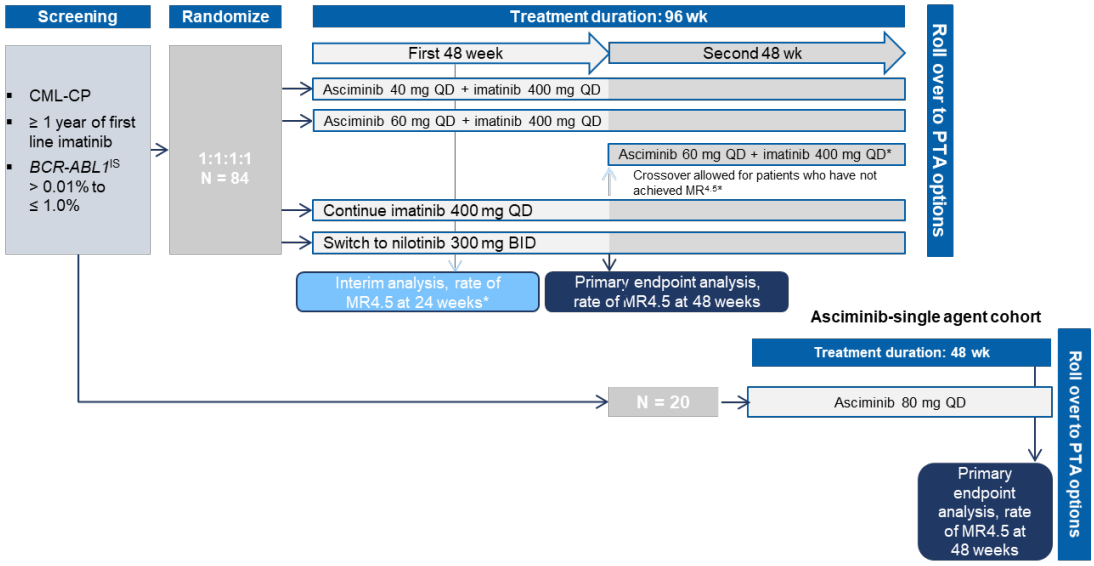
For patients in the asciminib single agent cohort, patients will continue on asciminib treatment until treatment failure, intolerability, or for up to 48 weeks after the last enrolled subject in the cohort received the first dose of treatment. After the last dose received every subject will be followed up for safety for 30 days.

Interim analysis An interim analysis will be performed when at least 40 (50%) patients have been randomized and have been followed for their 24 weeks visit assessment or have discontinued treatment. At the time of the interim analysis, if excessive toxicity without added benefit is observed in one of the investigational arms, discontinuation of that treatment arm will be considered. The decision to discontinue an investigational arm in the study will be taken based on the risk benefit balance of the two investigational arms, and in context of the other two treatment options available for the patients in the study, namely: continue on imatinib with no potential improvement of efficacy; or switch to nilotinib with a potential to improve efficacy however, with a relatively adverse safety profile as compared to imatinib. If a decision is taken to discontinue asciminib 60 mg + imatinib treatment arm at interim analysis, patients ongoing on that treatment arm will be provided an opportunity to continue on the study at a lower dose (asciminib 40 mg + imatinib) if the investigator considers that is in the best interest of the patient.

Crossover for patients in the imatinib arm

Patients who were randomized to continue on imatinib single agent treatment but who have not achieved $MR^{4.5}$ at 48 weeks may cross-over to receive the add-on within 4 weeks after week 48 visit (Figure 3-1). It is planned that these patients cross-over to receive the asciminib 60 mg + imatinib, as this dose provides higher exposure see (Section 4.2). If a decision is taken to discontinue asciminib 60 mg + imatinib treatment arm at interim analysis or upon emerging data, cross-over may be changed to asciminib 40 mg + imatinib treatment arm. The cross-over is at discretion of the investigator and the patient. Apart from a PCR result of below $MR^{4.5}$ at Week 48 visit, there are no other entry criteria for the cross-over part. Patients on nilotinib are not allowed to cross-over to receive the add-on treatment.

Figure 3-1 Study design



(*)Patients on the imatinib continuation arm who have not achieved $MR^{4.5}$ at 48 weeks may cross-over to receive the asciminib 60 mg add-on treatment. Based on the results of the interim analysis or emerging data, cross-over may be changed to asciminib 40 mg + imatinib arm.

Primary analysis

For patients in treatment arms 1 – 4, the primary analysis for the study will be performed when all patientshave completed the Week 48 visit or have discontinued treatment early.

End of Study Treatment period

The end of study treatment period for patients in Treatment arms 1-4 will be at 96 weeks (plus 30 days for the safety follow up) after the last randomized subject received the first dose of study treatment.

The end of study treatment period for patients in the asciminib single agent cohort will be at 48 weeks (plus 30 days for the safety follow up) after the last enrolled subject in that cohort received the first dose of study treatment.

Post-Trial Access

For patients who in the opinion of the investigator are continuing to benefit from the study drug(s), efforts will be made to continue providing the study treatment outside the study. Options include, but are not limited to, a post-trial access program or access to commercial supplies in applicable countries.

4 Rationale

4.1 Rationale for study design

The development of asciminib presents an opportunity to evaluate the beneficial effects of a combined inhibition of BCR::ABL1 together with ATP-binding site TKIs (e.g. imatinib) for greater pharmacological control of BCR::ABL1 in the treatment of patients with CML. The proposed study design will allow an assessment of the efficacy, safety, tolerability and patients reported outcomes of asciminib + imatinib in a population of patients with continuing medical need of achieving DMR. To characterize the pharmacokinetics of asciminib in the proposed patient population and assess the potential for drug-drug-interaction with imatinib (compared to historical data), PK samples of asciminib will be collected.

The study randomizes patients 1:1:1:1 in four arms to assess efficacy and safety of the combination of asciminib and imatinib *versus* imatinib, and to estimate the difference in efficacy and safety between nilotinib and the combination arms. For patients randomized to continue imatinib, a cross-over to receive asciminib + imatinib after 48 weeks is implemented should they not have achieved $MR^{4.5}$ at the time of the primary endpoint. This will allow patients without $MR^{4.5}$ after continuation of imatinib to potentially benefit from the combination treatment.

This study is conducted as an open label study; the conditions for drug administration being distinct for the four treatment arms makes blinding very complex and would increase the likelihood of dosing errors. Additionally, the characteristic adverse event profile of each of the drugs further preclude effective blinding.

4.1.1 Rationale for addition of asciminib single agent cohort

The primary analysis cut-off for the study was performed on 10-Jan-2022. The results of the primary analysis showed activity of asciminib as an add-on therapy to imatinib, assessed by deep molecular response ($MR^{4.5}$) rate at 48 weeks. $MR^{4.5}$ was achieved in higher number of patients in asciminib 60 mg + imatinib arm as compared to continued imatinib and switch to nilotinib arm. At Week 48, 6 (28.6%) patients in asciminib 60 mg + imatinib arm and 4 (19 %) patients in asciminib 40 mg + imatinib arm achieved $MR^{4.5}$ and 1 patient (4.8%) in the nilotinib arm achieved $MR^{4.5}$. No patients in the imatinib arm achieved $MR^{4.5}$ by Week 48.

In study A2301 in heavily pre-treated patients (≥3L CML-CP) treated with asciminib 40 mg BID, the $MR^{4.5}$ rate at week 48 was 7.6% in the asciminib arm. Of the patients with BCR::ABL1 levels >0.1≤1% at baseline, $MR^{4.5}$ response rate was 18.8% (3 responders among 16 patients) at Week 48.

Adding an asciminib single agent cohort to assess the efficacy and safety at the recommended dose of asciminib in >3L CML-CP of 80 mg QD will help to evaluate if the combination of asciminib with imatinib is needed to increase the likelihood of achieving DMR, or if this can be achieved by asciminib alone.

At the primary analysis in E2201, asciminib as add-on to imatinib was well tolerated. Adverse events leading to discontinuation were reported for 4.8% patients in the asciminib 40 mg + imatinib arm, 14.3% patients in the asciminib 60 mg + imatinib, 23.8% patients in nilotinib arm and none in imatinib arm. Safety profile of asciminib add-on to imatinib was similar to that of asciminib single agent observed in the studies in heavily pretreated patients (Hughes et al 2019; Mauro 2021).

The exposure (AUCtau) of asciminib obtained in this study with asciminib 60 mg QD + imatinib (in the fed state) was similar than the exposure in study X2101 obtained with single agent asciminib 80 mg QD (in the fasted state). The Cmax was approximately 60% higher in X2101 at 80 mg QD compared to asciminib 60 mg QD + imatinib in this study.

Single agent treatment, if able to deliver the same benefit to the patient would be preferable over treatment with two agents, with the potential to be safer and more tolerable for long term treatment needed by patients with CML-CP. Thus, the addition of the asciminib single agent cohort aims to investigate the efficacy and safety of single agent 80 mg QD asciminib in the current study.

4.2 Rationale for dose/regimen and duration of treatment

Currently the majority of newly diagnosed CML-CP patients are treated with imatinib at the dose of 400 mg QD. Imatinib is administered with a light meal at the dose of 400 mg QD in this study. Therefore, it is desirable to follow the same conditions of administration for asciminib. The exposure resulting from the Recommended Phase 2 Dose (RP2D) in CML-CP (40 mg BID monotherapy) is expected to be altered by the combined effect of drug interaction and food effect and may require a dose adjustment to achieve comparable exposure to the established RP2D (refer to Section 1.1.1.4).

The two doses of 40 mg or 60 mg administered daily in combination with imatinib 400 mg QD provide pharmacologically active exposure with different PK profiles; the benefit/risk ratio of each dose level needs to be further established. Indeed, 60 mg asciminib QD in combination with imatinib with low fat meals leads to comparable exposure to the monotherapy R2PD as measured by AUC, and higher C_{max} by approximately 1.6 to 1.9-fold, while AUC was lower with asciminib 40 mg QD (approximately 40%) but with C_{max} close to RP2D. Based on PK/DDI data, safety and tolerability, both combination doses will be investigated in this study.

The safety profile of asciminib QD doses (40mg, 60 mg and 80 mg) has been evaluated in combination with imatinib 400 mg QD. Dose Limiting Toxicities (DLTs) have been observed at all dose levels, 1 in 9 patients in the asciminib 40 mg QD cohort (neutrophil count decreased G4), 2 in 6 patients in the asciminib 60 mg QD cohort (abdominal pain G3, nausea G3) and 2 in 4 patients in the asciminib 80 mg QD cohort (pancreatitis G2, lipase increased G3). From clinical point of view and supported by the Bayesian Logistic Regression Model (BLRM), both

asciminib 40 mg QD and 60 mg QD seem to be appropriate in combination with imatinib 400 mg QD.

The duration of treatment will allow both for detection of early activity and tolerability of the combination *versus* continued imatinib or switch to nilotinib as well to confirm the results at later time points up to 96 weeks.

The asciminib single agent cohort will evaluate asciminib at a dose of 80mg once-daily (QD) for 48 weeks.

The asciminib dose of 80 mg QD is based on the clinical experience in patients with CML-CP in studies X2101 and A2301 and PK/PD modelling based exposure-response and exposure-safety analyses (Please refer to the latest [Asciminib Investigator's Brochure] for more details). Asciminib 80 mg QD has been approved by the FDA for the treatment of adult patients with Ph+ CML in CP, previously treated with 2 or more TKIs. The ongoing study CABL001J12301 investigating efficacy and safety of single agent asciminib in patients with newly diagnosed CML is assessing asciminib at a dose of 80 mg QD. The duration of treatment of 48 weeks will allow for detection of anti-leukemic activity and tolerability of single agent asciminib in the study.

4.3 Rationale for choice of comparator and combination drugs

Preclinical evidence supporting the rationale for the combination of an ATP-binding site TKI and asciminib is described in previous sections (Section 1.1.1.1, Section 1.1.1.2 and Section 1.2). The majority of newly diagnosed CML-CP patients are treated with imatinib, which has a well-defined tolerability profile. For patients on imatinib, where the treatment goal is to achieve DMR, e.g. in the context of attempting TFR, the addition of asciminib could be an efficacious and safe treatment option.

Both ELN (European Leukemia Network) and NCCN (National Comprehensive Cancer Network) guidelines recommend the use of imatinib as approved first line treatment for CML-CP, as well as other approved agents, including nilotinib. Robust clinical evidence has been generated so far with imatinib as first line treatment and it has been selected as comparator arm for the primary study endpoint. Being the investigational arms asciminib in combination with imatinib, keeping imatinib as comparator will support the assessment of the asciminib single agent contribution in the investigational arm. Imatinib will be administered at 400 mg QD.

The choice of nilotinib as comparator is supported by results from ENESTcmr [CAMN107A2405] Study which showed that patients with residual disease after at least two years of imatinib treatment can achieve higher rate of $MR^{4.5}$ when treatment is switched to nilotinib as compared to continuation with imatinib. Together with results from the ongoing ENESTop [CAMN107A2408] Study this suggests that a higher proportion of patientsswitching to nilotinib will be eligible for TFR (Hughes et al 2016). Thus nilotinib constitutes a current treatment option for patients in the target population with the goal of a deep molecular response. The comparison to nilotinib will allow to estimate the difference in regards of efficacy and tolerability *versus* the combination therapy.

Based on data from ENESTnd [CAMN107A2303], the safety profile of the nilotinib 300 mg BID dose is more favorable in terms of tolerability, AEs and laboratory evaluation than the

nilotinib 400 mg BID dose, while showing similar efficacy. Additionally, the frequency of AEs leading to discontinuation was lower in the 300 mg BID arm compared to the 400 mg BID arm. As CML-CPpatients who are in CCyR but less than MR^4 are not considered to be treatment failure according to current treatment guidelines, the selection of 300 mg BID dose for the nilotinib treatment arm is considered appropriate.

4.4 Purpose and timing of interim analyses/design adaptations

An interim analysis will be performed in order to gain an early insight into the safety and efficacy of the asciminib add-on combination which will help in planning the future development of the asciminib combination. The interim analysis will be performed when at least 40 (50%) patients have been randomized and have been followed for their 24 weeks visit assessment or have discontinued treatment. The enrollment will continue during this 24 weeks follow-up. The interim analysis will include all randomized patients until the date of data cut-off, and include both efficacy (e.g. BCR::ABL1 assessment overtime, MR^4 and $MR^{4.5}$ rate at different time-points) and safety (e.g. Adverse Events and laboratory values) summaries, which will be detailed in the Statistical Analysis Plan for the interim analysis.

The interim analysis is planned to provide early insights into the safety and efficacy parameters to inform the benefit risk assessment of asciminib as an add-on therapy to imatinib. If excessive toxicity without added benefit is observed in one of the investigational arms, discontinuation of that treatment arm will be considered. The decision of discontinuation of an investigational arm in the study will be taken based on the risk benefit balance of the two investigational arms, and in context of the other two treatment options available for the patients in the study, namely: continue on imatinib with no potential improvement of efficacy; or switch to nilotinib with a potential to improve efficacy however, with a relatively adverse safety profile as compared to imatinib. If a decision is taken to discontinue asciminib 60 mg + imatinib treatment arm at interim analysis, patients ongoing on that treatment arm will be provided an opportunity to continue on the study at a lower dose (asciminib 40 mg + imatinib) if the investigator considers that is in the best interest of the patient. Additionally, cross-over arm may be changed to asciminib 40 mg + imatinib treatment arm. It is not planned to write an interim CSR based on this interim analysis.

4.5 Risks and benefits

The benefit-risk for asciminib remains positive for the treatment of Ph+ CML and Ph+ALL patients with or without mutations conferring resistance to ATP-competitive inhibitors, including the T315I mutation.

