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ABL001/asciminib

Clinical Trial Protocol CABL001J12301

A phase III, multi-center, open-label, randomized study of oral asciminib versus Investigator selected TKI in patients with newly diagnosed Philadelphia Chromosome Positive Chronic Myelogenous Leukemia in Chronic Phase

Document type:	Amended Protocol Version (Clean)
EUDRACT number:	2021-000678-27
Version number:	02
Clinical Trial Phase:	III
Release date:	15-May-2023 (final)

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

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List of abbreviations

2G	Second Generation
ABL	Abelson proto-oncogene
AE	Adverse Event
AESI	Adverse event of special interest
ALL	Acute lymphoblastic leukemia
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
AP	Accelerated phase
AST	Aspartate Aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the curve
AV block	Atrioventricular block
BC	Blast crisis
BCR	Breakpoint Cluster Region gene
BCR-ABL1	BCR-ABL1 fusion gene (considered equivalent to BCR::ABL1)
BCR::ABL1	BCR::ABL1 fusion gene (considered equivalent to BCR-ABL1)
BCR-ABL1 BCR::ABL1	BCR-ABL- fusion protein (considered equivalent to BCR::ABL1) BCR::ABL1 fusion protein (considered equivalent to BCR-ABL1)
BCRP	Breast Cancer Resistant Protein
BID	*bis in diem*/twice a day
BLQ	Below the Limit of Quantification
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CBC	Complete Blood Count
CCI	Charlson Comorbidity Index
CCyR	Complete Cytogenetic Response
CD-transferrin	Carbohydrate Deficient transferrin
CFR	Code of Federal Regulations
CHR	Complete Hematological Response
CI	Confidence Interval
CrlCl	Creatinine Clearance
CML	Chronic Myelogenous Leukemia
CML-AP	Chronic Myelogenous Leukemia-Accelerated Phase
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	Central Nervous System
COA	Clinical Outcome Assessment
CP	Chronic phase
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed tomography

CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Clinical Trial Team
CV	coefficient of variation
CYP3A4	Cytochrome P450 3A4
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DS&E	Drug Safety and Epidemiology
DTI	Direct Thrombin Inhibitors
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EFS	Event free survival
EGFR	Epidermal Growth Factor Receptor
ELN	European Leukemia Network
ELTS	EUTOS Long-Term Survival
EMA	European Medicines Agency
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of life Questionnaire
EOT	End of Treatment
EQ	EuroQol
EQ-VAS	EuroQol Visual analog scale
ER	Emergency Room
ERCP	Endoscopic Retrograde Cholangio Pancreatography
eSAE	electronic Serious Adverse Event
eSource	electronic Source
EU	European Union
EU CTR	European Union Clinical Trial Regulation
EUTOS	EUropean Treatment Outcome Study
[redacted]	[redacted]
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFS	Failure Free Survival
FIH	First In Human
FSH	Follicle Stimulating Hormone
FU	Follow Up
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLDH	Glutamate Dehydrogenase
GP	General Practitioner

h	Hour
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCRU	Healthcare Resource Utilization
HCV	Hepatitis C Virus
HDL	High density lipoprotein
HEV	Hepatitis E Virus
HIV	Human immunodeficiency virus
HR	Hematological Response
HRQoL	Health-Related Quality of Life
HSV	Herpes Simplex Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
IE	Intercurrent Events
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IMA	Imatinib
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IS	International Scale
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LDL	Low density lipoprotein
LLN	lower limit of normal
LLOQ	lower limit of quantification
MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
MI	Myocardial Infarction
mL	milliliter(s)
MMR	Major Molecular Response
MR	Molecular Response
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
OATP1B	Organic anion-transporting polypeptide 1B
OHP	Off-site Healthcare Professional
OS	Overall survival
P-gp	Permeability glycoprotein
PAS	Pharmacokinetic analysis set
PBPK	Physiologically based pharmacokinetic

PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PDGF	Platelet-derived growth factor
PFS	Progression-Free Survival
Ph+	Philadelphia chromosome positive
PK	Pharmacokinetic(s)
PLT	Platelets
PRO	Patient Reported Outcomes
PSDS	Post-Study Drug Supply
PT	prothrombin time
PTA	Post Trial Access
QD	Once a day
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RD	Recommended Dose
RDE	Recommended dose for expansion
RNA	Ribonucleic acid
RoW	Rest of World
RQ-PCR	Real time quantitative polymerase chain reaction
RU	Resource Utilization
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering committee
SD	standard deviation
SOP	Standard Operating Procedure
Sp	Specialist
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total bilirubin
TdP	Torsades de Pointes
TFQ	Trial Feedback Questionnaires
TKI	Tyrosine Kinase Inhibitor
TSH	Thyroid Stimulation Hormone
TTDAE	Time To Discontinuation of study treatment due to AE
TTF	Time to treatment failure
UC	Urgent Care
UGT	Uridin diPhospho-glucuronosyltransferase
ULN	upper limit of normal
US	United States
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
CE marking	A marking by which a manufacturer indicates that a device is in conformity with the applicable requirements set out in European Union legislation providing for its affixing. CE marking of medical devices is required prior to lawfully placing them on the European Union market.
Clinical Outcome Assessment (COA)	A measure that described or reflects how a person feels, functions or survives
Clinical Trial Team	A group of people responsible for planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician, etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed- up or traced over time
Control drug	A study intervention (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained; The action of enrolling one or more participants
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to Novartis/Sponsors and other oversight authorities, as appropriate
Estimand	As defined in the ICH E9 (R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as

	well as the specification of how the remaining intercurrent events are addressed and a population- level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Investigational Product/ Investigational Medicinal product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference (such as an active comparator) in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Investigational Medical Device	Medical Device being assessed for safety or performance in a clinical investigation. This includes devices already on the market and being evaluated for new intended uses, new populations, new materials, or design changes
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient) "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the participant about the status of a participant's health condition without amendment or interpretation of the participant's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis/Sponsor for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol

Remote	Describes any trial activities performed at a location that is not the investigative site
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study device	Study device is a medical device (marketed or investigational) that is used in a circumstance that makes it part of the investigation.
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the Investigative site where the Investigator will conduct the trial
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

Amendment 02 (15-May-2023)

Amendment rationale

As of 15-May-2023 the enrollment in the study is complete, 475 participants have been screened, and 405 participants have been randomized and 347 are receiving treatment. The study is ongoing.

The main purpose of this protocol amendment is to:

Clarify dose modification guidelines for hepatotoxicity for asciminib and dose discontinuation rule as applicable to both treatment arms:

1. As the study includes patients with baseline total bilirubin elevation (< 3xULN are eligible), the dose modification guidelines for patients with elevated bilirubin or ALT/AST at baseline have been clarified as follows:
   - For ALT/AST elevations (when baseline elevated): Dose modification criteria have been revised to ensure that the combination of baseline values (3x, 5x etc. change from baseline) with ULN levels (5x ULN, 8x ULN, etc.) are taken into consideration
   - Update dose modification criteria for baseline elevated total bilirubin levels: The reference to baseline elevated bilirubin levels was removed in the recommendations for dose modification of asciminib in response to drug-induced elevation of bilirubin.

   In addition, guidance for discontinuing treatment for elevations of AST and ALT > 20 x ULN has been also clarified. In the current protocol, patients with (higher than 20 x ULN) may continue in the study as per guidelines "hold the dose and resume at a lower dose upon resolution". Although based on the current safety data on asciminib there is a low likelihood of a >20 x ULN of AST/ALT occurrence at first presentation of a hepatic adverse event, as a conservative measure guidance for discontinuing treatment for elevations > 20 x ULN has been clarified in this protocol amendment as below. Of note, no patient in this study has met this criterion till date. For additional information on liver abnormalities, please refer to ABL001 IB Ed10- 7.2.7.
- For isolated ALT/AST elevations (when baseline normal): Permanently discontinue if ALT/AST is > 20x ULN

The rules for discontinuation due to hematologic and non-hematologic AEs were placed more prominently in the protocol to clarify that these rules apply to both treatment arms for prolonged treatment interruption.

If a participant requires a dose interruption more than 28 days for a non-hematologic toxicity, then the participant must be discontinued from the study treatment. If a hematologic toxicity (cytopenia Grade 3 or 4) lasts for more than 42 days without recovery to at least a Grade 2, despite the study treatment interruption and adequate management (including hematopoietic growth factors), then the participant must be discontinued from the study treatment.

Additionally, the following changes have been implemented:

2. Re-escalation rules for participants receiving asciminib have been changed to allow more than one re-escalation in case the event is considered to be significantly different than the one(s) experienced previously.

3. The concomitant medications to be used with caution have been updated. 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 protocol marketing requirements request per FDA (ABL001 IB Ed.10 – Section 1.4.2).