The most frequent adverse reactions to asciminib administered in monotherapy (in >20% patients) include headache (23.6%), fatigue (22.8 %), thrombocytopenia (22.8%), arthralgia (21.3%) and nausea (20.2%). Thrombocytopenia (15.2%), neutropenia (11.8 %) and lipase increased (10.7%) were the most frequently reported (>10.0 %) Grade ≥3 events.

The important identified risks of asciminib include pancreatic toxicity (amylase and lipase elevations), myelosuppression and QT prolongation. Important potential risks include, hepatotoxicity including hepatic transaminase and bilirubin elevations, reproductive toxicity and Hepatitis B viral reactivation. Important potential class risks include cardiac failure, edema

and fluid retention, hemorrhage and ischemic heart and CNS conditions. Of note the risks which have been demoted are gastrointestinal toxicity, hypersensitivity and phototoxicity.

The most common adverse reactions to asciminib administered in combination with imatinib (in > 10% patients) include nausea (25%) and lipase increased (15%).

The important identified risks of nilotinib, authorized for over 10 years, include QT prolongation, myelosuppression, cardiovascular events, significant bleeding, severe infections, hepatotoxicity, pancreatitis, lipase and amylase elevations, fluid retention, blood glucose increased, blood cholesterol increased, use in patients with hepatic impairment and interactions with strong CYP3A4 inhibitors, strong CYP3A4 inducers, sensitive CYP3A4 substrates and food. The important identified risks of nilotinib include sudden death, cardiac failure, reproductive toxicity, skin malignancy, and interactions with P-gp inhibitors, drugs eliminated by CYP2C8, CYP2C9, CYP2D6 or substrates of UGT1A1, and P-gp and OCT1 transporters and drugs that may prolong the QT interval.

In this trial, the aforementioned risks are managed through detailed information provided in the IB and requirements delineated in the study protocol. The latter include exclusion criteria, which limit enrollment of patients at unacceptable safety risks, required assessments/monitoring and recommendations for the management of adverse events including dose reduction and interruption. There may be unforeseen risks with study treatment which could be serious.

Refer to the latest [Asciminib Investigator's Brochure] and the latest local product information for imatinib and nilotinib.

Women of child bearing potential must be informed that taking the study treatment may involve 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 subject will not reliably comply, they should not be entered or continue in the study.

Imatinib, on the other hand, already on the market for more than 15 years, has a well-known efficacy profile, with high molecular and cytogenetic response rates offering an efficacious treatment to CMLpatients, and very low rates of severe non-hematological adverse events, as well as an acceptable hematological toxicity. Only a minority of patients treated with imatinib first-line will have a high likelihood of achieving DMR, allowing patients to become eligible for TFR (Branford et al 2015).

Preclinical studies demonstrated that the combination of asciminib and imatinib is potentiating the inhibition of the BCR::ABL1 kinase (Saunders 2016), especially for patients predicted to respond poorly to imatinib. Furthermore targeting the kinase at two distinct locations and the value of non-overlapping resistance profiles was evident in a xenograft model, with durable treatment free remission observed with the administration of asciminib and an ATP-binding site TKI (Wylie et al 2017). This additive anti-tumor activity suggests a higher proportion of patients achieving a DMR compared to imatinib mono-therapy, and subsequently allow for consideration of TKI discontinuation.

In summary, the combination of imatinib and asciminib represents an oral therapy option with a potentially high benefit-risk ratio for the treatment of patients with CML. This is also

supported by data (albeit limited) from the ongoing combination cohort of [CABL001X2101] Study showing good tolerability and no new safety signals.

A potential risk for patients enrolling in the combination arm of the study is that the addition of asciminib may lead to no improved efficacy in terms of depth of response while exposing the subject to additional toxicity. However, the preclinical evidence to date (see Section 1.1.1.1) supports the hypothesis of a potentiation of activity. Furthermore, the adverse event profile of asciminib is similar qualitatively to that observed with other TKIs targeting BCR::ABL1. The risk of asciminib in combination with imatinib not being effective is mitigated by observing patients closely for evidence of efficacy, based on molecular response data, which will permit rapid decision making, and discontinuation of therapy if necessary (see Section 12 data analysis).

4.6 Rationale for public health emergency mitigation procedures

During a public health emergency as declared by local or regional authorities e.g., pandemic, epidemic, or natural disaster, mitigation procedures to ensure participant safety and trial integrity may be implemented. Notification of the public health emergency as declared by local or regional authorities should be discussed among investigators and Novartis. All procedures adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment for approval by local or regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures.

5 Population

Approximately eighty patients with CML-CP who have been previously treated with imatinib and have not achieved deep molecular response will be randomized in a 1:1:1:1 ratio to receive asciminib 60 mg as add-on therapy to imatinib, or asciminib 40 mg as add-on therapy to imatinib, or to continue imatinib, or to switch to nilotinib.

Approximately twenty patients with CML-CP who have been previously treated with imatinib for at least 1 year and have not achieved deep molecular response will be enrolled in the asciminib single agent cohort to receive asciminib 80 mg QD. The definition of CML-CP will be according to European Leukemia Network criteria (Baccarani et al 2013).

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

Patientseligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Male or female patients ≥ 18 years of age with a confirmed diagnosis of CML-CP defined as:
    - < 15% blasts in peripheral blood and bone marrow
    - < 30% blasts plus promyelocytes in peripheral blood and bone marrow

- < 20% basophils in the peripheral blood
- ≥ 100 x 10^9/L (≥ 100 000/mm^3) platelets
- No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly

3. b. Minimum of one year (12 calendar months) treatment with imatinib first line for CML-CP (patients have to be on imatinib 300 mg QD or higher)).
4. a. BCR::ABL1 levels > 0.01% IS and ≤ 1% IS at the time of randomization as confirmed with a central assessment at screening; patients must not have achieved deep molecular response (MR^4 IS) confirmed by 2 consecutive tests at any time during prior imatinib treatment. An isolated, single test result with BCR::ABL1 levels < 0.01 % (MR^4 IS) is allowed, however it should not have been observed within the 9 months prior to randomization
5. a. Patient must meet the following laboratory values before randomization:
   - Absolute Neutrophil Count ≥ 1.5 x 10^9/L
   - Platelets ≥ 75 x 10^9/L
   - Hemoglobin (Hgb) ≥ 9 g/dL
   - Serum creatinine < 1.5 mg/dL
   - Total bilirubin ≤ 1.5 x ULN except for patients with Gilbert's syndrome who may only be included with total bilirubin ≤ 3.0 x ULN
   - Aspartate transaminase (AST) ≤ 3.0 x ULN
   - Alanine transaminase (ALT) ≤ 3.0 x ULN
   - Alkaline phosphatase ≤ 2.5 x ULN
   - Serum lipase ≤ 1.5 x ULN. For serum lipase > ULN - ≤ 1.5 x ULN, value must be considered not clinically significant and not associated with risk factors for acute pancreatitis
6. a. Patients must have the following laboratory values (≥ LLN) or corrected to within normal limits with supplements prior to randomization:
   - Potassium (potassium increase of up to 6.0 mmol/L is acceptable 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 if associated with creatinine clearance* within normal limits)
   - Magnesium (magnesium increase of up to 3.0 mg/dL or 1.23 mmol/L if associated with creatinine clearance* within normal limits)

   *Creatinine clearance as calculated using Cockcroft-Gault formula

5.2 Exclusion criteria

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

1. Treatment failure according to European Leukemia Network criteria (Baccarani et al 2013) during imatinib treatment.

- after 3 months of treatment no Complete Hematologic Response (CHR) and/or Ph+ > 95%
- after 6 months of treatment BCR::ABL1 > 10% and/or Ph+ > 35%
- after 12 months of treatment BCR::ABL1 > 1% and/or Ph+ > 0
- at any time loss of CHR, loss of CCyR, confirmed loss of MMR*, mutations, clonal chromosomal abnormalities in Ph+ cells (CCA/Ph+)

*In 2 consecutive tests, of which one with a BCR::ABL level ≥1%.

2. Known second chronic phase of CML after previous progression to AP/BC.
3. Previous treatment with any TKIs other than imatinib.
4. History or current diagnosis of ECG abnormalities indicating significant risk or safety for patients participating in the study such as:
   - History of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG) within 6 months prior to randomization
   - Concomitant clinically significant arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
   - Resting QTcF ≥ 450 msec (male) or ≥ 460 msec (female) prior to randomization
   - 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 including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
     - Concomitant medications with a "known" risk of Torsades de Pointes per crediblemeds.org that cannot be discontinued or replaced by safe alternative medication
     - inability to determine the QTcF interval
5. 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, uncontrolled clinically significant hyperlipidemia and high serum amylase).
6. History of acute pancreatitis within 1 year prior to randomization or medical history of chronic pancreatitis.
7. a. History of chronic liver disease or ongoing acute liver disease.
8. History of other active malignancy within 3 years prior to randomization with the exception of basal cell skin cancer, indolent prostate cancer and carcinoma in situ treated curatively.
9. a. Known history of Human Immunodeficiency Virus (HIV), chronic Hepatitis B (HBV), or chronic Hepatitis C (HCV) infection. Testing for Hepatitis B surface antigen (HBsAg), and Hepatitis B core antibody (anti-HBc) will be performed at study entry. If HBsAg or anti-HBc is positive, Hepatitis B surface antibody (anti-HBs) and/or HBV-DNA measurement is recommended to confirm negative viral status.

10. 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).
11. a. Treatment with strong inducers or inhibitors of CYP3A that cannot be discontinued or switched to a different medication at least one week prior to the start of treatment and for the duration of the study.
12. Patients must avoid consumption of grapefruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.
13. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes.
14. Participation in a prior investigational study within 30 days prior to randomization or within 5 half-lives of the investigational product, whichever is longer.
15. c. (i) Pregnant or nursing (lactating) women.

    (ii) Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and for 14 days after stopping study medication in treatment arms 1- 4, or for 3 days after stopping asciminib single agent treatment. 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 bilateral tubal ligation, female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), or total hysterectomy, 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 patients on the study, the vasectomized male partner should be the sole partner for that subject.
    - 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 study treatment.

    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 prior to enrollment on study. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered to be not of child bearing potential.

If local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the Informed Consent Form (ICF).

16. Patients who have achieved deep molecular response (MR^4 IS), confirmed by 2 consecutive tests at any time during prior imatinib treatment.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

6 Treatment

6.1 Study treatment

The study treatments are asciminib (60 mg QD), asciminib (40 mg QD), asciminib (80 mg QD), imatinib (400 mg QD) and nilotinib (300 mg BID). Novartis will supply all compounds to the investigational sites: asciminib as 40 mg and 20 mg tablets, imatinib as 400 mg and 100 mg tablets and nilotinib as 150 mg and 200 mg hard gelatin capsules.

6.1.1 Study drugs

Table 6-1 Study drug

Treatment Title	Asciminib (ABL001) 20 mg	Asciminib (ABL001) 40 mg	Glivec®/Gleevec® (STI571) 100 mga	Glivec®/Gleevec® (STI571) 400 mg	Tasigna® (AMN107) 150 mg	Tasigna® (AMN107) 200 mgb
Treatment Description	Dose and treatment schedule are described in the Table 6-5 and all the information about the administration of the study drug are described in the Section 6.1.3. Dose reductions can be performed as described in Table 6-3					
Type	Drug	Drug	Drug	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Tablet	Tablet	Hard gelatin capsule	Hard gelatin capsule
Unit Dose Strength(s)	20 mg	40 mg	100 mg	400 mg	150 mg	200 mg
Dosage Level(s)	Dose amount and frequency are mentioned in Section 6.7.2					
Route of Administration	Oral	Oral	Oral	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental	Experimental	Experimental	Experimental
IMP	Yes	Yes	Yes	Yes	Yes	Yes

Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study treatment will be provided in a bottle. Each bottle will be labeled as required per country requirement.	Study treatment will be provided in a bottle. Each bottle will be labeled as required per country requirement.	Study treatment will be provided in a bottle. Each bottle will be labeled as required per country requirement.	Study treatment will be provided in HDPE bottle. Each HDPE bottle will be labeled as required per country requirement.	Study treatment will be provided in HDPE bottle. Each HDPE bottle will be labeled as required per country requirement.	Study treatment will be provided in HDPE bottle. Each HDPE bottle will be labeled as required per country requirement.

6.1.2 Additional study treatments

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

6.1.3 Treatment arms/group

At Baseline, patients will be randomized to one of the following 4 treatment arms: asciminib 60 mg + imatinib, asciminib 40 mg + imatinib, imatinib, or nilotinib in a ratio of 1:1:1:1.

Treatment arm 1: Asciminib 40 mg + imatinib arm: asciminib 40 mg and imatinib 400 mg will be administered orally daily on a continuous schedule (QD).

Treatment arm 2: Asciminib 60 mg + imatinib arm: asciminib 60 mg and imatinib 400 mg will be administered orally daily on a continuous schedule (QD).

Treatment arm 3: Imatinib arm: imatinib 400 mg will be administered orally daily on a continuous schedule (QD).

Treatment arm 4: Nilotinib arm: nilotinib will be administered orally at 300 mg twice daily on a continuous schedule (BID).

Asciminib single agent cohort: asciminib 80 mg will be administered orally once daily on a continuous schedule (QD).

6.1.4 Guidelines for continuation of treatment

Please refer to Section 6.5.1.

6.1.5 Treatment duration

Treatment arms 1-4

All patients will be given the opportunity to receive study treatment until the date that corresponds to 96 weeks after the last randomized subject receives the first study treatment dose. Patients may be discontinued from treatment at any time due to unacceptable toxicity, disease progression and/or at the discretion of the investigator or the subject.

Asciminib single agent cohort

All patients will be given the opportunity to receive study treatment until the date that corresponds to 48 weeks after the last enrolled subject in the asciminib single agent cohort receives the first study treatment dose. Patients may be discontinued from treatment at any time due to unacceptable toxicity, disease progression and/or at the discretion of the investigator or the subject.

6.1.5.1 Treatment beyond disease progression

Should a disease progression occur during study, the subject must be discontinued and can be treated at investigator's discretion outside of the study.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the subject are allowed, provided their use is documented in the subject records and on the appropriate electronic case report form (eCRF), 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 subject was enrolled into the study must be recorded in the concomitant medications/significant non-drug therapies section of the eCRF.

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

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 randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

Hormonal contraceptives are allowed as contraception methods. Highly effective contraception should be maintained throughout the study and for 14 days after study treatment discontinuation.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

6.2.1.1.1 Permitted concomitant medication requiring caution for asciminib combinations and asciminib single agent cohort

Based upon the clinical human ADME data and alignment with the *in vitro* human hepatocyte clearance and enzyme reaction phenotyping studies, the relative contribution of CYP- and UGT-mediated asciminib clearance was estimated to be 36.6 and 58.3%, respectively.

Strong Inhibitors of CYP3A4 when given to patients being treated with asciminib in combination with imatinib have the potential to increase asciminib and imatinib concentrations.

Therefore, strong CYP3A4 inhibitors should be used with caution in patients being treated with asciminib in combination with imatinib.

Inducers of CYP3A4 have the potential to decrease asciminib concentrations. Therefore, strong CYP3A4 inducers should be used with caution in patients being treated with asciminib single agent. Based on clinical data available, CYP3A4/5 and CYP2C9 substrates with narrow therapeutic index should be used with caution.

Use of anti-emetics is allowed. Prophylactic anti-emetics should be started only once the subject experiences nausea or vomiting, at the discretion of the investigator. It is recommended that patients use drugs that do not cause QT prolongation.

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

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

Caution is also advised when asciminib is co-administered with anti-platelet pro-drugs such as clopidogrel, ticlopidine and prasugrel, which require metabolic activation by CYP3A4 and CYP2C9. While the *in vivo* potential of asciminib to interact with sensitive CYP3A4 and CYP2C9 substrates has been evaluated by PBPK modeling and indicates a minimal or negligible risk, patients using anti-platelet pro-drugs should still be carefully monitored.