Editorial changes to correct typos and provide clarifications have been implemented throughout the protocol to improve readability and are summarized as follows:

- Clarification to the visit assessment section
- Clarification on the blood sampling for confirmed loss of MMR
- Clarification on the requirements of ePRO assessments
- Update on the duration of the storage of source documents and ICF documents of 15 years
- Clarification to the ELN treatment failure criteria at 3 months
- Requirement of unscheduled assessments of any type as per the Investigator's decision and their documentation in the eCRF
- Clarification on the post-trial access of asciminib. The eligibility criteria for the post-trial access were removed as they are specified in the rollover study protocol CABL001A2001B.
- The CRFs for collection of smoking history and Charlson comorbidity index were already a part of the study, the VES and Screening sections have been updated to reiterate that these should be collected as a part of baseline medical and cardiovascular history
- Definition of confirmed loss of MMR has been clarified where previously stated "subsequent sample analysis within 4-6 weeks" has been replaced by "analysis of another sample taken after an interval of not less than 4 weeks and not more than 6 weeks". This update does not change the collection of data, schedule of assessment or analysis for this molecular response parameter.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track-changes version of the protocol using red underlined font for insertions.

The following sections, tables and figures were changed:

- List of abbreviations
- Glossary of terms: Added the definition for 'Investigational Product/ Investigational Medicinal product' per latest mandatory template modification
- Section 1.2.2 Preliminary efficacy and safety: The whole section was updated based on ABL001 IB Ed.10
- Section 4.6 Rationale for Public Health Emergency mitigation procedures: Updated per latest mandatory template modification
- Section 6.1.5 The previous title "Guidelines for continuation of treatment" was updated to "Post-trial access to treatment" to be more precise. Clarification on post-trial access added. Removed the criteria to continue asciminib administration and to discontinue the treatment
- Section 6.1.6 Treatment duration: Treatment failure added to be consistent in wording throughout the protocol

- Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action: Updated for OATP1B, BCRP substrates as per ABL001 IB Ed.10
- Section 6.5.1 Dose modifications:
  - The rules for discontinuation due to hematologic and non-hematologic AEs were placed more prominently in the protocol to clarify that these rules apply to both treatment arms for prolonged treatment interruption
  - Change of re-escalation instructions. More than one re-escalation may be allowed under certain circumstances
  - Updates of table 6-2 Criteria for dose reduction / interruption and re-initiation of asciminib treatment for adverse drug reactions for hepatic investigations
    - Repetitive wording for dose interruption and discontinuation criteria removed
    - Updates and clarification on hepatic investigations: Isolated Total bilirubin (TBL) elevations, isolated Aspartate (AST) and Alanine (ALT) aminotransferases elevations, and combined AST and ALT and TBL elevations
  - Clarification added for participants treated with the Investigator selected TKI
  - Wording updated from Liver Function Tests (LFT) to liver tests to be more precise
- Section 6.5.2.1 Follow up on potential drug-induced liver injury (DILI) cases:
  - Information regarding pediatric patients was removed as it is not applicable for the trial.
  - Wording updated from Liver Function Tests (LFT) to liver tests to be more precise
- Section 8 Visit schedule and assessments:
  - Clarification for unscheduled visits added “In case unscheduled assessments of any type are required, they may be performed as per Investigator’s decision and will be recorded in the appropriate eCRF.”
  - Table 8-1 Assessment Schedule updated to include Smoking History and CCI assessments, Serum Pregnancy Test and Prior/ Concomitant Medication were updated
- Section 8.1 Screening: Clarification added for Smoking History and Charlson comorbidity index CCI assessments
- Section 8.3.1 Molecular Response: Clarification added for blood sampling for confirmed loss of MMR, for additional unscheduled samples and for discontinuation of treatment
- Section 8.4 Safety: Table 8-3 Safety and tolerability assessments updated to include the spleen size if extramedullary involvement is detected
- Section 8.5.1 Clinical Outcome Assessments (COAs): Clarification added that COA are required for patients who discontinued the treatment
- Section 8.5.2.3 Pharmacogenomics: Clarification for treatment arm for pharmacogenetics samples collection added
- Section 9.1.1 Discontinuation from study treatment: Added clarification in the Treatment Failure Criteria and for discontinuation of treatment
- Section 11.3 Site monitoring: Added the requirement to retain source documents and original ICFs signed by the participants for 15 years
- Section 12.8.1.1 Other Efficacy Endpoints:

  - Lack of efficacy was updated to unsatisfactory treatment response to be consistent in wording throughout the protocol
  - Clarification on treatment failure criteria at 3 months added
- Section 12.9.4 Exploratory Patient Reported Outcomes: Update of questionnaire naming
- Section 12.11 Sample size calculation: Typo corrected for primary endpoint
- Section 16.1 Appendix 1: Concomitant Medications.
  - Information for prohibited medication removed as the table for prohibited medication has been removed in a previous protocol amendment
  - OATP1B and BCRP substrates updated as per ABL001 IB Ed.10
- Section 16.2 Appendix 2: Wording updated from Liver Function Tests (LFT) to liver tests to be more precise

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 01 (09-May-2022)

Amendment rationale

As of 28-Mar-2022, 101 participants have been screened in the study and 69 participants have been randomized and are receiving treatment. The study is ongoing.

The main purpose of this protocol amendment is to:

- Further clarify requirements for eligibility, dose administration and pregnancy testing in view of the comparator arm being approved TKIs selected by Investigators with the below changes:
  - Clarify Inclusion Criterion 3 defining diagnosis of CML-CP to align with updated treatment recommendations (ELN 2020) and clinical practice
  - Exclusion criterion 1 has been updated to allow either imatinib, or nilotinib, or dasatinib or bosutinib for ≤ 2 weeks prior to randomization (Original Protocol only allowed imatinib). Based on feedback from Investigators, the use of any of these TKIs is standard for initial disease control, and is especially applicable to sites that are referral centers. It is not expected that a short course of TKI will impact on the efficacy endpoints. Allowing all comparators rather than only one will allow reduction of any selection bias based on early intolerance to any specific TKI.
  - Update of Exclusion Criteria 14 (ii) concerning use of effective contraception during treatment with asciminib
  - *ONLY for US Original Protocol*: the requirement for male contraception from the US Version of the protocol has now been removed following FDA acceptance of the non-requirement in the approved label for asciminib. Asciminib is not genotoxic, and no embryo- and fetotoxic effects can be anticipated via seminal fluid. Thus, male contraception is not required by the male participants in asciminib clinical trials.
  - Exclusion Criterion 15 updated to include known hypersensitivity to study treatment.
  - For drug administration of study treatments other than asciminib, instructions on following local labels have been emphasized, including for participants with hepatic and renal impairment for Investigator selected TKIs
  - Additional clarity has been provided for pregnancy testing which must be performed monthly during the treatment period and at the 30-days follow up visit when applicable.
- Analysis for BCR-ABL≤1% has been added as a secondary endpoint. BCR-ABL1 ≤1% is considered an important milestone for assessing response to treatment for patients with CML-CP. The NCCN and ELN treatment guidelines consider the achievement of this level of response at 1 year of treatment to be an optimal response to treatment. The statement that BCR-ABL≤1% is equivalent to CCyR has been removed as this is now being included as a separate endpoint.
- Update based on asciminib IB Ed.9
- Addition of information concerning FDA (US) and PMDA (Japan) approval of asciminib.
- Update 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

- Provide additional clarity on Exclusion Criterion 10 regarding eligibility based on serologic markers for hepatitis B
- Add details on remote procedures that can be implemented in case of a Public Health emergency that limits or prevents on-site study visits
- Add use of hydroxyurea for urgent control of high cell counts during the first 2 weeks of study treatments
- Mention vaccines in concomitant therapy to be recorded
- Add information on re-screening
- Update guidance for missed doses and compliance requirements
- Clarify the timing for visit schedule for assessment
- Add information on fasting condition for lab analysis
- Add collection of EORTC QLQ-C30 and QLQ-CML24 questionnaires 4, 8 and 12 weeks after EOT
- Add PROs guidance in case questionnaire(s) is/are not available in local language and specify timelines for ePRO completion
- Update for biomarker testing for patients enrolled in China
- Remove the recommendation to use sunblock and avoid tanning beds
    - Preclinical studies suggested that asciminib could cause phototoxicity and photosensitization. However, at the NOAEL of 60 mg/kg/day in animal studies, the Cmax was 12,000 ng/mL, an exposure that is 15- or 6-fold higher than the Cmax exposure in patients at the dose of 40 mg b.i.d. or 80 mg q.d respectively. . Among all patients with CML-CP/AP treated with any dose of asciminib as single agent phototoxicity AEs were reported in 12/356 patients (3.4%). Reported events included photosensitivity reaction (2.5%), sunburn (0.8%) and retinal phototoxicity (0.3%). These events were Grade 1-2 and resolved without dose interruption of asciminib. In study CABL001X2101, patients with CML-CP harboring the T315I mutation treated with single agent asciminib 200 mg BID, phototoxicity AEs (photosensitivity reaction) were reported in one patient (2.1%) only. Importantly, no serious adverse events of phototoxicity have been observed in any population investigated. Thus, as a minimal number of patients have shown low grade phototoxicity AEs, and symptoms can be managed with routine clinical practice guidelines
- Implement editorial changes throughout the protocol to correct typos and provide clarifications where required

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

Changes to the protocol

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

The following sections, tables and figures were changed:

- List of abbreviation: updated based on Protocol Amendment changes

- Glossary of terms: updated based on new Novartis template version implementation plan
- Protocol Summary: updated based on Protocol Amendment changes
- Section 1.1.1: The new nomenclature of BCR::ABL1 is mentioned.
- Section 1.2.2.2:
  - updated based on asciminib IB Ed.9 and
  - information concerning FDA (US) and PMDA (Japan) approval was added
- Section 2: Added secondary endpoint of BCR-ABL≤1%
- Section 3 and Section 4:
  - information on timelines for pre-randomization selection, dosing requirements for participants with baseline renal or hepatic impairment, remote procedure, updated wording regarding treatment allowed prior to randomization
  - Also in Section 5: Exclusion criterion 1 (renumbered from 1 to 1a) has been updated to allow either imatinib, or nilotinib, dasatinib or bosutinib for ≤ 2 weeks prior to randomization (Original Protocol only allowed imatinib)
- Section 4.5: *ONLY for US Original Protocol* - removed male contraception requirement
- Section 5.1: updated wording of Inclusion Criterion 3 (renumbered from 3 to 3a) defining diagnosis of CML-CP; clarified Inclusion criterion 6 (renumbered from 6 to 6a) for limits for laboratory values
- Section 5.2:
  - exclusion criterion 1 (renumbered from 1 to 1a) has been updated to allow either imatinib, or nilotinib, dasatinib or bosutinib for ≤ 2 weeks prior to randomization (Original Protocol only allowed imatinib)
  - included testing details for Exclusion Criterion 10 (renumbered from 10 to 10a)
  - updated Exclusion criterion 14 (renumbered from 14 to 14a) to:
    - update use of effective contraception during treatment with asciminib (subpoint ii)
    - *ONLY for US Original Protocol*: removed sub-point from the US local protocol to remove the requirement for male contraception by the male participants (following FDA approval)
    - update subpoint to address that males participants taking asciminib do not require contraception
  - added Exclusion Criterion 15 for known hypersensitivity to the study treatment
- Section 6.1 / 6.1.1 / 6.5: Inclusion of comment regarding for dosing requirements for participants with renal or hepatic impairment
- Section 6.1.1: update of Table 6-1 with additional dosage; updated information
- Sections 6.2 / 6.2.1 / 6.2.2:
  - clarification of local label use for study treatments other than asciminib
  - added vaccines in concomitant therapy to be recorded
  - also in Section 5: added use of hydroxyurea for urgent control of high cell counts during the first 2 weeks of study treatments
- Section 6.3.1: added information on re-screening in case 3 months are exceeded

- Section 6.3.2: clarity on ELTS score assessment at diagnosis
- Section 6.6 / 6.7: updated text in remote procedure
- Section 6.7.2:
  - inclusion of comment regarding dosing requirements for participants with renal or hepatic impairment and clarification of local label
  - update guidance for missed doses and compliance requirements
  - removal of the recommendation to use sunblock and avoid tanning beds
- Section 7:
  - updated text in remote procedure and ICF procedure based on Novartis template version implementation plan.
  - ONLY for US Original Protocol: removed section on male contraception
- Section 8: Clarification on the required timing for visit schedule for assessment and remote procedure
- Table 8-1: VES alignment with protocol text; addition of EORTC QLQ-C30 and QLQ-CML24 questionnaires 4, 8 and 12 weeks after EOT, added notes on study windows based on visits and assessments; Pregnancy Test (Urine) merged cells from Baseline to 30 Days Safety follow- up, update of footnotes
- Section 8.1: clarity on ELTS score assessment at diagnosis
- Section 8.1.2: based on Novartis template version implementation plan
- Section 8.3.1: clarify definitions for loss of MR4 and MR 4.5
- Section 8.3.2: removed statement of equivalence between BCR-ABL≤1% and CCyR
- Section 8.3.4: clarify timeline
- Section 8.4.1: clarity on fasting condition for lab analysis
- Section 8.4.2: update of ECG schedule and information
- Section 8.4.3: added 30 Days Safety follow- up urine pregnancy test; updated information on childbearing potential definition; updated childbearing potential definition due to new protocol template text; *ONLY for US Original Protocol*: removed section on male contraception
- Table 8-2 / 8-5 /8-6 / 8-7: footnote update
- Section 8.5.1: added clarity on PROs schedule and added guidance on PROs in case questionnaire is/are not available in local language; added information on TFQ data
- Section 8.5.2.3: updated amount of blood needed for pharmacogenomics
- Section 8.5.3: updated China biomarker testing and mutation analysis to support discontinuation criteria; whole blood analysis of cytokines removed from exploratory biomarkers due to technical infeasibility
- Section 9.1: update in Section title
- Section 9.1.1: inclusion of information on treatment failure criteria; update in Section title
- Section 9.1.2: new section added with updated text for discontinuation from study; subsequent numbering in Section 9 is updated accordingly:
  - Previous Section 9.1.2 is now 9.1.3
  - Previous Section 9.1.3 is now 9.1.4

  - Previous Section 9.1.4 is now 9.1.5
- Section 9.1.5: updated text for on early study termination
- Section 10.1.2: remove repetition
- Section 10.1.3: added requirements for SAE reporting timeline; update based on Novartis template version 5 implementation plan and guidance for protocols that will be submitted under European Union Clinical Trial Regulation (EU CTR)
- Section 10.1.4: ONLY for US Original Protocol - removed section on female partner
- Section 10.1.5: update to align to current safety guidance
- Section 10.2.1: update in categories information and Table references
- Section 12.8.1.1: added analysis for BCR-ABL≤1% as efficacy endpoint; added loss of MR4 and MR 4.5 definition; updated end-point of MMR and CCyR
- Section 12.8.2: update in AEs section
- Section 12.8.2: clarify timelines and data information
- Section 13.1 – 13.2 – 13.3: Update based on Novartis template version 5 implementation plan and guidance for protocols that will be submitted under European Union Clinical Trial Regulation (EU CTR)
- Section 13.5: new section added to meet the needs of protocols that will be submitted under EU CTR
- Appendix 16.1:
  - removed table for Prohibited concomitant medication since not applicable
  - updated table for Concomitant Medication
  - updated release date of the Pharmacokinetic Sciences memorandum on Drug-Drug Interaction list;
- Appendix 16.4: added new appendix to provide additional clarity on eligibility based on serologic markers for hepatitis B and C

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.

Protocol summary

Protocol number	CABL001J12301
Full Title	A phase III, multi-center, open-label, randomized study of oral asciminib versus Investigator selected Tyrosine Kinase Inhibitor (TKI) in patients with newly diagnosed Philadelphia Chromosome Positive Chronic Myelogenous Leukemia in Chronic Phase
Brief title	A study of oral asciminib versus other TKIs in adult patients with newly diagnosed Ph+ CML-CP.
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Asciminib inhibits the Abelson proto-oncogene 1 (ABL1) kinase activity of the BCR-ABL1 fusion protein, by specifically targeting the ABL myristoyl pocket. Due to asciminib specifically targeting the ABL kinase family (ABL1, ABL2, BCR-ABL1), asciminib offers the potential for improved safety and tolerability than currently approved Adenosine triphosphate (ATP)-competitive TKIs for treatment of patients with CML-CP.
Primary Objective(s)	To compare the efficacy of asciminib versus Investigator selected TKI with respect to the proportion of participants that are in Major Molecular Response (MMR) at Week 48. To compare the efficacy of asciminib versus Investigator selected TKI, within the stratum of participants with imatinib as the pre-randomization selected TKI, with respect to the proportion of participants that are in MMR at Week 48
Secondary Objectives	To compare the efficacy of asciminib versus Investigator selected TKI, with respect to the proportion of participants that are in MMR at Week 96. To compare the efficacy of asciminib versus Investigator selected TKI, within the stratum of participants with imatinib as the pre-randomization selected TKI, with respect to the proportion of participants that are in MMR at Week 96.
Study design	The study is designed to compare the efficacy of asciminib 80 mg QD versus Investigator selected TKI for the treatment of newly diagnosed, previously untreated patients with Ph+ CML-CP. The Investigator selected TKI will be one of the following treatment options for first-line treatment of CML-CP - imatinib 400 mg QD or nilotinib 300 mg BID (total daily dose of 600 mg) or dasatinib 100 mg QD or bosutinib 400 mg QD. Dose recommendations as per local label should be followed for participants with hepatic and renal impairment.
Study population	Adult patients with newly diagnosed Ph+ CML-CP. It is planned to randomize approximately 402 participants in the study in a 1:1 ratio to asciminib or Investigator selected TKI.

Key Inclusion criteria	Participants eligible for inclusion in this study must meet all of the following criteria:
	1. Male or female participants ≥ 18 years of age.
	2. Participants with CML-CP within 3 months of diagnosis.
	3a. Diagnosis of CML-CP (ELN 2020 criteria) with cytogenetic confirmation of the Philadelphia chromosome
	• Documented chronic phase CML will meet all the below criteria (Hochhaus et al 2020A):
	  • < 15% blasts in peripheral blood and bone marrow,
	  • < 30% blasts plus promyelocytes in peripheral blood and bone marrow,
	  • < 20% basophils in the peripheral blood,
	  • Platelet (PLT) count ≥ 100 x 10^9/L (≥ 100,000/mm^3),
	  • No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly.
	4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

	5. Adequate end organ function as defined by: • Total bilirubin (TBL) < 3 x upper limit of normal (ULN); participants with Gilbert's syndrome may only be included if TBL ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN • Creatinine clearance (CrCl) ≥ 30 mL/min as calculated using Cockcroft-Gault formula • 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 6a. Participants must have the following laboratory values within normal limits 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 CrCl* ≥ 90 mL/min) • 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 CrCl* ≥ 90 mL/min) • Magnesium (magnesium increase of up to 3.0 mg/dL or 1.23 mmol/L if associated with CrCl* ≥ 90 mL/min) • For participants with mild to moderate renal impairment (CrCl* ≥ 30 mL/min and <90 mL/min) - potassium, total calcium (corrected for serum albumin) and magnesium should be ≥ LLN or corrected to within normal limits with supplements prior to randomization. • CrCl* as calculated using Cockcroft-Gault formula 7. Signed informed consent must be obtained prior to any study related screening procedures being performed. 8. Evidence of typical *BCR-ABL1* transcript [e14a2 and/or e13a2] at the time of screening which is amenable to standardized Real time quantitative polymerase chain reaction (RQ-PCR) quantification.