Substrates of OATP1B, BCRP or both transporters, including, but not limited to sulfasalazine, methotrexate, pravastatin, atorvastatin, pitavastatin, rosuvastatin and simvastatin should be used with caution. Refer to OATP1B and BCRP substrates' dose reductions, as recommended in their prescribing information. As far as possible avoid co-administering rosuvastatin and consider alternative statins. If during the study co-administration of rosuvastatin is required, then the dose of rosuvastatin should be reduced, as recommended in its prescribing information.

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.

QT prolonging agents

As far as possible avoid co-administration of drugs with a "known" risk of Torsades de Pointes (TdP) during the course of the study.

If concomitant administration of drugs with a "known" risk of TdP is required based on the investigator assessment and clinical need, study treatment may be continued under close ECG monitoring to ensure subject's safety.

A list of drugs associated with QT prolongation and/or TdP is available online at //crediblemeds.org/.

Please refer to Section 16.3 for more details.

6.2.1.1.2 Permitted concomitant medication requiring caution for imatinib continuation arm and nilotinib arm

Nilotinib and imatinib should be administered according to the locally approved product information.

6.2.2 Prohibited medication

The concomitant administration of other investigational drugs is not allowed. 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 study after consultation with Novartis. The administration of other tyrosine kinase inhibitors indicated for treatment of Ph+ CML is not allowed.

Use of the treatments displayed in the below sections are not allowed after start of study treatment.

Please refer to Section 16.1 for more details.

6.2.2.1 Prohibited medication for asciminib combination arms

Strong CYP3A4/5 inducers

Every effort should be made NOT to concomitantly administer strong CYP3A4/5 inducers (Section 16.3). CYP3A4/5 inducers have the potential to reduce asciminib and imatinib concentrations. If administration of a strong CYP3A4/5 inducer cannot be avoided in the combination arms during the study and cannot be switched to an alternative therapy, temporary discontinuation of study treatment is NOT needed.

Herbal medications

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

Grapefruit and grapefruit products are prohibited.

6.2.2.2 Prohibited concomitant medication for imatinib continuation arm

Imatinib should be administered according to the locally approved product information.

In addition, the following applies:

- Every effort should be made NOT to administer strong CYP3A4 inhibitors. If administration of a strong CYP3A4 inhibitor cannot be avoided during the study and cannot be switched to an alternative therapy, study treatment must be STOPPED.
- Every effort should be made NOT to administer strong CYP3A4 inducers however, if administration of a CYP3A4 inducer cannot be avoided during the study, temporary discontinuation of study treatment is NOT required.

6.2.2.3 Prohibited concomitant medication for nilotinib treatment arm

Nilotinib should be administered according to the locally approved product information. Furthermore, the following applies:

Every effort should be made NOT to administer strong CYP3A4 inhibitors. If administration of a strong CYP3A4 inhibitor cannot be avoided during the study and cannot be switched to an alternative therapy, study treatment must be STOPPED.

Every effort should be made NOT to administer strong CYP3A4 inducers however, if administration of a CYP3A4 inducer cannot be avoided during the study, temporary discontinuation of study treatment is NOT required.

Whenever avoid co-administering drugs with a "Known", "Possible" or "Conditional" risk of Torsades de Pointe (per crediblemeds.org) during the course of the study:

- If concomitant administration of drugs with a "Known risk of Torsades de Pointe" is required and cannot be avoided, study drug must be interrupted. If, based on the investigator assessment and clinical need, study treatment is resumed, close ECG monitoring is advised.
- If during the course of the study, concomitant administration of a drug with "Possible risk" or "Conditional risk of Torsades de Pointe" is required, based on the investigator assessment and clinical need, study treatment may be continued under close ECG monitoring to ensure subject safety.

A list of drugs associated with QT prolongation and/or Torsades de Pointe is available online at qtdrugs.org.

If a medication listed in Section 16 appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

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

Once the subject number is assigned, it cannot be reused for any other subject.

6.3.2 Treatment assignment, randomization

Patients will be assigned to one of the 4 randomized treatment arms (Section 3) in a ratio of 1:1:1:1.

At visit "baseline", all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the subject.

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

The randomization scheme for patients will be reviewed and approved by a member of the Randomization Office.

6.3.3 Treatment assignment for asciminib single agent cohort

Patients will be enrolled in asciminib single agent cohort without randomization. The IRT will assign a number to the subject, which will be used to link the subject to the treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the subject.

6.4 Treatment blinding

This is an open-label study.

6.5 Dose escalation and dose modification

Dose escalation is not applicable. For dose re-escalation following dose reduction or interruption, please refer to Section 6.5.1.

6.5.1 Dose modifications

6.5.1.1 Criteria for dose reduction/interruption and re-initiation of study treatment for adverse drug reactions in asciminib + imatinib arm

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

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

These dose modifications are summarized in Table 6-2. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-2 .

These dose changes must be recorded on the appropriate CRF.

The following criteria apply to patients under asciminib + imatinib treatment.

Table 6-2 Criteria for dose reduction/interruption and re-initiation of asciminib + imatinib, or asciminib single agent treatment for adverse drug reactions

Dose modifications for asciminib + imatinib and asciminib single agent	
Worst toxicity as per CTCAE version5[a] during treatment	
Investigations (Hematologic)	
Hematologic toxicities If a hematologic toxicity (cytopenia Grade 3 or 4) lasts for more than 42 days without recovery to at least a Grade 2, despite TKI interruption and adequate management (including hematopoietic growth factors), then the patient must be discontinued from the study treatment.	
Grade 1	**Recommendation**: maintain dose level
Grade 2	**Recommendation**: maintain dose level
Grade 3	**Mandatory**: Hold dose until resolved to ≤ Grade 2 (recheck CBC (Complete Blood Count) 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	**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 all cytopenias	**Recommendation:** Hold dose until resolved to ≤ Grade 2, then maintain current dose level. For recurrent Grade 3-4 cytopenias: If resolved to ≤ Grade 2 in ≤ 14 days, then maintain dose level If resolved in > 14 days, then reduce dose ↓ 1 dose level
Non-hematologic adverse reactions except where further specified in individual sections If a subject requires a dose interruption of > 28 days for a non-hematologic toxicity, then the subject must be discontinued from the study treatment, unless otherwise specified.	

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 (max 28 days) until resolved to ≤ Grade 1 then resume at ↓ 1 dose level
Grade 4	**Mandatory**: Permanently discontinue subject from study drug treatment
Investigations (Hepatic)	
Combined[c] elevations of AST or ALT and total bilirubin	
For patients with normal baseline ALT and AST and total bilirubin value: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN without evidence of cholestasis[d] For patients with elevated baseline AST or ALT or total bilirubin value [AST or ALT > 2 x baseline AND > 3.0 xULN]	**Mandatory**: Permanently discontinue subject from treatment. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b], or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Refer to the Section 6.5.2 for additional follow-up evaluations as applicable.
Isolated AST or ALT elevation	
> 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:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN: Then If resolved in ≤ 14 days, maintain dose level If resolved in > 14 days, reduce dose ↓ 1 dose level
> 10.0 - 20.0 x ULN	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ baseline. Then reduce dose ↓ 1 dose level.
> 20.0 x ULN	**Mandatory:** Permanently discontinue
Isolated total Bilirubin elevation	
> ULN – 1.5 x ULN	**Recommendation:** Maintain dose level

> 1.5 - 3.0 x ULN	**Recommendation:** Hold dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: If resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, then reduce dose ↓ 1 dose level
> 3.0 - 10.0 x ULN*	**Mandatory:** Hold dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: If resolved in ≤ 14 days, then reduce dose ↓1 dose level If resolved in > 14 days, then discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks
> 10.0 x ULN*	**Mandatory:** Permanently discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
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 study drug treatment.
Grade 4 (> 6.0 x ULN)	**Mandatory:** Permanently discontinue patient from study drug treatment.
Investigation (metabolic)	
Asymptomatic amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 x ULN)	**Recommendation:** Maintain dose level, measure 2x week
Grade 2 (> 1.5 - 2.0 x ULN)	**Recommendation:** Maintain dose level, measure 2x week
Grade 3 (> 2.0 - 5.0 x ULN)	**Mandatory:** Hold dose until resolved to Grade ≤ 1 or baseline, then: If resolved in ≤ 7 days, then reduce dose ↓ 1 dose level If resolved in > 7 days, then discontinue treatment and obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).
Grade 4 (> 5.0 x ULN)	**Mandatory:** Permanently discontinue patient from study drug treatment. Obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).
Gastro intestinal	
Pancreatitis**	
Grade 2 (enzyme elevations with radiologic findings for pancreatitis as per CTCAE v5. For	**Mandatory:** If radiologic findings, hold treatment until resolved to ≤ Grade 1 or baseline. If treatment delay is ≤ 14 days, then reduce dose ↓ 1 dose level.

isolated increased enzymes please see table for asymptomatic amylase and/or lipase elevation)	If treatment delay >14 days, discontinue treatment and appropriate imaging (i.e. MRI, CT scan or ultrasound) should be obtained.
Grade ≥ 3	**Mandatory:** Permanently discontinue subject from study drug treatment. Appropriate imaging (i.e. MRI, CT scan or ultrasound) should be obtained.
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, then hold dose until resolved to ≤ grade 1, then reduce dose ↓ 1 dose level
Grade 3	**Recommendation:** Discontinue patient from study drug treatment
Grade 4	**Mandatory:** Permanently discontinue patient from study drug treatment
Skin and subcutaneous tissue disorders	
Rash/photosensitivity	
Grade 1	**Recommendation:** Maintain dose level. Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
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, then reduce dose ↓ 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then discontinue patient from study drug treatment
Grade 4, despite skin toxicity therapy	**Mandatory:** Permanently discontinue patient from study drug treatment.
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, then maintain dose level If resolved in > 7 days, then reduce dose ↓ 1 dose level
All dose modifications should be based on the worst preceding toxicity.	
[a] Common Toxicity Criteria for Adverse Events (CTCAE Version 5)	
[b] Core Liver Function Tests (LFTs) consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.)	
[c] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold. If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for general non-hematologic toxicity and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for	

another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction
[d] "Cholestasis" defined as ALP elevation (> 2.0 x ULN and R value < 2) Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R > 2 and < 5) liver injury
* Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator. ** Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study treatment.*** Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea

Dose re-escalation for asciminib and imatinib

Re-escalation to asciminib 60 mg QD or 40 mg QD, respectively, and imatinib 400 mg QD at the discretion of the investigator. Re-escalation will be allowed only once for any given subject on the asciminib + imatinib arms per protocol.

Dose re-escalation for asciminib 80 mg QD single agent

Re-escalation to asciminib 80 mg QD is permitted only once for any subject per protocol and only if there is a change in the subject's individual benefit/risk assessment at the lower dose level.

Any dose changes must be recorded on the appropriate eCRF (Dosage Administration Record eCRF).

Table 6-3 Dose reduction for asciminib and imatinib

Dose reduction*		
	Starting dose level – 0	Dose level – 1
Asciminib (ABL001)	60 mg (QD)	40 mg (QD)
Asciminib (ABL001)	40 mg (QD)	20 mg (QD)**
* Dose reduction should be based on the worst toxicity demonstrated at the last dose.		
** Dose reduction below 20 mg is not allowed.		
Dose reduction*		
	Starting dose level – 0	Dose level – 1
Imatinib (STI571)	400 mg (QD)	300 mg (QD)**
* Dose reduction should be based on the worst toxicity demonstrated at the last dose.		
** Dose reduction below 300 mg is not allowed.		

Table 6-4 Dose reduction for asciminib single agent cohort

Dose reduction*		
Asciminib (ABL001)	Starting dose level – 0 80 mg (QD)	Dose level – 1 40 mg (QD)**

* Dose reduction should be based on the worst toxicity demonstrated at the last dose.

** Dose reduction below 40 mg (QD) is not allowed.

6.5.1.2 Criteria for dose reduction/interruption and re-initiation of imatinib for adverse drug reactions in imatinib continuation arm

Dose reductions for imatinib should be done in accordance to locally approved product information for imatinib.

6.5.1.3 Criteria for dose reduction/interruption and re-initiation of nilotinib for adverse drug reactions

Dose reductions for nilotinib should be done in accordance to locally approved product information for nilotinib.

6.5.1.4 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 prolongation.
3. Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment.
4. Review concomitant medication use for other causes for QT prolongation (refer to qtdrugs.org for known QT prolonging drugs), and for drugs with the potential to increase the risk of drug exposure related QT prolongation (e.g., concomitant use of CYP3A4 inhibitors, if the study drug is a CYP3A4 substrate)
5. Check study drug dosing schedule and treatment compliance
6. Increased ECG safety monitoring is recommended during or in-between subsequent visits.

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

1. Interrupt study treatment
2. Repeat ECG and confirm ECG diagnosis by a cardiologist or central ECG lab
3. If QTcF confirmed > 500 msec
    - Correct electrolytes, eliminate culprit concomitant medication, and identify clinical conditions that could potentially prolong the QT interval
    - Consult with a cardiologist (or qualified specialist) and increase cardiac monitoring as indicated, until QTcF returns ≤ 480 msec

After resolution to ≤ 480 msec, consider reintroducing treatment at reduced dose, and increase ECG monitoring for the next treatment

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

Patients should be withdrawn from the study for any one of the following treatment-related, clinically significant safety findings, including, but not limited to:

- Documented episode of ventricular tachycardia, or ventricular fibrillation
- Complete heart block (Grade III AV block) or Second degree AV block Mobitz type II

6.5.2 Follow-up for toxicities

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

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

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

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

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

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2.

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

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

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl-transferase (GGT), prothrombin time (PT)/International Normalized Ratio (INR) and alkaline phosphatase.

2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample (for patients treated with asciminib + imatinib), as close as possible to last dose of study drug.
5. Additional testing for other hepatotropic viral infection (CMV (Cytomegalovirus), EBV (Epstein–Barr virus) or HSV (Herpes simplex virus)), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

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

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts (if applicable at the visit) and information provided by the subject. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log. Total daily dose of study treatment administered with start and end date will be collected on the dedicated eCRF page.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in the 20 patients randomized to asciminib 60 mg QD as add-on therapy to imatinib 400 mg QD in the 20 patients randomized to asciminib 40 mg QD as add-on therapy to imatinib 400 mg QD and in the 20 patients enrolled in the asciminib 80 mg QD single agent cohort, as detailed in pharmacokinetics section (Section 8.5.2).

6.6.2 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). Responsible site personnel will identify the study treatment package(s) to dispense by the medication number(s) assigned by IRT to the subject. Site personnel will add the subject number on the label. If the label has 2 parts (base plus tear-off label), immediately before dispensing the package to the subject, site personnel will detach the outer part of the label from the package and affix it to the subject's source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 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 on the imatinib and nilotinib labels and in the [Asciminib Investigator's Brochure]. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country 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 subject 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. Monitoring of drug accountability will be performed by monitors during site visits and at the completion of the trial. Patients 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.

As per Section 4.6, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic, geopolitical situation or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a subject'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 subject is no longer appropriate or possible, and that it is in the interest of the subject's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the subject's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 3 months supply. In this case, regular phone calls or virtual contacts (as needed) will occur between the site and the subject for instructional purposes, safety monitoring, investigation of any adverse events, ensuring patients continue to benefit from treatment, and discussion of the subject's health status until the patients can resume visits at the study site.

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

Study treatment (asciminib, imatinib and nilotinib) will be provided as global clinical open-label supply and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

Study treatment labels will comply with the legal requirements of each country and will include storage conditions and a unique medication number (corresponding to study treatment and strength).

Dose and treatment schedule are described in the Table 6-4 and all the information about the administration of the study drug are described in the Section 6.1.3. Dose reductions can be performed as described in Table 6-3.