Key Exclusion criteria	Participants meeting any of the following criteria are not eligible for inclusion in this study.
	1a. Previous treatment of CML with any other anticancer agents including chemotherapy and/or biologic agents or prior stem cell transplant, with the exception of hydroxyurea and/or anagrelide. Treatment with either imatinib, or nilotinib, or dasatinib or bosutinib for ≤ 2 weeks is allowed. No treatment with other tyrosine kinase inhibitors prior to randomization is permitted.
	2. Known cytopathologically confirmed CNS infiltration (in absence of suspicion of CNS involvement, lumbar puncture not required).
	3. Impaired cardiac function or cardiac repolarization abnormality including but not limited to any one of the following:
	  • History within 6 months prior to starting study treatment of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG).
	  • Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block).
	  • QTc ≥ 450 ms (male participants), ≥ 460 ms (female participants) on the average of three serial baseline ECG (using the QTcF formula) as determined by central reading. If QTcF ≥ 450 ms and electrolytes are not within normal ranges, electrolytes should be corrected and then the participant re-screened for QTc.
	  • Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
	  • Risk factors for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia.

	• Concomitant medication(s) with a "Known risk of Torsades de Pointes" per //.crediblemeds.org/ that cannot be discontinued or replaced 7 days prior to starting study drug by safe alternative medication. • Inability to determine the QTcF interval. 4. 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 arterial or pulmonary hypertension, uncontrolled clinically significant hyperlipidemia). 5. History of significant congenital or acquired bleeding disorder unrelated to cancer. 6. Major surgery within 4 weeks prior to study entry or who have not recovered from prior surgery. 7. History of other active malignancy within 3 years prior to study entry with the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively. 8. History of acute pancreatitis within 1 year prior to randomization or medical history of chronic pancreatitis. 9. History of chronic liver disease leading to severe hepatic impairment, or ongoing acute liver disease. 10a. Known history of chronic Hepatitis B (HBV), or chronic Hepatitis C (HCV) infection. Testing for Hepatitis B surface antigen (HBs Ag) and Hepatitis B core antibody (HBc Ab/anti HBc) will be performed at screening. If anti-HBc is positive, HBV-DNA evaluation must be carried out at screening. Patients having positive HBV-DNA must not be enrolled in the study. Also, patients with positive HBsAg must not be enrolled in the study. For details criteria see Appendix 16.4. 11. History of Human Immunodeficiency Virus (HIV) unless well-controlled on a stable dose of anti-retroviral therapy at the time of screening. 12. 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). 13. Participation in a prior investigational study within 30 days prior to randomization or within 5 half-lives of the investigational product, whichever is longer. 14a. If local regulations deviate from the contraception methods listed below to prevent pregnancy, local regulations apply and will be described in the ICF. 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 a period of time after stopping study medication. For asciminib, this period of time is 3 days after the last dose; if local regulations or locally approved prescribing information differ from the protocol required duration of contraception, the longer duration must be followed and the same requirements will be described in the ICF. Participants taking Investigator selected TKI should be willing to follow contraception requirements in the locally-applicable prescribing information for the TKI received in the study. Highly effective contraception methods include: • Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. 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 partner's sterilization (at least 6 months prior to screening): the vasectomized male partner should be the sole partner for that participant. • Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. • Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms). Women are considered not of child bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking study medication. In the case of oophorectomy alone, women are considered post-menopausal and not of child bearing potential only when the reproductive status of the woman has been confirmed by follow up hormone level assessment. iii. Sexually active males taking Investigator selected TKI should be willing to follow contraception requirements in the locally-applicable prescribing information for the TKI received in the study. Sexually active males taking asciminib do not require contraception. 15. Known hypersensitivity to the study treatment.
Study treatment	Asciminib vs imatinib, or nilotinib, or dasatinib, or bosutinib
Treatment of interest	Asciminib versus Investigator selected TKI, in patients with newly diagnosed CML-CP, with respect to the proportion of participants achieving major molecular response (MMR) at Week 48. Asciminib versus Investigator selected TKI, within the stratum of participants with imatinib as their pre-randomization selection of TKI, in patients with newly diagnosed CML-CP, with respect to the proportion of participants that are in MMR at Week 48.
Efficacy assessments	Molecular, Cytogenetic and Hematological response are assessed: To estimate the efficacy of asciminib versus Investigator selected TKI, within the strata of participants with a second generation (2G) TKI as their pre-randomization selected TKI, with respect to achieving MMR To compare the efficacy of asciminib versus Investigator selected TKI with respect to the additional efficacy endpoints. To compare the efficacy of asciminib versus Investigator selected TKI, within the stratum of participants with imatinib as their pre-randomization selected TKI, with respect to the additional efficacy endpoints. To estimate the efficacy of asciminib versus Investigator selected TKI, within the strata of participants with a 2G TKI as their pre-randomization selected TKI, with respect to the additional efficacy endpoints.
Pharmacokinetic assessments	To characterize the pharmacokinetics (PK) of asciminib. The PK parameters will be determined by using the PK profile of asciminib in participants with full PK sampling. All PK samples may be used for popPK analysis. Trough plasma concentrations. PK parameters in full PK group: Cmax, Tmax, Area under the curve (AUC)tau, AUClast, CL/F.
Key safety assessments	To characterize the safety and tolerability profile of asciminib versus Investigator selected TKI (imatinib, nilotinib, dasatinib, or bosutinib) during the course of study: The type, frequency and severity of adverse events (AEs), Changes in laboratory values that fall outside the pre-determined ranges

	Clinically notable ECG changes, Other safety data (vital signs, physical examination).
Other assessments	**Exploratory objectives for Biomarkers**: · To characterize mutations in the [redacted] and their association with molecular response. · To conduct gene expression analysis in peripheral blood to predict treatment response · To explore the impact of immune landscape of peripheral blood on treatment response. **Exploratory objective for Pharmacogenetics:** · To explore [redacted] activity variation on asciminib exposure **Exploratory objectives for healthcare resource utilization:** · To compare the impact of treatment on health care resource utilization between treatment arms in all participants **Exploratory objective for patient reported outcomes (PROs):** · To evaluate health-related quality of life and other patient reported outcomes in each treatment arm · To explore participant self-reported treatment related symptomatic adverse events between treatment arms · To explore participant self-reported overall impact of side effects of treatment on patient reported outcomes (PROs) from baseline during the course of the study
Data analysis	The study has multiple primary and key secondary objectives; which are to compare the efficacy between asciminib, and Investigator selected TKI arms (overall and within the stratum of participants with imatinib as their pre-randomization selection of TKI) with respect to MMR at Week 48 (primary end-points) and MMR at Week 96 (key secondary end-points). A combined approach of treatment policy and composite strategies will be implemented for the multiple primary and key secondary estimands. The estimands aim to address the following clinical questions: 1. what is the efficacy of asciminib (80 mg QD) compared to Investigator selected TKI; with respect to MMR (at Week 48 for the primary and at Week 96 for the key secondary end-points); 2. what is the efficacy of asciminib (80 mg QD) compared to Investigator selected TKI within the stratum of participants that have imatinib as their pre-randomization selection of TKI; with respect to MMR (at Week 48 for the primary and at Week 96 for the key secondary end-points); in patients with newly diagnosed CML-CP, dose interruption/ reduction/ allowed escalations, dosing errors, changes on concomitant medication, intake of prohibited medication , and taking a TKI different than the pre-randomization selection of TKI in the comparator arm (*treatment policy strategy*); where meeting treatment failure criteria prior to Week 48 or discontinuation of treatment prior to Week 48 are considered non-response (*composite strategy*). The primary and key secondary comparisons of MMR rate at Week 48 and at Week 96 respectively, between asciminib and Investigator selected TKI arms (overall and within the stratum of participants with imatinib as their pre-randomization selection of TKI) will be performed using one-sided stratified Mantel-Haenszel tests. The corresponding stratified Mantel-Haenszel estimates of the common risk differences (along with the two-sided 95% confidence intervals (CI)s) will also be provided. The overall type 1 error (alpha) control will be achieved through the graphical gate-keeping multiple testing procedure.