Table 6-5 Dose and treatment schedule

Study Drug	Dose	Frequency
Asciminib (ABL001)	60 mg	once daily
Asciminib (ABL001)	40 mg	once daily
Imatinib (STI571)	400 mg	once daily
Nilotinib (AMN107)	300 mg	twice daily

At baseline visit the patients will be randomized into one of the 4 arms, and the responsible site personnel will identify the study treatment package(s) to dispense by the medication number(s) assigned by IRT to the subject.

Asciminib + Imatinib arms: asciminib 60 mg or 40 mg and imatinib 400 mg will be administered orally daily on a continuous schedule (QD). Asciminib and imatinib tablets should be ingested as follows:

- Patients should take asciminib daily at approximately the same time each day in the morning, immediately followed by imatinib 400 mg administration.
- On days that PK samples are obtained, the subject should take asciminib and imatinib during the clinic visit after the pre-dose PK samples, when instructed by the study staff.
- Patients should take asciminib and imatinib with a low-fat meal and a large glass of water, approximately 240 mL (8 ounces) of water. A low-fat meal is defined as any meal with less than 20% fat and not more than 400 calories.
- Patients should be instructed to swallow whole tablets and not to chew or to break them.
- If vomiting occurs during the first hour after taking the drug, re-dosing is allowed before the next scheduled dose.
- If the subject does not take asciminib and imatinib within 6 hours after the usual dosing time, that dose should be skipped and treatment should continue with the next daily dose at the prescribed level.

- Patients should avoid consumption of grapefruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed. Consumption of the aforementioned fruits or juices containing the fruits may enhance and prolong the exposure of patients to the study treatment.
- Patients should use sunblock when going out in the sun and avoid tanning beds.

Imatinib arm: imatinib 400 mg tablets will be administered orally daily on a continuous schedule (QD). Imatinib tablets should be ingested as follows:

- Patients should take imatinib daily at approximately the same time each day in the morning.
- Patients should take imatinib with a low-fat meal and a large glass of water, approximately 240 mL (8 ounces) of water. A low-fat meal is defined as any meal with less than 20% fat and not more than 400 calories.
- Patients should be instructed to swallow whole tablets and not to chew or open them.
- If vomiting occurs during the first hour after taking the drug, re-dosing is allowed before the next scheduled dose.
- If the subject does not take imatinib within 6 hours after the usual dosing time, that dose should be skipped and treatment should continue with the next daily dose at the prescribed level.
- Patients should avoid consumption of grapefruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed. Consumption of the aforementioned fruits or juices containing the fruits may enhance and prolong the exposure of patients to the study treatment.
- Patients must avoid concomitant intake of strong and moderate CYP3A4/5 inhibitors and inducers.
- Patients should use sunblock when going out in the sun and avoid tanning beds.

Nilotinib arm: nilotinib will be administered orally at 300 mg twice daily (BID). Nilotinib hard gelatin capsules for oral use should be ingested as follows:

- Patients should take nilotinib daily at approximately the same time each day in the morning and in evening at approximately 12 hour intervals
- Patients should take nilotinib on an empty stomach. No food should be consumed for two hours before and at least one hour after the dose is taken. Each dose may be taken with a glass of water, approximately 240 mL (8 ounces) of water.
- Patients should be instructed to swallow whole capsules and not to chew or open them.
- If vomiting occurs during the course of treatment, no re-dosing of the subject is allowed before the next scheduled dose.
- If the subject does not take the drug within 6 hours after the usual dosing time, that dose should be skipped and treatment should continue with the next daily dose at the prescribed level.
- Patients should avoid consumption of grapefruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study

medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed. Consumption of the aforementioned fruits or juices containing the fruits may enhance and prolong the exposure of patients to the study treatment.

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

The patients randomized in the imatinib arm who have not achieved $MR^{4.5}$ at 48 weeks may cross-over to receive the add-on treatment (asciminib 60 mg + imatinib) within 4 weeks after week 48 visit (Figure 3-1).

Patients who choose to cross-over will have to perform the "CO baseline" visit; in the timeframe from week 48 to CO baseline visit, these patients will continue to take imatinib. At the CO baseline visit, they will be registered in the cross-over arm in the IRT system and will be dispensed the new medication number(s) of asciminib and imatinib.

The patients who prefer to continue the imatinib treatment will continue to take imatinib until the end of treatment.

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

6.7.3 Asciminib single agent cohort - Instruction for prescribing and taking study treatment

Asciminib will be provided as global clinical open-label supply and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

Study treatment labels will comply with the legal requirements of each country and will include storage conditions and a unique medication number (corresponding to study treatment and strength).

Asciminib single agent cohort: asciminib 80 mg will be administered orally daily on a continuous schedule (QD). Asciminib tablets should be ingested as follows:

- Patients should take asciminib daily at approximately the same time each day in the morning.
- On days that PK samples are obtained, the subject should take asciminib during the clinic visit after the pre-dose PK samples, when instructed by the study staff.
- 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.
- Subject should be instructed to swallow whole tablets and not to chew or to break them.
- If vomiting occurs during the first hour after taking the drug, re-dosing is allowed before the next scheduled dose.
- If the subject does not take asciminib within 12 hours after the usual dosing time, that dose should be skipped and treatment should continue with the next daily dose at the prescribed level.

All dosages for all compounds prescribed and dispensed to the patients and all dose changes during the study must be recorded on the Dosage Administration Record eCRF. All kits of study treatment assigned by the IRT will be recorded in the IRT system.

7 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject 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 subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Counsel for Harmonization Good Clinical Practice (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.

Information about common side effects already known about the investigational drug can be found in the [Asciminib Investigator's Brochure] and/or the latest local approved product information for imatinib and nilotinib. This information will be included in the subject informed consent and should be discussed with the subject 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 subject.

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 while taking study treatment and for 14 days after stopping study medication in treatment arms 1 – 4, and for 3 days after stopping asciminib single agent. If local regulations or locally approved prescribing information are more stringent than the protocol required duration of contraception, the longer duration must be followed.

patientsAs per Section 4.6, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic, geopolitical situation or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local health 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 subject and person obtaining informed consent, etc.).

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

8 Visit schedule and assessments

Assessment schedule lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Note: week 2, 4, 6, 8, and 10 visits are not mandatory for patients randomized to imatinib or nilotinib arms.

For all visits, a ± 3 day visit window is allowed.

Patients who prematurely discontinue the study for any reason should be scheduled for a visit 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 study drugs should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

As per Section 4.6, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic, geopolitical situation or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consultation) or visits by site staff/off-site healthcare professional(s) staff to the subject´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the subject to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 8-1 Assessment Schedule, randomized treatment arms 1 – 4 and asciminib single agent cohort

Period	**Screening**		**Randomized Treatment**										**End of Treatment**	**Post-Treatment Follow-Up**	
Visit Name	**Screening**	**Baseline**	**Week 2[1]**	**Week 4[1]**	**Week 6[1]**	**Week 8[1]**	**Week 10[1]**	**Week 12**	**Week 24**	**Week 36**	**Week 48[2]**	**Every 12 weeks up to 96 / 48 weeks after the first dose of the last randomized / enrolled subject[3]**	**End of Treatment[4,5]**	**Safety Follow-Up**	**End of Study Visit[4,5]**
Days	**-21 to -1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**168**	**252**	**336**	**-**	**Within last dose +14**	**Last dose +30 days**	**-**
Informed consent	X														
IWRS/IRT Registration	X		X	X	X	X	X	X	X	X	X	X	X		
Randomization		X													
Demography	X														
Inclusion / Exclusion criteria	X														
Medical history/current medical conditions	X														
Disease History	X														

Period	**Screening**		**Randomized Treatment**										**End of Treatment**	**Post-Treatment Follow-Up**	
Visit Name	**Screening**	**Baseline**	**Week 2[1]**	**Week 4[1]**	**Week 6[1]**	**Week 8[1]**	**Week 10[1]**	**Week 12**	**Week 24**	**Week 36**	**Week 48[2]**	**Every 12 weeks up to 96 / 48 weeks after the first dose of the last randomized / enrolled subject[3]**	**End of Treatment[4,5]**	**Safety Follow-Up**	**End of Study Visit[4,5]**
Days	**-21 to -1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**168**	**252**	**336**	**-**	**Within last dose +14**	**Last dose +30 days**	**-**
Prior Antineoplastic Therapy	X														
Prior concomitant medications	X														
Concomitant medications		Ongoing basis													
Physical Examination	S	S	S	S	S	S	S	S	S	S	S	S	S		
Extramedullary involvement	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X		
Body Height	X														
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X		

Period	**Screening**		**Randomized Treatment**										**End of Treatment**	**Post-Treatment Follow-Up**	
Visit Name	**Screening**	**Baseline**	**Week 2[1]**	**Week 4[1]**	**Week 6[1]**	**Week 8[1]**	**Week 10[1]**	**Week 12**	**Week 24**	**Week 36**	**Week 48[2]**	**Every 12 weeks up to 96 / 48 weeks after the first dose of the last randomized / enrolled subject[3]**	**End of Treatment[4,5]**	**Safety Follow-Up**	**End of Study Visit[4,5]**
Days	**-21 to -1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**168**	**252**	**336**	**-**	**Within last dose +14**	**Last dose +30 days**	**-**
Peripheral Blood BCR-ABL1 RT-qPCR	X			X		X		X	X	X	X	X	X		
Bone marrow assessment for cytogenetic assessment			Upon Treatment Failure												
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X		
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X		
HbA1c	X							X	X		X	Week 72	X		
Hepatitis screen	X														
Pregnancy Test (serum)	X	X		X		X		X	X	X	X	X	X		
Pregnancy Test (urine)			S - Every 4 weeks if serum pregnancy test is not performed												

Period	**Screening**		**Randomized Treatment**										**End of Treatment**	**Post-Treatment Follow-Up**	
Visit Name	**Screening**	**Baseline**	**Week 2[1]**	**Week 4[1]**	**Week 6[1]**	**Week 8[1]**	**Week 10[1]**	**Week 12**	**Week 24**	**Week 36**	**Week 48[2]**	**Every 12 weeks up to 96 / 48 weeks after the first dose of the last randomized / enrolled subject[3]**	**End of Treatment[4,5]**	**Safety Follow-Up**	**End of Study Visit[4,5]**
Days	**-21 to -1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**168**	**252**	**336**	**-**	**Within last dose +14**	**Last dose +30 days**	**-**
Electrocardiogram (ECG)	X	X	X	X				X	X		X	Every 48 weeks up to 96 weeks after the first dose of the last randomized / enrolled subject	X		
Adverse Events	Ongoing basis														
Study drug dispensation		X						X	X	X	X	X			
Study drug administration		Ongoing basis													
PK sampling (Asciminib + Imatinib arms and			X	X				X	X	X		Week 60 and 96			

Period	**Screening**		**Randomized Treatment**										**End of Treatment**	**Post-Treatment Follow-Up**	
Visit Name	**Screening**	**Baseline**	**Week 2[1]**	**Week 4[1]**	**Week 6[1]**	**Week 8[1]**	**Week 10[1]**	**Week 12**	**Week 24**	**Week 36**	**Week 48[2]**	**Every 12 weeks up to 96 / 48 weeks after the first dose of the last randomized / enrolled subject[3]**	**End of Treatment[4,5]**	**Safety Follow-Up**	**End of Study Visit[4,5]**
Days	**-21 to -1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**168**	**252**	**336**	**-**	**Within last dose +14**	**Last dose +30 days**	**-**
asciminib single agent cohort only)															
Whole blood for CCI by CCI	CCI														
CCI	CCI														
CCI	CCI														
EORTC QLQ-C30 plus CML24		X		X				X	X		X	Week 96			
TSQM		X		X				X	X		X	Week 96			

Period	**Screening**		**Randomized Treatment**										**End of Treatment**	**Post-Treatment Follow-Up**	
Visit Name	**Screening**	**Baseline**	**Week 2[1]**	**Week 4[1]**	**Week 6[1]**	**Week 8[1]**	**Week 10[1]**	**Week 12**	**Week 24**	**Week 36**	**Week 48[2]**	**Every 12 weeks up to 96 / 48 weeks after the first dose of the last randomized / enrolled subject[3]**	**End of Treatment[4,5]**	**Safety Follow-Up**	**End of Study Visit[4,5]**
Days	**-21 to -1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**168**	**252**	**336**	**-**	**Within last dose +14**	**Last dose +30 days**	**-**
FACIT GP5		X		X				X	X		X	Week 96			
Antineoplastic therapies since discontinuation of study treatment														X	
Disposition													X		X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Not mandatory visits for patients in imatinib and nilotinib arm
[2] Patients in imatinib continuation arm may cross-over to receive asciminib+imatinib after Week 48 visit
[3] Asciminib single agent cohort, every 12 weeks up to 48 weeks after the first dose of the last enrolled subject
[4] Treatment arms 1 – 4: the study treatment will end at 96 weeks (plus 30 days for the safety follow up) after the last randomized subject received the first dose of study treatment.
[5] Asciminib single agent cohort: the study treatment will end at 48 weeks (plus 30 days for the safety follow up) after the last enrolled subject received the first dose of study treatment

Period	**Screening**		**Randomized Treatment**										**End of Treatment**	**Post-Treatment Follow-Up**	
Visit Name	**Screening**	**Baseline**	**Week 2[1]**	**Week 4[1]**	**Week 6[1]**	**Week 8[1]**	**Week 10[1]**	**Week 12**	**Week 24**	**Week 36**	**Week 48[2]**	**Every 12 weeks up to 96 / 48 weeks after the first dose of the last randomized / enrolled subject[3]**	**End of Treatment[4,5]**	**Safety Follow-Up**	**End of Study Visit[4,5]**
Days	**-21 to -1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**168**	**252**	**336**	**-**	**Within last dose +14**	**Last dose +30 days**	**-**

[6] Whole blood for CCI by CCI will NOT be collected in asciminib single agent cohort.

Table 8-2 Assessment Schedule, patients randomized to the continued imatinib arm who cross-over to receive asciminib 60 mg + imatinib

Period	**Cross-Over Baseline**	**Cross-Over Treatment**						**End of Treatment**	**Post-Treatment Follow-Up**	
Visit Name	**CO Baseline[1]**	**CO Week 2**	**CO Week 4**	**CO Week 6**	**CO Week 8**	**CO Week 10**	**Start from 12 weeks after cross-over, every 12 weeks up to 96 weeks after the first dose of the last randomized subject**	**End of Treatment**	**Safety Follow-Up**	**End of Study**
Days	**1**	**14**	**28**	**42**	**56**	**70**	**-**	**Within last dose +14**	**Last dose +30**	**-**
IWRS/IRT Registration	X	X	X	X	X	X	X	X		
Concomitant medications	Ongoing basis									
Physical Examination	S	S	S	S	S	S	S	S		
Extramedullary involvement	X	X	X	X	X	X	X	X		
Vital Signs	X	X	X	X	X	X	X	X		
Body Weight	X	X	X	X	X	X	X	X		
Peripheral Blood BCR-ABL1 RT-qPCR			X		X		X	X		
Bone marrow assessment for cytogenetic assessment	Upon Treatment failure									
Hematology	X	X	X	X	X	X	X	X		
Clinical Chemistry	X	X	X	X	X	X	X	X		

Period	**Cross-Over Baseline**	**Cross-Over Treatment**						**End of Treatment**	**Post-Treatment Follow-Up**	
Visit Name	**CO Baseline[1]**	**CO Week 2**	**CO Week 4**	**CO Week 6**	**CO Week 8**	**CO Week 10**	**Start from 12 weeks after cross-over, every 12 weeks up to 96 weeks after the first dose of the last randomized subject**	**End of Treatment**	**Safety Follow-Up**	**End of Study**
Days	**1**	**14**	**28**	**42**	**56**	**70**	**-**	**Within last dose +14**	**Last dose +30**	**-**
HbA1c							12, 24, 48 and 72 weeks after cross-over	X		
Pregnancy Test (serum)	X		X		X		X	X		
Pregnancy Test (urine)	S - Every 4 weeks if serum pregnancy test is not performed									
Electrocardiogram (ECG)	X	X	X				12, 24, 48 weeks after cross-over and every 48 weeks up to 96 weeks after the first dose of the last randomized subject	X		
Adverse Events	Ongoing basis									
Study drug dispensation	X						X			
Study drug administration	Ongoing basis									
EORTC QLQ-C30 plus CML24							CO week 48, CO Week 96			
TSQM							CO Week 48, CO Week 96			
FACIT GP5							CO Week 48, CO Week 96			
Antineoplastic therapies since									X	

Period	**Cross-Over Baseline**	**Cross-Over Treatment**						**End of Treatment**	**Post-Treatment Follow-Up**	
Visit Name	**CO Baseline[1]**	**CO Week 2**	**CO Week 4**	**CO Week 6**	**CO Week 8**	**CO Week 10**	**Start from 12 weeks after cross-over, every 12 weeks up to 96 weeks after the first dose of the last randomized subject**	**End of Treatment**	**Safety Follow-Up**	**End of Study**
Days	**1**	**14**	**28**	**42**	**56**	**70**	**-**	**Within last dose +14**	**Last dose +30**	**-**
discontinuation of study treatment										
Disposition								X		X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] If the cross-over treatment starts within 7 days from Week 48 visit, it is not required to perform again hematology, chemistry and serum pregnancy test as well as the ECG assessments at the CO Baseline visit.