1 Introduction

1.1 Background

1.1.1 Disease background

Chronic Myelogenous Leukemia (CML) is a clonal myeloproliferative disorder of transformed, primitive hematopoietic progenitor cells characterized by overproduction of immature myeloid cells and mature granulocytes in the spleen, bone marrow, and peripheral blood. The hallmark of CML is the Philadelphia (Ph) chromosome found in up to 95% of patients (Seong et al 1999). The Ph chromosome results from a reciprocal translocation t(9;22)(q34;q11) which fuses a portion of the Abelson (*ABL1*) gene on chromosome 9 with a portion of the breakpoint cluster region (*BCR*) gene on chromosome 22. The new nomenclature for the fusion gene of *BCR::ABL1* is considered equivalent to *BCR-ABL1* for this protocol (Bruford et al 2021). The resulting fusion gene encodes a chimeric protein (BCR-ABL1), which lacks an autoregulatory N-terminal segment of ABL1, resulting in it having a constitutively active tyrosine kinase domain (Faderl et al 1999, Soverini et al 2019). This oncoprotein promotes aberrant cell growth and replication through downstream signaling pathways such as RAS, RAF, JUN kinase, MYC, and STAT (Jabbour and Kantarjian 2018).

With a constant worldwide incidence of 1-2/100000 per year the prevalence of CML is steadily increasing due to improved long term outcomes with tyrosine kinase inhibitor (TKI) treatment (Jabbour and Kantarjian 2018, Hochhaus et al 2020A). CML mainly affects adult patients with a median age at diagnosis of 67 years. In the US, it is estimated that approximately 8,450 new cases of CML will be diagnosed and about 1,130 people will die of the malignancy during 2020 (NCCN 2020). In Europe, a similar CML incidence has been reported with 10 to 15 cases/million/year, without any major geographic or ethnic differences (Hochhaus et al 2017B).

Clinically, CML can progress through three distinct phases which become increasingly refractory to therapy: chronic phase (CP), accelerated phase (AP), and blast crisis (BC) (Enright and McGlave 2000). Most patients are diagnosed in the CP, characterized by anemia, splenomegaly and leukocytosis with generally few constitutional symptoms like fatigue, weight loss, malaise, easy satiety, and left upper quadrant fullness or pain. CML-AP might be insidious or present with worsening anemia, splenomegaly and organ infiltration; most patients evolve into AP prior to BC, but without treatment around 20% may transition into BC without a preceding AP (Faderl et al 1999).

The response to treatment in CML is monitored based on hematological, cytogenetic and molecular responses. Monitoring of molecular response using a real-time quantitative polymerase chain reaction (RQ-PCR) test for *BCR-ABL1* deoxyribonucleic acid (DNA) in peripheral blood or bone marrow aspirates, is a sensitive measure of burden of disease in CML and results are standardized to an International scale (IS) as the ratio of *BCR-ABL1* transcripts to *ABL1* transcripts. Molecular responses provide an objective measure of efficacy for guiding treatment and monitoring patients with CML (Press 2010, Cross et al 2012, Greiner et al 2020). Treatment guidelines consider *BCR-ABL1* transcript levels at mainly 3, 6, and 12 months time points to determine the patient's response to treatment and to guide treatment decisions. A *BCR- ABL1* IS level of > 1% at 12 months is considered a failure of treatment, whereas

BCR- ABL1 IS level of ≤ 0.1% (Major Molecular Response; MMR) at 12 months is considered an optimal response to treatment (Hochhaus et al 2020A, NCCN 2020).

1.1.2 Current management recommendations and unmet medical need

In 2001, the introduction of the TKI imatinib (Glivec®), the first drug to be targeted against an oncogenic mutation, revolutionized the treatment of patients with CML. Subsequently, several second generation (2G) TKI agents, nilotinib, dasatinib, bosutinib, have been approved for the first-line treatment of CML. TKI treatment has improved the survival rates for patients with CML, and patients with optimal treatment response may expect near-normal life expectancy (Jabbour and Kantarjian 2018, García-Gutiérrez and Hernández-Boluda 2019). Increased survival rates and the requirement of chronic therapy for CML has underlined the importance of selection of first-line treatment for newly diagnosed patients. The treatment for newly diagnosed patients with CML aims to deliver early optimal responses to decrease the possibility of disease progression, maintain the quality of life for patients requiring potentially life-long treatment, and to decrease possibility of serious side effects.

Treatment guidelines recommend selection of the first-line option for the treatment of CML- CP based on individual patient and disease characteristics determining risk score (Sokal, Hasford, EUTOS or ELTS), as well as the preexisting comorbidities and concomitant medications determining the ability of the patient to tolerate therapy (Saglio and Jabbour 2018, Hochhaus et al 2020A, NCCN 2020). Considering the differences in safety and efficacy profiles of imatinib and 2G TKIs, i.e. nilotinib, dasatinib and bosutinib, first-line treatment recommendations vary for these agents.

In general, newly diagnosed patients with a low risk score, elderly patients or patients with multiple comorbidities are treated with imatinib, which has been shown to provide good efficacy with a tolerable safety profile. However, many patients treated with imatinib experience events such as fluid retention or muscle cramps (Cortes and Kantarjian 2016). From an efficacy perspective, imatinib is less potent than 2G TKIs, delivering lower cytogenetic and molecular response rates, as demonstrated in many comparative studies against 2G TKIs (Hochhaus et al 2016, Cortes and Kantarjian 2016, Cortes 2018). The sub-optimal responses to imatinib lead to poor disease control which correlates with higher rates of advanced disease in CML, namely progression to AP or BC (Hochhaus et al 2016, Cortes and Kantarjian 2016, Cortes 2018). The rate of emergent mutations with frontline imatinib has been shown to be higher than that with dasatinib leading to higher rates of resistance and loss of responses on treatment with frontline imatinib (Hughes et al 2015).

Newly diagnosed younger patients with CML-CP and those with high risk scores are recommended to be treated with 2G TKIs which have shown to be more potent than imatinib (Hochhaus et al 2020A, NCCN 2020). Studies comparing 2G TKIs to imatinib demonstrated higher rates of efficacy responses and reduced rates of progression to AP or BC; however, the safety profile of these drugs is significantly more adverse as compared to imatinib. The development of vascular side effects such as peripheral arterial occlusive disease, cerebrovascular accidents, and coronary artery disease with nilotinib, cardiopulmonary toxicities such as pleural effusions, interstitial pneumonitis and pulmonary hypertension with dasatinib and gastrointestinal and liver related events with bosutinib, warrant caution while

prescribing these agents for first-line treatment of newly diagnosed patients with CML-CP (Hochhaus et al 2016, Cortes and Kantarjian 2016, Cortes 2018).

Many AEs associated with imatinib and 2G TKIs are attributable to off-target activities of these inhibitors as they are not specific for ABL / BCR-ABL1 inhibition. For example, hypophosphatemia with imatinib has been attributed to inhibition of PDGF (PLT-derived growth factor) signaling affecting the formation and resorption of bone (Berman et al 2006). Multi-kinase inhibitor-induced rash is common in patients on imatinib therapy (Grávalos et al 2019). For bosutinib, a higher rate of diarrhea is considered to be due to EGFR (Epidermal Growth Factor Receptor) inhibition (Rugo et al 2019). Off-target inhibition by TKIs of SRC family kinases have been implicated in occurrence of fluid retention and pleural effusion (Eliceiri et al 1999).

Asciminib has been shown to be highly selective against BCR–ABL1-positive cell lines when compared with imatinib, nilotinib, dasatinib, and bosutinib, which varied considerably in their degree of specificity (Wylie et al 2017). Hence, it is anticipated that the specificity of asciminib for ABL1 and ABL2, may limit off-target effects resulting in an improved safety profile as compared with ATP-binding TKIs.

Considerable advancements in treatment of patients with CML-CP have been made in the last two decades. Increase in life expectancy of patients living with CML have made it a chronic disease requiring long term medication. This emphasizes the need for treatments that combine high efficacy with a favorable safety profile as compared to the available options. There remains an unmet medical need for newly diagnosed patients with CML-CP requiring chronic treatment for a specific targeted treatment option that is highly efficacious while minimizing AEs.

1.2 Purpose

1.2.1 Scientific rationale and purpose

Asciminib is an oral, potent inhibitor of BCR-ABL1 tyrosine kinase with a novel mechanism of action. In contrast to BCR-ABL1 TKIs, such as imatinib, nilotinib, dasatinib, bosutinib and ponatinib that bind to the ATP-site on the SH1 domain of the enzyme, asciminib inhibits the ABL1 kinase activity by specifically targeting the ABL myristoyl pocket. Asciminib functionally mimics the role of the myristoylated Gly2 residue by occupying the vacant binding site and restoring the negative regulation to the kinase activity.

Asciminib does not directly interact with the ATP-binding site and inhibits ABL tyrosine kinase activity by binding to a particular allosteric site on the kinase domain. This site has only been implicated in the autoregulation of ABL1, ABL2 and BCR-ABL1, thus explaining the specificity of asciminib towards these three enzymes (Manley et al 2020). As most AEs associated with TKIs are attributable to off-target activity, the lack of specificity to ABL kinases leads to off-target effects in a substantial proportion of patients (Steegmann et al 2012, Hantschel 2015). Asciminib is specific for ABL kinases and it is expected that this limited off-target kinase inhibition will translate into a better safety profile than currently approved ATP-competitive TKIs.The purpose of this pivotal study is to compare the efficacy of asciminib with that of BCR-ABL1 TKIs, such as imatinib, nilotinib, dasatinib, bosutinib in adult patients with newly diagnosed Philadelphia Chromosome Positive Chronic

Myelogenous Leukemia in Chronic Phase (Ph+ CML-CP). For additional information please see Section 4.3.