8.1 Screening

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

All screening/baseline assessments should occur within 21 days before randomization.

Screening assessments include: physical examination, extramedullary involvement, vital signs, body height and weight, ECG, laboratory (hematology, biochemistry, hemoglobin A1c (HbA1c), Hepatitis screen, serum pregnancy test, peripheral blood collection for BCR-ABL1 RT-qPCR), evaluation of all relevant medical history including cardiovascular risk factors, CML disease history, including prior TKI therapy, antineoplastic medication, prior and concomitant medication and must be performed prior to randomization. For details of assessments required during screening please refer to Table 8-1.

During the screening visit, inclusion and exclusion criteria will be assessed. Screening assessments to confirm eligibility must be performed prior to randomization.

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 randomization.

The central reading of the screening ECGs as well as the results of the BCR-ABL1 RT-qPCR, hematology, chemistry and hepatitis screen must be available prior to randomization to evaluate eligibility.

A subject who has a laboratory test (peripheral blood test) or ECG 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 21 day screening period. In this case, the subject will not be required to sign another ICF, and the original subject identification (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 subject 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 subject after a subject has screen failed and the subject will be assigned a new subject ID number. All required screening activities must be performed when the subject is re-screened for participation in the study. An individual subject may only be re-screened once for the study. Once the number of patients screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the patients who screen failed will not be permitted to re-screen.

8.1.1 Eligibility screening

Following registering in the IRT for screening, subject eligibility check will be embedded in the IRT system by an eligibility transaction. The eligibility will be confirmed in the IRT after

screening procedures and prior to randomization visit. 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 and subsequently are found to be ineligible prior to randomization for treatment arms 1- 4, and prior to enrollment for asciminib single agent cohort will be considered a screen failure. 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 subject experienced a serious adverse event during the screening phase (see SAE section for reporting details). If the subject fails to be randomized or enrolled, the IRT must be notified within 2 days of the screen fail that the subject was not randomized or enrolled.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data to be collected on all patients include: age, gender, race, ethnicity, height, weight, source of subject referral, relevant medical history/current medical condition present before signing informed consent where possible, CML disease history, and prior and concomitant medication including prior TKI therapy and antineoplastic medication. Diagnoses and not symptoms will be recorded.

Baseline assessments include: physical examination, extramedullary involvement, vital signs, body weight, ECG, laboratory (hematology, biochemistry, serum pregnancy test, blood collection for BCR-ABL1 mutational analysis), biomarker assessments and PROs.

If the baseline assessments will be performed within 7 days from screening, it is not required to perform again the hematology, chemistry and serum pregnancy test as well as the ECG assessments.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the subject's eCRF.

8.3 Efficacy

8.3.1 Molecular response and BCR::ABL1 RT-qPCR

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

Levels of BCR::ABL1 transcripts will be determined by real-time quantitative PCR (RT-qPCR) testing of peripheral blood and analyzed at a central testing laboratory. Log reduction in BCR::ABL1 transcripts levels from the standardized baseline value, or the percent ratio of BCR::ABL1 transcripts *versus* control gene (ABL) transcripts converted to a reference standard, international scale (IS), will be calculated for each sample.

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

- MMR: BCR::ABL $\leq$ 0.1% (IS)

- $MR^{4.0}$: BCR::ABL ≤ 0.01% (IS)
- $MR^{4.5}$: BCR::ABL ≤0.0032% (IS)

Unconfirmed loss of MMR is defined as increase of BCR::ABL to > 0.1% by International Scale (IS) in association with 5-fold rise in the BCR::ABL from the lowest value achieved on study treatment and confirmed by a duplicate analysis of the same sample. Loss of MMR is confirmed by a subsequent analysis of a sample collected within 4-6 weeks unless the loss of MMR is associated with confirmed loss of CHR, loss of CCyR, progression to AP/BC, or CML-related death.

Upon confirmed loss of MMR by RT-qPCR, mutation analysis will be performed at a designated laboratory by Sanger sequencing using remnant RNA from sample already collected and tested for RT-qPCR.

BCR::ABL1 RT-qPCR analysis will be performed at a designated laboratory at screening, Week 4 (if applicable), Week 8 (if applicable), Week 12, 24, 36, 48, every 12 weeks up to 96 weeks after the first dose of the last randomized subject and at end of treatment; for the cross-over arm at CO Week 4, 8, start from 12 weeks after cross-over, every 12 weeks up to 96 weeks after the first dose of the last randomized subject and at end of treatment.

The blood samples will be taken as described in Table 8-3 and Table 8-4.

Table 8-3 Blood samples for PCR (primary and secondary efficacy endpoints) in all randomized treatment arms 1- 4, and asciminib single agent cohort

Sample Type	Volume	Visit	Time point
Blood for BCR::ABL quantification by RT-qPCR	20 mL	Screening	Pre-dose
	20 mL	Week 4*	Pre-dose
	20 mL	Week 8*	Pre-dose
	20 mL	Week 12	Pre-dose
	20 mL	Week 24	Pre-dose
	20 mL	Week 36	Pre-dose
	20 mL	Week 48	Pre-dose
	20 mL	Every 12 weeks up to 96 / 48 weeks after the first dose of the last randomized / enrolled subject**	Pre-dose
	20 mL	End of Treatment	Anytime

*Not mandatory visits for patients in Imatinib and Nilotinib arm

**Asciminib single agent cohort, every 12 weeks up to 48 weeks after the first dose of the last enrolled subject

Table 8-4 Blood samples for PCR in cross-over

Sample Type	Volume	Visit	Time point
	20 mL	CO Week 4	Pre-dose
	20 mL	CO Week 8	Pre-dose

Blood for BCR::ABL quantification by RT-qPCR	20 mL	Start from 12 weeks after cross-over, every 12 weeks up to 96 weeks after the first dose of the last randomized subject	Pre-dose
	20 mL	End of Treatment	Anytime

8.3.2 Bone marrow analysis and cytogenetics

Bone marrow aspirate for cytogenetic analyses will be performed only upon treatment failure (for definition of treatment failure, see Section 9.1.1).

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

8.3.3 Appropriateness of efficacy assessments

Assessing molecular response with RT-qPCR is considered as standard in CML therapy and recommended in treatment guidelines (Baccarani et al 2013, NCCN 2018). It is acknowledged that response can be assessed using only standardized results via International Scale (IS) as BCR::ABL%. Mutational analysis is required in case of treatment failure. Cytogenetic assessment is required in case of treatment failure (Baccarani et al 2013, Baccarani et al 2015).

8.4 Safety and tolerability

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

As per Section 4.6, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic, geopolitical situation or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (as needed) for safety monitoring and discussion of the subject´s health status until it is safe for the subject to visit the site again.

Table 8-5 Safety and tolerability 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 for all physical examinations must be included in the source documentation at the study site as unique source data, this information will not be captured in the CRF. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after first administration of study drug

Assessment	Specification
	which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF. Physical examination will be evaluated during each performed visit.
Extramedullary involvement	Presence of extramedullary leukemic involvement will be checked with each physical examination as outlined above. Findings on physical examination consistent with extra-medullary leukemic involvement will be recorded (e.g. any organ involvement). With regards to lymph nodes, only those palpable lymph nodes should be considered to be CML related if leukemic blast infiltration has been confirmed via biopsy/histology or by technically adequate aspiration cytology. When extramedullary involvement other than of the spleen or liver is the only evidence of blast crisis, this finding must be confirmed by technically adequate (not contaminated with peripheral blood) aspiration cytology and/or biopsy (especially for isolated lymph nodes) and data entered into the extramedullary involvement eCRF. Extramedullary involvement will be evaluated during each performed visit.
Vital signs	Vital signs include systolic and diastolic blood pressure (supine position preferred when ECG is collected), pulse rate measurement, and body temperature. Vital signs will be evaluated during each performed visit.
Height and weight	Height in inches or centimeters (cm) and body weight (in pounds or to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured. Body height will be evaluated only during screening visit. Body weight will be evaluated during each performed visit.

8.4.1 Laboratory evaluations

Central laboratory will be used for analysis of hematology, biochemistry, serum pregnancy and hepatitis marker specimens collected (safety monitoring). Details on the collections, shipment of the samples and reporting of results by the central laboratory are provided to investigators in the [CABL001E2201 laboratory manual]. The time windows granted for laboratory evaluations are identical with the corresponding visit time windows for each visit (see Section 8).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria: 1) they induce clinical signs or symptoms, 2) they are considered clinically significant, or 3) they require concomitant therapy or procedures. Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from screening or the previous visit.

Unscheduled local laboratory assessments may be performed if medically indicated to assess a (potential) adverse event or when the treating physician cannot wait for central laboratory results for decision making (e.g. therapeutic intervention, interruption of study treatment). In this particular situation, if possible, the blood sample obtained at the same time point should be submitted to the central laboratory for analysis in parallel with local analysis. The results of the local laboratory will be recorded in the eCRF if any of the following criteria are met:

- A treatment decision was made based on the local results, or

- Local lab results document an adverse event not reported by the central lab, or
- Local lab results document an adverse event severity is worse than the one reported by the central lab, or
- There are no concomitant central results available

For assessment of patients' eligibility to the study, only laboratory results from the central laboratory will be used.

As per Section 4.6, during a public health emergency as declared by local or regional authorities' i.e. pandemic, epidemic, geopolitical situation or natural disaster, that limits or prevents on-site study visits, if patients cannot visit the site for protocol specified safety lab assessments during the trial, an alternative lab (local) collection site may be used.

At any time during the study, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. Laboratory data will be summarized using the Common Terminology Criteria for Adverse events (CTCAE) version 5. Additional analyses are left to the discretion of the investigator.

Novartis must be provided with a copy of the local laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the CRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the date of revalidation. Additionally, if at any time a patient has laboratory parameters obtained from a different laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

Table 8-6 Laboratory assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV), Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Blasts, Promyelocytes, Myelocytes, Metamyelocytes, Bands)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Total Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting), Hemoglobin A1c
Hepatitis markers	HBsAg, anti-HBc

Test Category	Test Name
Pregnancy Test*	Serum beta fraction of human chorionic gonadotropin (ß-HCG) testing
* For details on pregnancy testing, please refer to Section 8.4.3.	

8.4.1.1 Hematology

Hematology assessments have to be analyzed at each scheduled visit by a central laboratory, according to Table 8-1 and Table 8-2. For details of the Hematology panel refer to Table 8-6.

8.4.1.2 Clinical chemistry

Clinical chemistry assessments have to be analyzed by a central laboratory, according to Table 8-1 and Table 8-2. For details of the clinical chemistry panel refer to Table 8-6 .

Clinical chemistry assessments have to be analyzed at each scheduled visit.

HbA1c assessment has to be analyzed as reported below:

- Randomized treatment: Screening, Week 12, 24, 48, 72 and End of Treatment.
- Crossover treatment: CO Week 12, 24, 48, 72 and End of Treatment.

The hepatitis markers are analyzed only at screening visit.

8.4.2 Electrocardiogram (ECG)

ECGs should be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Three serial ECGs (triplicate) should be performed half an hour prior to dosing for pre-dose assessment and prior to any PK blood draws scheduled for the visit. The serial ECGs should be taken approximately 5 minutes apart. After the subject has rested approximately 10 minutes in a supine position, three sequential standard 12-lead ECGs (triplicate) must be obtained with a recommended minimal interval of 5 minutes between each ECG at the time points specified in Table 8-1, Table 8-2, for details please refer to Table 8-7 and Table 8-8.

These three sequential 12-lead ECGs are to be collected with ECG machines supplied by the central laboratory (eRT) and all three ECGs for each time point should be sent to eRT. All ECGs performed will be independently reviewed. Instructions for the collection and transmission of these ECGs to the independent central reader (eRT) will be provided in the [CABL001E2201 ECG Manual].

For any ECG with subject safety concerns, two additional ECGs must be performed as soon as possible to confirm the safety finding. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment.

Readings for QTc prolongation will be based on the average seen in the scans for each time point. The enrollment of patients has to be based on centrally assessed QTcF time. If one of the 3 serial ECGs prior to dosing on day 1 shows a QTcF ≥ 450 msec (male) or ≥ 460 msec (female) by automated reading, an immediate manual central reading must be requested by calling eRT. The subject may not be dosed if the average of the manually read ECGs confirms a QTcF ≥ 450 msec (male) or ≥ 460 msec (female).

In the event that a clinically significant ECG abnormality is identified at the site (e.g. severe arrhythmia, conduction abnormality of QTcF > 500 msec), a copy of the assessment is sent to the core laboratory for expedited review if applicable, and the ECG is repeated to confirm the diagnosis. If the subject is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

A standard 12 lead ECG will be performed at the following time points.

Randomized treatment arms 1 – 4, asciminib single agent cohort:

- at screening and baseline
- at Week 2, 4, 12, 24, 48, every 48 weeks until the end of treatment
- at the end of treatment

Cross-over treatment:

- at CO baseline, CO Week 2, 4, 12, 24, 48, every 48 weeks until the end of treatment
- at the end of treatment

Table 8-7 Central ECG collection plan in all randomized treatment arms 1- 4, and asciminib single agent cohort

Week	Day	Time	ECG Type
Screening	-21 to -1	Anytime	12 Lead, triplicate
Baseline	1	Pre-dose, *Post-dose 2 hours	12 Lead, triplicate
Week 2**	14	Pre-dose, *Post-dose 2 hours, 3 hours, 4 hours	12 Lead, triplicate
Week 4**	28	Pre-dose, *Post-dose 2 hours, 3 hours, 4 hours	12 Lead, triplicate
Week 12	84	Pre-dose	12 Lead, triplicate
Week 24	168	Pre-dose	12 Lead, triplicate
Week 48	336	Pre-dose	12 Lead, triplicate
Every 48 weeks up to 96 weeks after the first dose of the last	-	Pre-dose	12 Lead, triplicate

Week	Day	Time	ECG Type
randomized / enrolled subject			
EOT	-	Pre-dose	12 Lead, triplicate
Unscheduled ECG	-	Anytime	12 Lead, triplicate
*Post-dose ECGs for asciminib + imatinib arms, and asciminib single agent cohort only			
** Not mandatory visits for patients in imatinib and nilotinib arm			

Table 8-8 Central ECG collection plan in cross-over

Week	Day	Time	ECG Type
Baseline cross-over	1	Pre-dose, Post-dose 2 hours	12 Lead, triplicate
2 weeks after cross-over	14	Pre-dose, Post-dose 2 hours, 3 hours, 4 hours	12 Lead, triplicate
4 weeks after cross-over	28	Pre-dose, Post-dose 2 hours, 3 hours, 4 hours	12 Lead, triplicate
12 weeks after cross-over	84	Pre-dose	12 Lead, triplicate
24 weeks after cross-over	168	Pre-dose	12 Lead, triplicate
48 weeks after cross-over	336	Pre-dose	12 Lead, triplicate
Every 48 weeks up to 96 weeks after the first dose of the last randomized subject	-	Pre-dose	12 Lead, triplicate
EOT	-	Pre-dose	12 Lead, triplicate
Unscheduled ECG	-	Anytime	12 Lead, triplicate

In order to enable ECG evaluation by the central laboratory for eligibility assessment, ECGs should be submitted to the ECG core laboratory in adequate time prior to the planned randomization date.

In the event that a QTcF value of > 500 msec is observed or if an unscheduled ECG is performed for safety reasons, it is recommended to collect a time-matched PK sample and record the time and date of the last study drug intake to determine the drug exposure. Dose adjustments in case of QT prolongation should be performed per Section 6.5.1.4.

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

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

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

8.4.3 Pregnancy and assessments of fertility

All women of childbearing potential have to complete a serum pregnancy test (Serum ß-HCG) as indicated in Table 8-1 and Table 8-2. Pregnancy testing is not required for patients who are determined to be post-menopausal. The time windows granted for pregnancy testing are identical with the corresponding visit time windows for each visit.

Serum pregnancy assessments have to be analyzed by a central laboratory, according to Table 8-1 and Table 8-2, during the following time points:

- Randomized treatment: screening, baseline, Week 4 (if applicable), Week 8 (if applicable), and at each visit from Week 12 onwards until the end of treatment.
- Crossover treatment: CO baseline (if the crossover treatment starts within 7 days from Week 48 visit, it is not required to perform serum pregnancy test again), CO Week 4, CO Week 8 and at each visit from CO Week 12 onwards until the end of treatment.

Urine pregnancy tests have to be performed at home every 4 weeks if serum pregnancy test is not performed. 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.

As per Section 4.6, during a public health emergency as declared by local or regional authorities' i.e. pandemic, epidemic, geopolitical situation or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant patients can perform the urine pregnancy test at home and report the result to the site. It is important that patients are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the subject so that the site is informed and can verify the pregnancy test results (e.g., following country specific measures).

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

During the whole study, women of childbearing potential should employ the use of highly effective contraception. Highly effective contraception methods are defined in Section 5.2.

A woman is considered of childbearing potential from menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or bilateral 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..

8.4.4 Appropriateness of safety measurements

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

8.5 Additional assessments

The following additional assessments will be performed on patients entered into this study:

- Patient Reported Outcomes
- Pharmacokinetics
- Biomarker

8.5.1 Clinical Outcome Assessments (COAs)

Patient Reported Outcomes (PRO)

The following PROs will be used:

- European organization for research and treatment of cancer - quality of life questionnaire (EORTC QLQ-C30 and EORTC QLQ-CML24)
- Functional assessment of chronic illness therapy - general population 5 (FACIT GP5)
- Treatment satisfaction questionnaire for medication (TSQM)

These questionnaires will capture data on the patient-reported outcome measures of health-related quality-of life, treatment satisfactions and treatment-related side effects per Section 8 . The TSQM Version 1.4 will be used to assess how satisfied the subject is with treatment overall and FACIT GP5 to assess treatment-related side effects. All tools require subject's direct completion and will be administered utilizing a tablet provided by a third party vendor. Data transfers of cleaned data will be performed by the PRO vendor.

All questionnaires should be administered in the language most familiar to the subject at the beginning of scheduled visit prior to any interaction with the study investigator including any tests, treatments or receipt of results from any tests to avoid biasing the subject's perspective. At baseline, the questionnaire(s) will be applied prior to randomization. This is to avoid potentially biasing patients or their responses to study questionnaires.

The subject should be given sufficient space and time to complete the questionnaires and the administered questionnaire should be reviewed for completeness. If missing responses are noted, patients should be encouraged to complete any missing responses. Attempts should be made to collect responses to all questionnaires for all patients, however, if patients refuse to complete all or any part of a questionnaire, this should be documented in the study data capture system and should not be captured as a protocol deviation.

Completed questionnaire(s) should be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study

investigators should not encourage the subject to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 10 (e.g. reference "Adverse Events" section) of the study protocol.

PRO assessments have to be performed from all patients during the treatment period, but not from patients who discontinue from study treatment.

As per Section 4.6, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic, geopolitical situation or natural disaster, that limits or prevents on-site study visits, COA data may be collected remotely.

For PRO time points, please refer to Table 8-1 and Table 8-2.

The PRO measure(s) should be completed in the following order: EORTC QLQ-C30, EORTC QLQ-CML24, TSQM and FACIT GP5.

8.5.1.1 EORTC QLQ-C30 and EORTC QLQ-CML24

The EORTC QLQ-C30 Version 3.0 is a questionnaire developed to assess the quality of life of cancer patients which has been translated and validated into 81 languages and has been used in more than 3000 studies worldwide. The EORTC contains 30 items and is composed of both multi-item scales and single-item measures. These include five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea and vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status and QoL scale (Aaronson et al 1993). The EORTC QLQ-CML24 (Efficace et al 2014) is used in conjunction with the EORTC QLQ-C30 and provides information on an additional 24 items specifically related to chronic myeloid leukemia. The QLQ-CML24 incorporates four multi-item scales assessing symptom burden (13 items), impact on worry/mood (4 items), impact on daily life (3 items), and satisfaction with care and information (2 items), as well as two single items assessing body image problems and satisfaction with social life. For countries where the EORTC QLQ-CML24 will not be available, because of missing language validation, it will not be completed by the patients. Those questionnaires will be locked within the application and will not be available for completion.

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high/healthy level of functioning; a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems. All scoring will follow the scoring procedures defined by the EORTC Scoring Manual (Fayers 2001).

8.5.1.2 TSQM

The 14-item Treatment Satisfaction Questionnaire for Medication (TSQM, Version 1.4) is a generic, multidimensional, self-administered measure of patient satisfaction with a medication. The instrument has 14 items measuring four domains: effectiveness, side effects, convenience, and global satisfaction. Domain scores range from 0 to 100, with a higher score indicating higher satisfaction (Atkinson et al 2004).

Responses to items are summed and transformed so that higher scores indicate greater satisfaction. Specifically, TSQM scale scores are computed by adding the items loading on each domain. The lowest possible score is subtracted from the composite score and divided by the greatest possible score range. This provides a transformed score between 0 and 1 that is then multiplied by 100. If more than one item is missing from a subscale of the TSQM for a particular patient, this subscale should be considered invalid for that respondent.

8.5.1.3 FACIT GP5

The FACIT GP5 Version 04, which is a single question, will be used to assess the overall bothersomeness with treatment side effects. The GP5 has a seven-day recall period and uses a 5-point rating scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a bit; and 4 = Very much) to assess how bothered the subject is by side effects of treatment rated on a 5-point Likert scale.

8.5.2 Pharmacokinetics

Plasma samples will be obtained to characterize the disposition of the study drugs (asciminib, imatinib) after oral administration. In addition to parent drug analyses, exploratory metabolite analyses on remaining plasma material may be performed using a non-validated, semi-quantitative or qualitative liquid chromatography/tandem mass spectrometry (LC-MS/MS) method, if deemed appropriate. Plasma samples remaining from the analysis may be retained by Novartis for additional investigations (i.e. long term stability, reproducibility).

8.5.2.1 Pharmacokinetic blood collection and handling

PK samples will be collected for both the combination arms asciminib 60 mg + imatinib and asciminib 40 mg + imatinib, as well as for the asciminib single agent cohort. Blood samples will be taken from the arm by either direct venipuncture or an indwelling catheter inserted in a forearm vein. At specified time points, 4 mL blood (see) will be collected.

The remaining aliquots, must be kept at the clinical site as backup samples, and should only be disposed of after approval by Novartis.

The sample requisition form should be completed and the tubes labeled appropriately. On the requisition form, it is important to record the EXACT time the sample was drawn rather than being close to the scheduled sampling time. Any sampling problems (e.g. subject took study drug before a draw took place) must be noted in the patient records. PK sampling scheme may be modified to optimize the sampling time for the study treatment disposition as needed. The label in the PK kits (i.e. PK plasma sample) should be used and the actual collection date and time should be noted on the label and recorded in the eCRF. Labels will be provided by the site with all label information preprinted. Labels will have a barcode, along with the subject number and the sequential PK sample number as reported in the PK Sample Scheduling Table ().

Table 8-9 Pharmacokinetic blood collection log

Week	Day	Scheduled Time Point	Asciminib Dose Reference ID	Imatinib Dose Reference ID	Asciminib PK Sample No	Imatinib PK Sample No	Sample Volume
2	14	Pre-dose (0h)	1	201	1	101	4
2	14	1 h (± 10 min)	1	201	2	102	4
2	14	2 h (± 10 min)	1	201	3	103	4
2	14	3 h (± 15 min)	1	201	4	104	4
2	14	4 h (± 15 min)	1	201	5	105	4
2	14	8 h (± 60 min)	1	201	6	106	4
2	14	24 h (± 60 min)/ Pre-dose	1	201	7	107	4
4	28	Pre-dose (0h)	5	205	8	108	4
4	28	2 h (± 10 min)	5	205	9	109	4
4	28	3 h (± 15 min)	5	205	10	110	4
4	28	4 h (± 15 min)	5	205	11	111	4
12	84	Pre-dose (0h)	6	206	12	112	4
24	168	Pre-dose (0h)	7	207	13	113	4
36	252	Pre-dose (0h)	8	208	14	114	4
60	420	Pre-dose (0h)	9	209	15	115	4
96	672	Pre-dose (0h)	10	210	16	116	4
Unscheduled	-				1001+	2001+	4
Total							64

8.5.2.2 Analytical method

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

Plasma concentrations of imatinib and its metabolite N-desmethyl imatinib (CGP74588) will be determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of 20.0 ng/mL.

8.5.3 Biomarkers

Biomarker analyses will be used to CCI as well as to determine CCI . In addition, potential predictive markers of CCI will also be explored.

All assessments will be performed by a Novartis-designated laboratory. Instructions for collection, storage and shipment of all biomarker samples will be provided in the [CABL001E2201 laboratory manual]. Required sample collection information must be entered on the appropriate CRF pages and requisition forms.

Biomarker assessments in blood samples

Characterization of CCI

Approximately 10 mL of blood sample will be collected to assess CCI via CCI for patients in treatment arms 1-4. The analysis aims to CCI will be performed at a Novartis designated laboratory at CCI , at CCI and at CCI in treatment arms 1-4 only, a sample is not collected or analyzed for patients in the asciminib single agent cohort.

CCI

Approximately 12 mL of blood will be collected for CCI at the visits as indicated in Table 8-10 . The analysis aims to CCI .

CCI

Approximately 2.5 mL of blood will be collected for CCI at the visits indicated in Table 8-10 . CCI samples may be used to CCI CCI

Table 8-10 Biomarker sample collection plan

	Volume	Visit	Time point
Whole blood for CCI analysis by CCI (treatment arms 1-4 only)	10 mL	CCI	Pre-dose
	10 mL	CCI	Anytime
	10 mL	CCI	Anytime
CCI	12 mL	CCI	Pre-dose
	12 mL	CCI	Anytime
	12 mL	CCI	Anytime
	12 mL	CCI	Anytime
CCI	2.5 mL	CCI	Pre-dose
	2.5 mL	CCI	Anytime
	2.5 mL	CCI	Anytime

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

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

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision
- Pregnancy
- Use of prohibited treatment as per e prohibited treatment section
- Any situation in which study participation might result in a safety risk to the subject
- Treatment failure and disease progression
- In the case of certain adverse events and re-occurrence of adverse events (see Section 6.5.1)

Progression is defined by one of the following criteria:

1. CML-related death as determined by investigator.
2. Progression to 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, but < 30% blast in peripheral blood or bone marrow aspirate

- ≥ 20% basophils in the peripheral blood
- Thrombocytopenia (< 100 x 10^9/L) unrelated to therapy

3. Progression to blast crisis (BC) defined by any of the following:

- ≥ 30% blasts in peripheral blood or bone marrow aspirate
- Appearance of extramedullary involvement other than hepato-/splenomegaly 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 or the treating physician determines there is unsatisfactory therapeutic effect within the first 8 weeks.

Treatment failure is defined according to ELN guidelines (Baccarani et al 2013) as no CHR and/or Ph+ > 95% after 3 months, BCR::ABL1 > 10% and/or Ph+ > 35% after 6 months, BCR-ABL1 > 1% and/or Ph+ > 0 after 12 months of treatment initiation, or as loss of CHR, loss of CCyR, confirmed loss of MMR*, BCR::ABL mutations, and major route clonal chromosome abnormalities in Ph+ cells at any time.

* In 2 consecutive tests, of which one with a BCR::ABL level ≥1%.

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

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdrawal of informed consent, Section 9.1.2). **Where possible, they should return as soon as possible for the assessments indicated for the end of treatment visit** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

The following assessments, according to Table 8-1 and Table 8-2, will be performed during the end of treatment visit: physical examination, extramedullary involvement, vital signs, body weight, blood collection (for hematology, chemistry, BCR::ABL1 RT-qPCR, CCI [redacted] analysis, biomarkers, serum pregnancy test), ECG, assessments of adverse events and concomitant medications.

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

After study treatment discontinuation, 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 subject's discontinuation from study treatment.

9.1.2 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

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

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject's welfare and safety. Should early termination be

necessary, patients must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. 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 subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

End of Study will be declared 96 weeks after the last randomized subject received the first dose of treatment (plus 30 days for the safety follow up) in arms 1 to 4, or 48 weeks after the last enrolled subject in the asciminib single agent cohort received the first dose of study treatment (plus 30 days for the safety follow up), whichever occurs later, or when all patients complete their end of study visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator. In the event of an early study termination decision, soon after the date of that decision each subject will be required to complete the end of study visit in its entirety and thereafter no further study treatment will be made available to them. All randomized and/or treated patients should have a safety follow-up 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 10.1.3. Documentation of attempts to contact the subject should be recorded in the source documentation.

- The primary analysis for the study will be performed when all patients in randomized treatment arms 1 - 4 have completed the Week 48 visit or have discontinued early.
- The Week 96 analysis will occur when all patients in randomized treatment arms 1 - 4 have completed the end of the study visit. The results will be summarized in a week 96 Clinical Study Report (CSR).
- All available data from asciminib single agent cohort up to the End of Study will be analyzed and summarized in a final Clinical Study Report (CSR).

At the time of the end of study visit , patients who ho in the opinion of the investigator are continuing to benefit from the study drug(s), efforts will be made to continue providing the study treatment outside the study. Options include, but are not limited to, a post-trial access program or access to commercial supplies in applicable countries.

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 subject or clinical investigation subject 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 subject 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 subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded in the Adverse Events CRF 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. The Common Toxicity Criteria (CTC) AE grade (version 5).

Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used.

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 subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved 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
    a. not recovered/not resolved;
    b. recovered/resolved;
    c. recovered/resolved with sequelae;

d. fatal; or unknown.

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 subject.

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 fatal outcomes), if documented by use of appropriate method (for example, loss of response, progression to accelerated phase or blast crisis), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy 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 [Asciminib Investigator Brochure].