1.2.2 Preliminary efficacy and safety

Asciminib is mainly being studied in clinical studies in CML. As of 15-Jan-2023, asciminib has been investigated in 11 completed studies and 11 ongoing studies [Asciminib Investigator's Brochure]. In completed studies, 388 healthy volunteers, including 24 participants with hepatic impairment, and 8 participants with renal impairment were exposed to asciminib. In addition, 200 patients with CML-CP/ AP have been treated with single agent asciminib in CABL001X2101. This ongoing first-in-human (FIH) phase I clinical study provides preliminary evidence of safety and efficacy of asciminib in patients with CML-CP/AP who have been previously treated with two or more TKIs over a wide range of doses. In addition, safety and efficacy of asciminib in 233 patients with CML-CP who had treatment failure on or were intolerant to at least 2 prior TKIs is available from the ongoing randomized, controlled study CABL001A2301. Asciminib as an add-on to imatinib is also being studied in patients with CML-CP who did not achieve deep molecular response after at least 1 year of treatment with imatinib [Study CABL001E2201].

1.2.2.1 Study CABL001X2101

Study CABL001X2101 is an ongoing first-in-human (FIH), multi-center, open-label, dose escalation study of asciminib given as single agent or in combination with either nilotinib, imatinib or dasatinib in patients with CML or Ph+ Acute Lymphoblastic Leukemia (ALL). The objectives of this study include the determination of the maximum tolerated dose (MTD)/ recommended dose for expansion (RDE) and the characterization of the safety profile of single agent asciminib, as well as to provide preliminary evidence for efficacy of asciminib in CML.

At the time of the primary analysis, a total of 317 patients with Ph+ CML (chronic phase, CP; accelerated phase, AP; or blast crisis, BC) or Ph+ ALL who have failed or are intolerant to at least two prior TKIs, had been enrolled in the study. Patients in the study have been treated with increasing doses of single agent asciminib or with asciminib in combination with nilotinib, imatinib, or dasatinib [CABL001X2101 CSR]. The results from Arm 1 evaluating single agent asciminib are presented below. The results from Arm 2 (single agent asciminib for treatment of CML-BC or Ph+ ALL) and Arm 3, 4, 5 (asciminib in combination with nilotinib, imatinib or dasatinib, respectively) are not included.

As a single agent, asciminib has been studied in 200 heavily pre-treated patients with CML-CP/ AP in Arm 1 of the CABL001X2101 study. In this Arm of the study, asciminib was evaluated at the following dose levels and regimens: 10 mg BID (n=1), 20 mg BID (n=14), 40 mg BID (n=35) which was declared as RDE, 80 mg BID (n=12), 150 mg BID (n=13), 160 mg BID (n=11), 200 mg BID (n=62) which was declared as RDE in CML-CP/AP harboring the T315I mutation, 80 mg QD (n=18), 120 mg QD (n=22), and 200 mg QD (n=12). Among 200 patients with CML-CP/-AP enrolled across treatment cohorts, 185 (92.5%) patients had CML-CP of which 115 had CML-CP without T315I mutation and 70 with CML-CP harbored T315I mutation. The majority of patients had received at least two prior TKIs (185 (92.5%) patients); with dasatinib being the TKI received by a majority of patients (79.0%), followed by imatinib (70.0%), and nilotinib (69.0%).

As of the data cut-off date, 123 (61.5%) patients in Arm 1 were receiving treatment with asciminib single agent and 77 (38.5%) patients had discontinued treatment. Physician's decision was the most frequent reason for discontinuation of treatment in 32 (16.0%) patients followed by discontinuation due to AEs in 19 (9.5%) patients. The median duration of exposure was 124.6 weeks (min-max: 0 to 302 weeks).

The most common AEs reported in at least 50 patients among the 200 with CML-CP/-AP treated with asciminib single agent when considering all doses and all grades were fatigue (29.0%), headache, lipase increase, nausea (26.0%, each) and diarrhea (25.5%). Eighteen patients with CML-CP/-AP who were treated with asciminib single agent (9.0%) had at least one SAE assessed by the investigator as suspected to be related to the study drug. No pattern for dose-dependent increase in frequency of AEs was observed with the multiple doses of asciminib monotherapy, up to the highest evaluated dose of 200 mg BID in CML-CP and -AP patients treated. Six (3.0%) patients died on-treatment (within 30 days after last dose of study treatment). Of these, 3 deaths were due to underlying disease and 3 were due to other primary causes of death being [redacted], [redacted], and [redacted], respectively. None of these events due to 'other causes' were considered to be related to study treatment.

Efficacy data from the study CABL001X2101 show that asciminib demonstrates anti-leukemic activity in the broad range of doses tested and across later lines of therapy. Among the 200 patients with CML-CP/-AP treated with asciminib single agent across treatment cohorts, 164 were evaluable for MMR analysis. A clinically meaningful and durable MMR rate was observed across all asciminib dose levels ≥ 20 mg BID and across all lines of therapy. In 164 MMR evaluable patients with CML-CP/-AP, MMR was achieved by 77/164 (47.0%) patients. The cumulative MMR was 26.2% by Week 24 (25.0% at Week 24).

In this study, the MTD for single agent asciminib was not reached. Based on totality of data available from study CABL001X2101, a single agent dose of asciminib 40 mg BID was determined as the RDE for patients with CML-CP or CML-AP and further investigated in study CABL001A2301.

1.2.2.2 Study CABL001A2301

Study CABL001A2301 (ASCEMBL) is an ongoing phase III, multi-center, active-controlled, open-label randomized study that compares the efficacy and safety of asciminib with that of bosutinib in the treatment of patients with CML-CP who received at least 2 prior ATP-binding site TKIs.

A total of 233 patients were randomized in a 2:1 ratio and stratified according to patients' cytogenetic response at screening (major or no major cytogenetic response) to receive either asciminib 40 mg BID (157 patients) or bosutinib 500 mg QD (76 patients). The primary study endpoint was MMR at week 24. Patients in the study were heavily pre-treated, with approximately half (52.2%) of the patients in the asciminib arm having received asciminib as 3rd-line therapy and 47.8% as 4th-line or greater, while 39.5% of the patients in the bosutinib arm received bosutinib as 3rd-line and 60.5% as 4th-line or greater.

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. This corresponded to a common treatment difference (after adjusting for baseline MCyR status) of 21.74% (95% CI: 10.53, 32.95) which was clinically relevant and statistically significant (p=0.001) (two-sided Cochrane-Mantel-Haenszel chi-square test, stratified by the major cytogenetic response status at baseline).

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 group (≥ 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%). Since the primary analysis cut-off, the incidence of arthralgia, nasopharyngitis and anemia on asciminib and abdominal pain on bosutinib increased to above 10%.

The proportion of patients experiencing myelosuppression was similar in the asciminib (38.5% all grades, 26.9% Grade ≥ 3 events) and bosutinib treatment groups (36.8% all grades, 23.7% Grade ≥ 3 events) with the exception of thrombocytopenia which was reported more frequently in the asciminib arm than in the bosutinib arm(any grade 23.1% vs. 14.5%).

The proportion of patients with gastrointestinal toxicity, hepatotoxicity and hypersensitivity AESIs were substantially lower in the asciminib treatment group compared to the bosutinib treatment group (both all grades and Grade ≥ 3). Comparable proportion of patients with

pancreatic enzyme increase was seen without clinical events of pancreatitis in both treatment groups. Serious adverse events were reported in a lower proportion of patients in the asciminib treatment group (17.9%) compared to the bosutinib treatment group (26.3%).

Grade ≥ 3 AEs, AEs suspected to be study treatment related, AEs requiring dose interruption, dose adjustments, and additional therapies were reported less frequently in the asciminib treatment group as compared to the bosutinib treatment group.

Three deaths occurred during the study two in the asciminib arm and one in the bosutinib arm. The 2 deaths in the asciminib arm were not considered study treatment related by the Investigators (causes of death reported as [redacted] and [redacted] . The death of the one patient in the bosutinib arm was due to [redacted] and was considered related to study treatment. Please refer to the latest [Asciminib Investigator's Brochure] for more details.

In summary, study CABL001A2301 showed significantly improved efficacy with favorable safety and tolerability of asciminib as compared to bosutinib in CML-CP patients treated with at least 2 prior TKIs.

Asciminib was granted accelerated approval by the US FDA in Oct-2021 for adult patients with Ph+ CML-CP, previously treated with two or more TKIs. The recommended dose of asciminib is a total daily dose of 80 mg, taken either as 80 mg QD or 40 mg BID. The FDA also approved asciminib for adult patients with Ph+ CML in CP with T315I mutation. The recommended dose of asciminib in patients with Ph+ CML in CP with T315I mutation is 200 mg BID.

Asciminib was also approved by the Japan PMDA in Mar-2022, for the treatment CML with resistance or intolerance to previous therapy. The posology is 40 mg BID. Novartis did not apply for the T315I indication and for the 80 mg QD dose in Japan.