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 patients 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 subject 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 (e.g. loss of response, treatment failure, progression to AP/BC)
    - 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 subject'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 subject 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 subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered 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.

All malignant neoplasms will be assessed as serious 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 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after subject stopped the study treatment must be reported to Novartis safety immediately without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: if more stringent, local regulations regarding reporting timelines prevail). The Investigator must complete and submit

the SAE report form directly in the CRF. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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

The following SAE reporting timeframes apply:

1. Screen Failures (e.g. a subject who is screened but is not treated or randomized): SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.
2. Randomized OR Treated Patients: SAEs collected between time subject signs ICF until 30 days after the subject has discontinued or stopped study treatment

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 within 24 hours of 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.

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, EU Clinical Trial Regulation 536/2014 *(once transfer is completed),* or as per national regulatory requirements in participating countries. Any SAEs experienced after the 30 day safety evaluation period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

SAE Reporting via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE to Novartis will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or by telephone.

SAE Reporting via Paper Data Collection Tool

Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to Novartis.

In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.

10.1.4 Pregnancy reporting

Pregnancies

To ensure subject 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 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 the study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

For all pregnancies with live birth and/or unknown outcome the newborn has to be followed up to obtain infant health status and development up to twelve months after delivery.

10.1.5 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, subject or consumer (definition from European Medicines Agency).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and (until transition to EU CTR) reported to Safety only if associated with an SAE. Misuse or abuse (and upon transition to EU CTR, also study treatment errors and uses outside of what is foreseen in the protocol) will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

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

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of a study drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities/adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring

Please refer to Table 16-1 in Section 16.1 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2. Repeat liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and GGT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unplanned local laboratory CRF .
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the study drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more

detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

10.2.2 Renal safety monitoring

Every renal laboratory trigger or renal event as defined in Table 16-3 should be followed up by the investigator or designated personnel at the trial site as summarized in Section 16.2.

10.2.3 Steering Committee

A steering committee (SC) will be established comprising of investigators participating in the trial, i.e. not being members of the Novartis/sponsor representatives from the Clinical Trial Team. Additionally, a patient advocate will be an active member of this committee.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. 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

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the electronic data capture (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 subject data for archiving at the investigational site.

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

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 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.

Randomization codes and data about all study treatment (s) dispensed to the subject and all dosage changes 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. Any changes to the database after that time can only be made after written agreement by Novartis development management.

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

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/delegated CRO representative will review the protocol and data capture requirements (i.e. 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/Clinical Research Associate (CRA) will visit the site to check the completeness of subject 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/delegated CRO/CRA 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 subject 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

subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

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 patients will be disclosed.

12 Data analysis and statistical methods

Primary safety and efficacy analysis will be conducted on all randomized subject data at the time all patients will have completed at least 48 weeks of study treatment or discontinued earlier.

Any additional data for patients continuing to receive study treatment past this time, as allowed by the protocol, will be further summarized in a final study report once these patients complete the study.

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

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

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

12.1 Analysis sets

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

The **Safety Set** includes all patients who received any study treatment (i.e. at least one dose of the investigational drug or control drug in case of monotherapy, or at least one dose of any component of the study treatment in case of a combination therapy). Patients will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

For the asciminib single agent cohort the treatment received is defined as the asciminib single agent if the subject took at least one dose of that.

The **Pharmacokinetic analysis set (PAS)** includes all patients randomized to asciminib + imatinib arm or asciminib single agent cohort who received at least one dose of asciminib or imatinib and provide at least one evaluable PK concentration.

For a concentration to be evaluable, patients are required to:

- Take a dose of asciminib or imatinib prior to sampling,
- For post-dose samples, do not vomit within 4 hours after the dosing of asciminib or imatinib.
- For pre-dose samples, have the sample collected before the next dose administration.

The **$MR^{4.5}$ Responder set** consists of the patients in the FAS who achieved $MR^{4.5}$ by the corresponding cut-off date. It will be used for the time to $MR^{4.5}$ and duration of $MR^{4.5}$ analysis.

The **Cross-over set** consists of the patients randomized to the continued imatinib arm who crossed over to receive asciminib add-on treatment after 48 weeks of study treatment. This will be used in the analyses of the data after cross-over.

12.2 Subject demographics and other baseline characteristics

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

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25^{th} and 75^{th} percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, by treatment arm and for asciminib single agent cohort.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum, and maximum will be presented.

The duration of exposure in days to asciminib, imatinib and nilotinib 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 treatment arm and for asciminib single agent cohort by means of descriptive statistics using the safety set. The duration of exposure will also be presented for asciminib + imatinib.

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

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

12.4 Analysis of the primary endpoint(s)

The primary objective of the study is:

- To assess whether asciminib 40 mg + imatinib or asciminib 60 mg + imatinib is more effective than continued imatinib in patients with CML-CP who have received imatinib for at least one year (12-calendar months) and have not achieved DMR

12.4.1 Definition of primary endpoint(s)

The primary efficacy endpoint of the study is the rate of $MR^{4.5}$ at 48 weeks, defined as the proportion of patients still treated with the randomized treatment at 48 weeks and are in $MR^{4.5}$ (BCR::ABL1 ratio of $\leq$ 0.0032%) at 48 weeks ($\pm$ assessment window), among all patients randomized to the respective treatment arm. Patients who discontinue the randomized treatment for any reason prior to 48 weeks are included in the denominator and considered as non-responders.

12.4.2 Statistical model, hypothesis, and method of analysis

The rate of $MR^{4.5}$ at 48 weeks will be calculated based on the FAS.

The rate of $MR^{4.5}$ at 48 weeks and its 2-sided 90% confidence interval based on the Clopper-Pearson method will be presented by treatment arm (asciminib 60 mg + imatinib, asciminib 40 mg + imatinib and continued imatinib). The difference in rate of $MR^{4.5}$ between 1) asciminib 60 mg + imatinib *versus* continued imatinib and 2) asciminib 40 mg + imatinib *versus* continued imatinib with its 2-sided 90% confidence interval will be provided using the Wald method.

12.4.3 Handling of missing values/censoring/discontinuations

Only patients still treated with the randomized treatment at 48 weeks with $MR^{4.5}$ at 48 weeks are considered responders. In other words, any subject who achieves $MR^{4.5}$ before 48 weeks, but is no longer in $MR^{4.5}$ at 48 weeks, will be considered as a non-responder for this endpoint. Patients discontinuing the randomized treatment prior to 48 weeks due to any reason will be considered as non-responders. One exception to the rule above is if the 48-week PCR evaluation is missing, but both a PCR evaluation at 36 weeks and a PCR evaluation at 60 weeks are available and indicate $MR^{4.5}$, then the 48-week assessment is imputed as a 'Response'.

12.4.4 Supportive analyses

The following supportive analyses for the primary endpoint will be performed on the FAS.

1) The rate of $MR^{4.5}$ at 48 weeks and its 2 sides 90% confidence interval based on the Clopper-Pearson method will be presented by treatment arm (asciminib 60 mg + imatinib, asciminib 40 mg + imatinib and continued imatinib) for the following subgroups if, within each treatment arm, each subgroup includes at least 5 patients:

- prior imatinib duration < 5 years *versus* $\geq$ 5 years
- molecular response at screening (0.1% < BCR::ABL1 $\leq$ 1.0% *versus* 0.01% < BCR::ABL1 $\leq$ 0.1%)

2) A logistic regression of $MR^{4.5}$ status at 48 weeks on treatment arm (asciminib 60 mg + imatinib, asciminib 40 mg + imatinib and continued imatinib), prior imatinib duration category and molecular response status at screening will be performed.

12.5 Analysis of secondary endpoints

The secondary objectives are:

- To estimate efficacy (Rate of $MR^{4.5}$ at 48 weeks) of switch to nilotinib
- To estimate the difference in efficacy (Rate of $MR^{4.5}$ at 48 weeks) between asciminib 60 mg QD + imatinib and switch to nilotinib
- To estimate the difference in efficacy between asciminib 40 mg QD + imatinib and switch to nilotinib
- To assess additional parameters of the efficacy of asciminib 60 mg QD or 40 mg QD added to imatinib *versus* continued imatinib or switch to nilotinib
- To characterize the safety and tolerability profile of asciminib 60 mg or 40 mg + imatinib vs continued imatinib or switch to nilotinib
- To assess the pharmacokinetic profile of asciminib 60 mg or 40 mg and imatinib when administered in combination
- To estimate efficacy (Rate of $MR^{4.5}$ at 48 weeks) of asciminib 80 mg QD
- To characterize the safety and tolerability profile of asciminib 80 mg QD
- To assess the pharmacokinetic profile of asciminib 80 mg QD.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The secondary efficacy endpoints of this study are:

- Rate of $MR^{4.5}$ at 48 weeks for switch to nilotinib, for asciminib single agent and difference between asciminib + imatinib and nilotinib
- Sustained rate of $MR^{4.5}$ at 96 weeks (for all 4 randomized treatment arms)
- Rate of $MR^{4.5}$ at 96 weeks (for all 4 randomized treatment arms)
- Rate of $MR^{4.5}$ by 48 and 96 weeks (for all 4 randomized treatment arms)
- Rate of $MR^{4.5}$ by 48 weeks (for asciminib single agent cohort)
- Time to $MR^{4.5}$ (for all 4 randomized treatment arms and asciminib single agent cohort)
- Duration of $MR^{4.5}$ (for all 4 randomized treatment arms and asciminib single agent cohort)

12.5.1.1 Rate of $MR^{4.5}$ at 48 weeks

To estimate the efficacy of switch to nilotinib, the rate of $MR^{4.5}$ at 48 weeks and its 2 sided 90% confidence interval based on the Clopper-Pearson method will be presented for the switch to nilotinib arm using the FAS.

In addition, the difference in efficacy will be estimated between:

- asciminib 60 mg + imatinib and switch to nilotinib

and between

- asciminib 40 mg + imatinib and switch to nilotinib

To estimate the difference in efficacy between asciminib 60 mg + imatinib (or asciminib 40 mg + imatinib) and switch to nilotinib, the difference in the rate of $MR^{4.5}$ between asciminib 60 mg + imatinib (or asciminib 40 mg + imatinib) and switch to nilotinib at 48 weeks and its 2 sided 90% confidence interval will be provided using the Wald method.

To estimate the efficacy of asciminib single agent, the rate of $MR^{4.5}$ at 48 weeks and its 2 sided 90% confidence interval based on the Clopper-Pearson method will be presented using the FAS**–ASAC**. No formal comparison or estimate of the difference with the other treatment arms will be performed for this additional cohort.

12.5.1.2 Rate of sustained $MR^{4.5}$ at 96 weeks

The rate of sustained $MR^{4.5}$ at 96 weeks is defined as the proportion of patients who are in $MR^{4.5}$ at both 48 and 96 weeks under randomized treatment and who have no loss of $MR^{4.5}$ in between those two time points among all patients randomized to the respective treatment arm. Rate of sustained $MR^{4.5}$ and its 2 sided 90% confidence interval based on the Clopper-Pearson method will be presented by treatment arm using the FAS.

As the treatment duration for the asciminib single agent cohort is shorter, the rate of sustained $MR^{4.5}$ at 96 weeks will not be presented for the asciminib single agent cohort.

12.5.1.3 Rate of $MR^{4.5}$ at 96 weeks

The rate of $MR^{4.5}$ at 96 weeks will be calculated based on the FAS.

In this analysis "at" 96 weeks, only patients with $MR^{4.5}$ under randomized treatment at 96 weeks are considered as responders. A subject who has achieved $MR^{4.5}$ before 96 weeks, but who is no longer in $MR^{4.5}$ at 96 weeks, will be considered as a non-responder at 96 weeks. Patients who discontinued the randomized treatment for any reason prior to 96 weeks will be considered as non-responders.

Rate of $MR^{4.5}$ and its 2 sided 90% confidence interval based on the Clopper-Pearson method will be presented by treatment arm.

The rate of $MR^{4.5}$ at 96 weeks will not be presented for the asciminib single agent cohort.

12.5.1.4 Rate of $MR^{4.5}$ by 48 and 96 weeks

The rate of $MR^{4.5}$ by 48 and 96 weeks for all 4 randomized treatment arms will be calculated based on the FAS.

The rate of $MR^{4.5}$ by 48 weeks for asciminib single agent cohort will be calculated based on the FAS **- ASAC**.

In the analyses "by" a specific time point, patients who had achieved $MR^{4.5}$ under randomized treatment at or before the time point will be displayed as responders, whether they lost the response/discontinued treatment or not. Therefore, this response rate represents the best observed rate of $MR^{4.5}$ under randomized/ assigned treatment up to that specific time point.

Rate of $MR^{4.5}$ and its 2 sided 90% confidence interval based on the Clopper-Pearson method will be presented by treatment arm and for asciminib single agent cohort.

The cumulative incidence of $MR^{4.5}$ will also be graphically displayed by an increasing step-function. This curve will increase each time (after randomization) at which a new responder is observed and thus will increase up to the best observed response rate (e.g. up to 50% if half of the patients in the analysis population are able to achieve response).

12.5.1.5 Time to $MR^{4.5}$

Time to $MR^{4.5}$ is defined for patients in the $MR^{4.5}$ Responder set at the corresponding cut-off as: date of first $MR^{4.5}$ – date of randomization + 1. Descriptive statistics (range, median, quartiles, mean, SD) of time to $MR^{4.5}$ will be provided for the 4 randomized treatment arms and for asciminib single agent cohort separately.

12.5.1.6 Duration of $MR^{4.5}$

Duration of $MR^{4.5}$ is defined for patients in the $MR^{4.5}$ Responder set as the time from first documented $MR^{4.5}$ and the end date of $MR^{4.5}$ i.e. the earliest date of loss of $MR^{4.5}$ or CML-related death. Loss of $MR^{4.5}$ is defined as an increase of the BCR::ABL ratio to >0.0032% in a single blood sample, by International Scale.

For patients for whom none of the events above are reported, the duration will be censored. The duration of $MR^{4.5}$ (in weeks) is calculated as: (end date or censoring date of $MR^{4.5}$ - date of first $MR^{4.5}$ + 1)/7.

The survival distribution of duration of $MR^{4.5}$ will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals [Brookmeyer and Crowley 1982] of the medians, along with the proportion of patients who are still in $MR^{4.5}$ at 24, 48, 72 and 96 weeks and the associated 95% confidence intervals, will be presented for each treatment arm and for asciminib single agent cohort.

An additional analysis of the duration of **$MR^{4.5}$** will be performed where the end date of $MR^{4.5}$ is defined as the earliest date of **confirmed** loss of $MR^{4.5}$ or CML-related death. **Confirmed** loss of $MR^{4.5}$ is defined as an increase of the BCR::ABL ratio to >0.0032% in two consecutive blood samples, by International Scale. The date of **confirmed** loss of $MR^{4.5}$ is the date of the first one of the two blood sample assessments.

12.5.2 Safety endpoints

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

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). Data from the cross-over period will be summarized separately. Data from the asciminib single agent cohort (SS - ASAC) will be summarized separately.

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

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

1. pre-treatment period: from day of subject'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 (for patients who will crossover to receive asciminib 60 mg + imatinib, the on-treatment period will be from day of first administration of study medication to the day before the first administration of asciminib),
3. post-treatment period: starting at day 31 after last dose of study treatment (for patients who will crossover, the post-treatment period will start at day 31 after last dose of crossover study treatment),
4. cross-over period (for patients who will crossover to receive asciminib add-on treatment), from day of first dose of asciminib add-on treatment to 30 days after last dose of crossover study treatment.

Adverse Events

All information obtained on adverse events will be displayed by treatment arm and subject.

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

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

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

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

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

Vital signs

All vital signs data will be listed by treatment arm, subject, and visit/time and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

12-lead ECG

All ECG data will be listed by treatment arm, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

PR, QRS, QT, QTcF, and RR intervals will be obtained for each subject during the study. ECG data will be read and interpreted centrally.

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

Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (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, results will be categorized as low/normal/high based on laboratory normal ranges.

The following 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 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE version 5,

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE version 5 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE version 5,

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

For total cholesterol, calculated LDL and HbA1c, additional analyses will be conducted to describe the number and percentage of patients developing values outside of defined thresholds.

In addition to the above mentioned tables and listings, other exploratory analyses might be specified in the analysis plan.

12.5.3 Pharmacokinetics

PAS will be used in all pharmacokinetic data analysis and PK summary statistics. Descriptive summary statistics will be provided by treatment and visit/sampling time point. Plasma concentration data will be listed by treatment, subject, and visit/sampling time point for patients

treated with asciminib + imatinib in the Safety set. Data from the asciminib single agent cohort (PAS - ASAC) will be summarized separately.

Summary statistics will include mean (arithmetic and geometric), standard deviation (SD), CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations but will not be included in the geometric mean and CV calculation. The mean and individual plasma concentration by treatment and visit/sampling time point will be displayed graphically.

Pharmacokinetic parameters will be determined by non-compartmental method(s) using the pharmacokinetic profile of asciminib and imatinib. Pharmacokinetic parameters listed in Table 12-1 will be derived and reported, when feasible. For imatinib metabolite (N-desmethyl imatinib [CGP74588]), only C_{max}, T_{max}, AUC_{last} and the metabolite-to-parent AUC ratio will be calculated.

Pharmacokinetic parameters will be listed by treatment and subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is T_{max} where median, minimum and maximum will be presented.

Table 12-1 Non-compartmental pharmacokinetic parameters

AUC_{last}	The AUC from time zero to the last measurable concentration sampling time (Tlast) (mass x time x volume-1)
AUC_{tau}	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
C_{max}	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
T_{max}	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T_{last}	Time of last measurement (time)

If appropriate, the potential relationship between asciminib exposure and primary efficacy endpoint or most critical safety endpoints may be assessed by graphic exploration and/or statistical modeling as appropriate. Details of the analysis and results may be reported separately.

12.6 Analysis of exploratory endpoints

12.6.1 Efficacy exploratory endpoints

One exploratory objective for this trial is to assess the proportion of patients eligible for TFR at end of the study. For the purpose of endpoint definition to meet the TFR criteria, patients have to be treated with randomized treatment up to the end of study (96 weeks after the first dose of study drug of the last randomized subject) and based on the last five quarterly performed PCR assessments: (1) both first and last assessments are $MR^{4.5}$, (2) no assessment is worse than MR^4, and (3) no more than two assessments are between MR^4 and $MR^{4.5}$, among all patients randomized to the respective treatment arm.

12.6.2 Other exploratory endpoints

For cross-over patients (see Section 12.1), the efficacy (e.g. the time from cross-over to MR[4.5]) and safety of cross-over treatment (asciminib add-on treatment) will be summarized. Additional analyses may be performed. The details will be further specified in the statistical analysis plan (SAP).

12.6.3 Biomarkers

As a project standard, only biomarkers collected in the clinical database will be analyzed. Since this study is not adequately powered to assess specific biomarker related hypotheses, the statistical analyses of these data should be considered exploratory and hypotheses generating 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 or discontinue the analysis of blood due to either practical or strategic reasons (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.

The biomarker analyses may be reported in a separate biomarker report.

The proposed data analysis aligned with the exploratory biomarker objectives as well as the relevant aspects of data handling will be addressed in a dedicated SAP.

Unless otherwise specified, all patients with evaluable biomarker measurements in the FAS will be included in the biomarker data analysis.

Additional exploratory biomarker analyses may be performed depending on the data.

For all patients, the biomarker objectives are:

- To explore mechanisms of resistance associated with asciminib and other TKI treatments via assessment of CCI [redacted] This analysis will be done for only treatment arms 1-4, a sample is not collected or analyzed for patients in the asciminib single agent cohort.
- To explore relevant CCI [redacted]
- To evaluate CCI [redacted].

12.6.4 Patient Reported Outcomes

The EORTC QLQ-C30 questionnaire along with the disease-specific chronic myeloid leukemia module (EORTC QLQ-CML24), TSQM and FACIT GP5 will be used to collect data on the patient-reported outcome measures of health-related quality-of life, treatment satisfactions and treatment-related side effects from baseline to EOT by treatment arms. Scoring of raw QoL data

and methods for handling of missing items or missing assessments will be handled according to scoring manuals for each respective patient questionnaire (Fayers 2001). No imputation will be applied if the total or subscale scores are missing at a visit. The number of patients completing each patient questionnaire and the number of missing or incomplete assessments will be summarized by each treatment arm for each scheduled assessment time points.

The FAS will be used for analyzing PRO data. No formal statistical tests will be performed of PRO data.

Descriptive statistics will be used to summarize the scored scales for the EORTC, GP5 and TSQM questionnaires at each scheduled assessment time point by treatment arm. Additionally, change from baseline in the domain scores at the time of each assessment will be summarized. 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.

Additional analysis may be performed and details will be described in the analysis plan.

12.7 Interim analyses

An interim analysis will be performed in order to gain an early insight into the safety and efficacy of the asciminib add-on combination which will help in planning the future development of the asciminib combination. The interim analysis will be performed when at least 40 (50%) patients have been randomized and have been followed for their 24 weeks visit assessment or have discontinued treatment. The enrollment will continue during this 24 weeks follow-up. The interim analysis will include all randomized patients until the date of data cut-off, and include both efficacy (e.g. BCR::ABL1 assessment overtime, MR^4 and $MR^{4.5}$ rate at different time-points) and safety (e.g. Adverse Events and laboratory values) summaries, which will be detailed in the Statistical Analysis Plan for the interim analysis. It is not planned to write an interim CSR based on this interim analysis. Based on the results of the interim analysis a benefit risk balance will be assessed for the two add-on treatment arms.

The primary analysis will be performed after all patients in the 4 randomized treatment arms have completed Week 48 or discontinued prior to Week 48. A Week 96 analysis will be performed after all patients in the 4 randomized treatment arms have completed Week 96 and/or discontinued study prior to Week 96. A final analysis will be performed with all available data from asciminib single agent cohort at the End of Study.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Based on the subset data in ENESTcmr [CAMN107A2405] and ENESTnd [CAMN107A2303], it is assumed that the rate of $MR^{4.5}$ at 48 weeks is ranging between 3% and 10% in the continued imatinib arm.

With 20 patients per arm enrolled in the two asciminib + imatinib arms and the continued imatinib arm, the precision of the estimates of the difference between 1) asciminib 60 mg + imatinib *versus* continued imatinib and 2) asciminib 40 mg + imatinib *versus* continued imatinib for different scenarios is shown in Table 12-2.

Table 12-2 90% Confidence intervals for 30% difference rate between the arms

Continued imatinib $MR^{4.5}$ rate	Asciminib + imatinib $MR^{4.5}$ rate	Difference	90% CI
3%	33%	30%	[12% - 48%]
5%	35%	30%	[11% - 49%]
7%	37%	30%	[10% - 50%]
10%	40%	30%	[9% - 51%]

With 20 patients per arm, the width of the two-sided 90% confidence interval for the difference in $MR^{4.5}$ rate at 48 weeks between each asciminib + imatinib and switch to nilotinib will not be larger than 0.520 (corresponding to the situation when the estimated $MR^{4.5}$ rate is 0.5 in both arms (i.e. no difference)). Its lower bound will exclude 0 assuming a true 30% difference in the $MR^{4.5}$ rate at 48 weeks.

In addition, the two-sided 90% Clopper-Pearson confidence interval for the $MR^{4.5}$ rate at 48 weeks will have a width not larger than 0.396 (the worst case corresponding to the situation when the $MR^{4.5}$ rate at 48 weeks is 0.5).

An interim analysis will be performed when at least 40 (50%) patients have been randomized and have been followed for their 24 weeks visit assessment or have discontinued treatment. The interim analysis will include all randomized patients until the date of data cut-off, and include both efficacy (e.g. BCR::ABL1 assessment overtime, MR^4 and $MR^{4.5}$ rate at different time-points) and safety (e.g. Adverse Events and laboratory values) summaries. There will however be no adjustment for multiplicity due to the interim analysis as there is no formal comparison to be performed between the treatment arms, and only the estimation of effect size is planned in the primary analyses.

These calculations were made using the software package PASS 11.

12.8.2 Secondary endpoint(s)

For the primary objective, 20 patients per arm will be enrolled in the two asciminib + imatinib arms and the continued imatinib arm. With the same number of patients, i.e. 20 patients, in the switching to nilotinib arm, the two-sided 90% Clopper-Pearson confidence interval for the $MR^{4.5}$ rate at 48 weeks will have a width not larger than 0.396 (the worst case corresponding to the situation when the $MR^{4.5}$ rate at 48 weeks is 0.5).

In addition, the width of the two-sided 90% Wald confidence interval for the difference in $MR^{4.5}$ proportions rate at 48 weeks between each asciminib + imatinib and switch to nilotinib will not be larger than 0.520 (corresponding to the situation when the estimated $MR^{4.5}$ rate is 0.5 in both arms (i.e. no difference)).

For the 20 patients enrolled in the asciminib single agent cohort, the two-sided 90% Clopper-Pearson confidence interval for the $MR^{4.5}$ rate at 48 weeks will have a width not larger than 0.396 (the maximum width corresponding to the situation when the $MR^{4.5}$ rate at 48 weeks is 0.5).

These calculations were made using the software package PASS 11.

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, EU Clinical Trial Regulation 536/2014 once transfer is completed, 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, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to participant patients.

Any amendments to the protocol will require IRB/IEC and Health Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Signing a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance represantatives, designated agents of Novartis, IRBs/ IECs, and regulatory authorities as required.
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Taking 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 must be notified of this action and the IRB/IEC at the study site must be informed according to local regulations.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.
- Informing Novartis immediately if an inspection of the clinical site is requested by a regulatory authority.

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 the European Union Drug Regulatoring Authorities Clinical Trials (EudraCT) or the Clinical Trials Information System (CTIS) public website. 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 or CTIS public website once transfer to EU Clinical Trial Regulation 536/2014 is completed , etc).

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

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.

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

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 (SOPs) 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 SOPs, and are performed according to written Novartis processes.

13.5 Participant engagement

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

- Thank You letter
- Plain language trial summary - after CSR publication
- Individual study results – 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 patients 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 subject 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 subject 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 Appendix 1: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-1 Liver Event and Laboratory Trigger Definitions

	Definition/threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT/AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal

Table 16-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	• Establish causality	
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality	Investigator discretion

[a] Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

[b] (General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

[c] Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal

16.2 Appendix 2: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-3 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50%[+] compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥ 1+ Albumin- or Protein-creatinine ratio increase ≥ 2-fold Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; Protein-creatinine ratio (PCR) ≥ 150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption or discontinuation
New dipstick glycosuria ≥ 1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥ 1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed	
Monitor patient regularly (frequency at investigator's discretion) until either:	
Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or	
Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.	

[+] Corresponds to KDIGO criteria for Acute Kidney Injury

16.3 Appendix 3: List of concomitant medications which are prohibited or to be used with caution

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.

The following lists are based on the [Oncology Clinical Pharmacology Drug-Drug Interaction Database] (release date: April 2021), 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). These lists are not comprehensive and are only meant to be used as a guide. Please contact the medical monitor with any questions. If a medication appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.

16.3.1 Concomitant medications to be used with caution for asciminib + imatinib arms

Table 16-4 Concomitant medications to be used with caution for asciminib + imatinib arms

Category	Drug Names
Strong CYP3A4 inhibitors	ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[3], indinavir/ritonavir[3], tipranavir/ritonavir[3], ritonavir, cobicistat, indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir[3], elvitegravir/ritonavir[3], saquinavir/ritonavir[3], lopinavir/ritonavir[3], itraconazole, voriconazole, mibefradil, clarithromycin, posaconazole, telithromycin, grapefruit juice[2], conivaptan, nefazodone, nelfinavir, idelalisib, boceprevir, atazanavir/ritonavir[3], darunavir/ritonavir[3]
Narrow Therapeutic index substrates of CYP2C9	phenytoin, warfarin
CYP3A4/5 substrates with narrow therapeutic index	alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus, tacrolimus, terfenadine
Torsade de pointe (TdP) TdP/QT risk: Known*	amiodarone, anagrelide, arsenic trioxide, astemizole (off US market), azithromycin, bepridil (off US market), chloroquine, chlorpromazine, cilostazol, cisapride (off US market), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on US market), donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, grepafloxacin (off market worldwide), halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (off market worldwide), mesoridazine (off market worldwide), methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine hydrochloride, pentamidine, pimozide, probucol (off market worldwide), procainamide (oral off US market), propofol, quinidine, sevoflurane, sotalol, sparfloxacin (off US market), sulpiride (not on US market), terfenadine (off US market), thioridazine, vandetanib

[1] Herbal product

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

[3] Combination ritonavir-boosted regimens are listed here as strong CYP3A inhibitors (to avoid potential confusion), even though some are considered moderate CYP3A inhibitors in the University of Washington's DDI Database

16.3.2 Prohibited comedications for asciminib + imatinib arms

Table 16-5 Prohibited comedication for asciminib + imatinib arms

Category	Drug Names
Strong CYP3A4 inducers	carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, rifampicin, mitotane, St. John’s wort (*Hypericum perforatum*)

16.3.3 Concomitant medications to be used with caution for asciminib single agent cohort

Table 16-6 Concomitant medications to be used with caution for asciminib single agent cohort

Category	Drug Names
Strong CYP3A4 inducers	carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, rifampicin, mitotane, St. John’s wort (*Hypericum perforatum*)
CYP3A4/5 substrates with narrow therapeutic index	alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus, terfenadine
Narrow Therapeutic index substrates of CYP2C9	phenytoin, warfarin
OATP1B substrates	aliskiren, ambrisentan, anacetrapib, atenolol, asunaprevir, atogepant, atorvastatin, bosentan, bromocriptine, caspofungin, celiprolol, danoprevir, digoxin, docetaxel, eliglustat, empagliflozin, ezetimibe, fimasartan, fexofenadine, fluvastatin, glyburide, ibrexafungerp, maraviroc, methotrexate, montelukast, nateglinide, olmesartan, paclitaxel, pirataprevir, pitavastatin, pravastatin, repaglinide, revefenacin, rifampicin, rosuvastatin, saquinavir, simvastatin, telmisartan, tezacaftor, ticlopidine, valsartan
BCRP substrates	alpelisib, atorvastatin, baricitinib, daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib**, methotrexate, mitoxantrone, ozanimod, paritaprevir, pitavastatin, rimegepant, rosuvastatin, irinotecan, ethinyl estradiol, simvastatin, sofosbuvir, sulfasalazine, tenofovir, tezacaftor, topotecan, ubrogepant, venetoclax

Category	Drug Names
Torsade de pointe (TdP) TdP/QT risk: Known*	amiodarone, anagrelide, arsenic trioxide, astemizole (off US market), azithromycin, bepridil (off US market), chloroquine, chlorpromazine, cilostazol, cisapride (off US market), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on US market), donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, grepafloxacin (off market worldwide), halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (off market worldwide), mesoridazine (off market worldwide), methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine hydrochloride, pentamidine, pimozide, probucol (off market worldwide), procainamide (oral off US market), propofol, quinidine, sevoflurane, sotalol, sparfloxacin (off US market), sulpiride (not on US market), terfenadine (off US market), thioridazine, vandetanib

*Check crediblemeds.org/healthcare-providers/drug-list for the most updated list.

**Imatinib must not be combined with ABL001 in asciminib single agent cohort.