1.2.2.3 Study CABL001E2201

Study CABL001E2201 is a phase II, multi-center, open-label, randomized study of oral asciminib added-on to imatinib versus continued imatinib versus single agent nilotinib in patients with CML-CP who have been previously treated with imatinib for at least 1 year and have not achieved deep molecular response (MR4). The primary endpoint of the study is to compare the activity of asciminib at the dose of 40 mg QD and 60 mg QD added-on to imatinib versus imatinib continuation and versus switch to nilotinib, assessed by the rate of MR4.5 at 48 weeks. The MR4.5 rate at 96 weeks is the key secondary endpoint. Secondary endpoints include safety and tolerability, PK and additional efficacy endpoints. Approximately 80 eligible patients will be randomized in a 1:1:1:1 ratio to receive asciminib 60 mg QD add-on to imatinib 400 mg QD, or asciminib 40 mg QD add-on to imatinib 400 mg QD, or continue imatinib 400 mg QD, or switch to nilotinib 300 mg BID..

The primary analysis (cut-off date 10-Jan-2022) was conducted when all randomized subjects had completed the week 48 visit or discontinued treatment early.

At the data cut-off date (10-Jan-2022), 84 subjects were randomized, eighty-three (98.8%) subjects were treated in one of the 4 arms. Out of the 83 subjects, 52 (61.9%) subjects were still receiving trial therapy and 31 (36.9%) subjects had discontinued the study.

The median duration of exposure to study drug was longer in the asciminib 40 mg + imatinib (104.7 weeks, range 27-160) and asciminib 60 mg + imatinib (94 weeks, range 1-148) arms as

compared to monotherapy with nilotinib (78.9 weeks, range 1-146). The median duration of exposure in the imatinib arm was 53.4 weeks (range 50-142), subjects in the imatinib arm were allowed to cross-over after week 48, if MR4.5 was not achieved by then.

At week 48, there were 4 subjects in the asciminib 40 mg + imatinib arm and 6 subjects in the asciminib 60 mg arm + imatinib arm who achieved MR4.5 (BCR::ABL1 ratio of ≤ 0.0032%) compared to 0 subjects in the imatinib arm, corresponding to an MR4.5 rate of 19% (90% CI: 6.8, 38.4) and 28.6% (90% CI: 13.2, 48.7), in the two investigational arms respectively.

The estimated MR4.5 difference for asciminib 40 mg + imatinib arm was 19.05 (90% CI: 5, 33.1) and for asciminib 60 mg + imatinib arm was 28.57 (90% CI: 12.4, 44.8).

The most common (≥ 15% subjects in any of the treatment arm) AEs were: in asciminib 40 mg + imatinib arm: nausea (33.3%), diarrhoea (23.8%), myalgia (23.8%) and pruritus (19%), in asciminib 60 mg + imatinib arm: no AEs by PT were observed in ≥ 15 % of subjects, in imatinib arm: lipase increased (15%), diarrhoea (15%) and hypophospataemia (15%) and in nilotinib arm: alanine aminotransferase increased (23.8%), rash (38.1%) and hypertension (19%).

SAEs were more frequent in nilotinib arm (23.8%) as compared to asciminib 40 mg +imatinib

(14.3%) and asciminib 60 mg + imatinib (14.3%) arm.

AEs leading to discontinuation of study treatment were more frequent in nilotinib (23.8%)

arm compared to asciminib 40 mg + imatinib (4.8%) and asciminib 60 mg + imatinib (14.3%).

No AEs leading to discontinuation of study treatment was observed in imatinib arm.

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

1.2.3 Preliminary pharmacokinetics

The PK profile of asciminib has been evaluated both as single agent in CML patients at a dose range between 10 mg to 280 mg BID and 80 mg to 200 mg QD, as well as in healthy subjects. Asciminib was rapidly absorbed following single dose and repeated administration with a median time to reach maximum plasma concentration (Tmax) 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 Cmax and area under the curve (AUC), increase in a slightly more than dose proportional manner based on statistical analysis. No time-dependent PK was observed. The apparent terminal elimination half-life (T1/2) was estimated to be between 7 and 15 hours and steady-state was reached by 3 days. With the once-daily dosing regimen there was almost no accumulation of asciminib (1.1 to 1.4). Generally, the variability of exposure was low to moderate with inter-patient variability (coefficient of variation (CV) %) ranging from approximately 25% to 70% for both Cmax and AUClast.

A negative food effect was observed with asciminib. Low-fat and high-fat meals decreased the exposure (Cmax and AUC) of asciminib by ~30% and ~60%, respectively, compared to asciminib given in the fasted state. The negative food effect may be explained by sequestration of asciminib with bile acids when present at high levels in the gastrointestinal tract in vivo.

A 1.56 fold and 1.66 fold increase in AUCinf of asciminib was observed in subjects with severe renal impaired function and severe hepatic impaired function, respectively, compared to the normal renal function cohort [CABL001A2103, CABL001A2105]. No dose adjustment is

considered necessary in participants with mild, moderate, and severe renal or hepatic impairment based on these study results.

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

[redacted]

Asciminib is a substrate of both the breast cancer resistant protein (BCRP) and permeability glycoprotein (P-gp transporters). In a recently reported DDI study ([CABL001A2107]) coupled with a PBPK report, asciminib was shown to be negligibly affected by strong CYP3A4, P-gp and BCRP inhibition at 40 mg BID and 80 mg QD, while weakly by strong CYP3A induction at the same doses. Cautionary use is recommended with strong CYP3A4 inducers. A covariate analysis for heavy smokers from a population PK report ([CABL001A2301]) indicated that the potential for clinical DDIs with co-medications that inhibit a single Uridin diPhospho-glucuronosyltransferase (UGT) enzyme is low. Study [CABL001A1101] suggested that asciminib's bioavailability was not affected by the co-administration with acid-reducing agents.

In vitro, asciminib has shown to be a reversible inhibitor of CYP3A4/5, CYP2C8, CYP2C9, CYP2B6, CYP2C19, with weak to no inhibition of CYP2D6, CYP1A2, CYP2A6, CYP2E1, UGT1A1 and UGT2B7. Under therapeutic conditions, clinical interactions of asciminib with CYP2B6 and CYP2C19 substrates are unlikely to occur. The results from a dedicated clinical DDI study [CABL001A2106] showed that asciminib is a weak inhibitor of CYP3A and CYP2C9, and does not affect CYP2C8. In the same study, following multiple doses of asciminib at steady-state, asciminib did not appear to be a relevant CYP3A inducer. Consequently, CYP3A or CYP2C9 substrates with a narrow therapeutic index should be used with caution. No dose adjustments are needed.

Based on data available from 241 patients in the Study CABL001X2101, the concentration-QTcF analysis identified a positive relationship with asciminib treatment. The estimated mean and upper bound of the 90% CI QTcF increase did not exceed 10 ms (the threshold that is considered clinically significant according to the regulatory guidance) at all the therapeutic doses as well as at the estimated HCRE (determined based on the geometric mean Cmax at 200 mg BID dose, and accounting for a 1.59-fold increase in Cmax observed in a drug-drug interaction study). The upper bound of the 90% CI ΔQTcF at geometric mean Cmax observed at 40 mg BID, 80 mg QD and 200 mg BID were 4.32 ms, 4.57 ms, and 6.66 ms, respectively. However, it cannot be excluded that the positive slope would cross this threshold at higher exposures. At 2-fold the estimated HCRE (3.2-fold increase in exposure at 200 mg BID) the estimated mean QTcF increase was 10.41 ms (upper bound 90% CI: 14.75 ms) [QT/QTc and ECG Assessment Report].

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

2 Objectives, endpoints, and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• The study has **multiple primary objectives**: 1. To compare the efficacy of asciminib versus Investigator selected TKI, with respect to the proportion of participants that are in Major Molecular Response (MMR) at Week 48. 2. To compare the efficacy of asciminib versus Investigator selected TKI, within the stratum of participants with imatinib as the pre-randomization selected TKI, with respect to the proportion of participants that are in MMR at Week 48. **The study will be declared positive if it meets either of the two primary objectives** (i.e. if the null hypothesis associated with either of these two objectives is rejected).	• The end point associated with both primary objectives is: • Major Molecular response (MMR) **at** Week 48 (Yes/No)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• The study has multiple **key secondary objectives**: 1. To compare the efficacy of asciminib versus Investigator selected TKI, with respect to the proportion of participants that are in MMR at Week 96. 2. To compare the efficacy of asciminib versus Investigator selected TKI, within the stratum of participants with imatinib as the pre-randomization selected TKI, with respect to the proportion of participants that are in MMR at Week 96.	• The end point associated with both key secondary objectives is: • Major Molecular response (MMR) **at** Week 96 (Yes/No)
• **Secondary objective for safety** • To characterize the safety and tolerability profile of asciminib versus 2G TKIs (nilotinib, dasatinib, or bosutinib) during the course of study treatment.	• Time to discontinuation of study treatment due to AE (TTDAE).
• **Other secondary objectives for efficacy**: To estimate the efficacy of asciminib versus Investigator selected TKI, within the strata of participants with a 2G TKI as their pre-randomization selected TKI, with respect to the proportion of participants that are in: • MMR at Week 48. • MMR at Week 96.	• The end points associated with the other secondary objectives are: • Major Molecular response (MMR) **at** Week 48 (Yes /No) • Major Molecular response (MMR) **at** Week 96 (Yes /No)
• **Other secondary objectives for efficacy**: • To compare the efficacy of asciminib versus Investigator selected TKI, with respect to additional parameters of efficacy. • To compare the efficacy of asciminib versus Investigator selected TKI, within the stratum of participants with imatinib as	• MMR **at** all scheduled data collection time points (except at Week 48 and at Week 96). • MMR **by** all scheduled data collection time points. • MR4.0 and MR4.5, **at** and **by** all scheduled data collection time points.

Objective(s)	Endpoint(s)
their pre-randomization selected TKI, with respect to additional parameters of efficacy. • To estimate the efficacy of asciminib versus Investigator selected TKI, within the strata of participants with a 2G TKI as their pre-randomization selected TKI, with respect to additional parameters of efficacy.	• Complete Hematological response (CHR), **at** and **by** all scheduled data collection time points. • BCR-ABL1 ≤1% **at** and **by** all scheduled data collection time points. • Complete Cytogenetic response (CCyR) **by** Week 48 and **by** Week 96. • Duration of MMR, MR4.0, MR4.5. • Time to first MMR, first MR4.0, first MR4.5. • Time to treatment failure (TTF). • Failure Free Survival (FFS). • Event Free Survival (EFS). • Progression free survival (PFS). • Overall survival (OS).
• **Other secondary objectives for PK**: • To characterize the PK of asciminib.	• Trough plasma concentrations. • PK parameters in Full PK group: Cmax, Tmax, AUCtau, AUClast, CL/F.
• **Other secondary objectives for safety**: • To characterize the safety and tolerability profile of asciminib versus Investigator selected TKI (imatinib, nilotinib, dasatinib, or bosutinib) during the course of study.	• Type, frequency and severity of adverse events, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG changes, and other safety data (vital signs, physical examination).
• **Other secondary objectives for patient reported outcomes (PROs):** • To assess the effect of asciminib versus Investigator selected TKI on patient-reported disease-related symptoms, functioning, and health-related quality of life (HRQoL)	• Change from baseline in overall scores and individual scales of the EORTC QLQ-C30, EORTC QLQ-CML24

Exploratory objective(s)	Endpoint(s) for exploratory objective(s)
• **Exploratory objectives for Biomarkers**: • To characterize mutations in the [redacted] and their association with molecular response. • To conduct gene expression analysis in peripheral blood to predict treatment response • To explore the impact of immune landscape of peripheral blood on treatment response.	• Proportion of patients who develop any [redacted] • Correlation/association between expression profiles changes from baseline and on treatment with response as an effect of asciminib. • Baseline and changes from baseline of immune markers and their correlation with treatment molecular response (MMR and MR4.0 when applicable).
• **Exploratory objective for Pharmacogenetics:** • To explore [redacted] activity variation on asciminib exposure	• [redacted] activity variation on asciminib exposure.
• **Exploratory objectives for healthcare resource utilization (HCRU):** • To compare the impact of treatment on health care resource utilization between treatment arms in all participants	• Health care resource burden over time
• **Exploratory objective for PROs:** • To evaluate health-related quality of life and other PROs in each treatment arm	• Change in score from baseline over time in according to [redacted]

Objective(s)	Endpoint(s)
• To explore patient self-reported treatment related symptomatic adverse events between treatment arms • To explore patient self-reported overall impact of side effects of treatment on PROs from baseline during the course of the study	[redacted]

2.1 Primary estimands

Primary estimands will be based on the treatment policy and composite approaches as defined in this section. Supplementary estimands for the end-point of MMR at Week 48 are defined in Section 12.

The clinical questions of interest are:

1. What is the efficacy of asciminib (80 mg QD) compared to Investigator selected TKI; with respect to MMR at Week 48,
2. What is the efficacy of asciminib (80 mg QD) compared to Investigator selected TKI within the stratum of participants that have imatinib as their pre-randomization selection of TKI; with respect to MMR at Week 48,

without meeting any treatment failure criteria (as per European Leukemia Network (ELN) criteria, Hochhaus et al 2020A) and without treatment discontinuation, prior to Week 48, in newly diagnosed CML-CP patients; *regardless of* dose interruptions/reductions/allowed dose escalations; *regardless of* dosing errors, changes on concomitant medication, intake of prohibited medication; and *regardless of* taking a TKI different from their pre-randomization selection of TKI in the comparator arm.

The justification for the primary estimands are that these will capture the effects of the study treatments in a manner that reflects their use in practice.

Primary estimands are described by the following attributes:

Population: Newly diagnosed adult Ph+ CML-CP patients, as defined by Inclusion/ Exclusion criteria; (1) overall and (2) within the stratum with imatinib as their pre-randomization selection of TKI.

Endpoint: the composite end point of MMR at Week 48, without meeting any treatment failure criteria prior to Week 48 and without discontinuation due to any reasons prior to Week 48. A participant will be counted as being in MMR at Week 48 if he/she meets the MMR criterion (BCR-ABL1 transcript level $\leq$ 0.1% IS) at Week 48. If the participant meets any treatment failure criteria prior to Week 48 or discontinues treatment due to any reason prior to Week 48 the patient is counted as not being in MMR at Week 48.

Intercurrent events (IE):

- Taking a TKI different from their pre-randomization selection of TKI (i.e. the first dose of TKI is different from their pre-randomization selection of TKI): *treatment policy strategy (ignore)*
- Change on study treatment per protocol (dose reduction/interruption/allowed dose escalations): *treatment policy strategy (ignore)*
- Dosing errors (e.g., missed dose): *treatment policy strategy (ignore)*
- Deviation in any intake of concomitant medications: *treatment policy strategy (ignore)*
- Intake of prohibited medications: *treatment policy strategy (ignore)*
- Meeting any treatment failure criteria prior to Week 48 or treatment discontinuation due to any reason prior to Week 48: *composite (consider these as non-response)*

Handling of remaining intercurrent events: no other IE foreseen.

Treatment:

1. The randomized treatment arm (the investigational treatment asciminib 80 mg QD, or the Investigator selected TKI); with or without dose modifications (reductions/interruptions/allowed dose escalations); regardless of dosing errors, deviation in any intake of concomitant medications, intake of prohibited medication; and regardless of taking or not taking a TKI different from their pre-randomization selection of TKI in the comparator arm. Further details about the investigational treatment and control treatments are provided in Section 6.
2. The randomized treatment arm (the investigational treatment asciminib 80 mg QD, or the Investigator selected TKI), within the stratum of patients that had imatinib as their pre-randomization selection of TKI; with or without dose modifications (reductions/interruptions/allowed dose escalations); regardless of dosing errors, deviation in any intake of concomitant medications, intake of prohibited medication; and regardless of taking or not taking a TKI different from their pre-randomization selection of TKI in the comparator arm. Further details about the investigational treatment and control treatments are provided in Section 6.

The summary measure: stratum adjusted difference in the proportion of participants that are in MMR at Week 48 and corresponding 95% CI, between the

1. Randomized treatments (asciminib versus Investigator selected TKI).
2. Randomized treatments (asciminib versus Investigator selected TKI), within the stratum of participants that have imatinib as their pre-randomization selection of TKI.

2.2 Secondary estimands

2.2.1 Key Secondary Estimands

Key secondary estimands will be based on the treatment policy and composite approaches as defined in this section. Key secondary estimands are similar to the primary estimands, with the only difference being that these will be assessed for the end-point of MMR at Week 96. Supplementary estimands for the end-point of MMR at Week 96 are defined in Section 12.5.

Key secondary clinical questions of interest are:

1. What is the efficacy of asciminib (80 mg QD) compared to Investigator selected TKI; with respect to MMR at Week 96,
2. What is the efficacy of asciminib (80 mg QD) compared to Investigator selected TKI within the stratum of participants that have imatinib as their pre-randomization selection of TKI; with respect to MMR at Week 96,

without meeting any treatment failure criteria and without treatment discontinuation, prior to Week 96, in newly diagnosed CML-CP patients; *regardless of* dose interruptions/reductions/allowed dose escalations; *regardless of* dosing errors, changes on concomitant medication, intake of prohibited medication; and *regardless of* taking a TKI different from their pre-randomization selection of TKI in the comparator arm.

The **justification** for the key secondary estimands are that these will capture the effects of the study drugs in a manner that reflects their use in practice.

Key secondary estimands are described by the following attributes:

- **Population**: Newly diagnosed adult Ph+ CML-CP patients, as defined by Inclusion/ Exclusion criteria; (1) overall and (2) within the stratum with imatinib as their pre-randomization selection of TKI.
- **Endpoint**: the composite end point of MMR at Week 96, without meeting any treatment failure criteria prior to Week 96 and without discontinuation due to any reasons prior to Week 96. A participant will be counted as being in MMR at Week 96 if he/she meets the MMR criterion (BCR-ABL IS $\leq$ 0.1%) at Week 96. If the participant meets any treatment failure criteria prior to Week 96 or discontinues treatment due to any reason prior to Week 96 the participant is counted as not being in MMR at Week 96.
- **Intercurrent events (IE):**
  - Taking a TKI different from their pre-randomization selection of TKI (i.e. the first dose of TKI is different from pre-randomization selection of TKI): *treatment policy strategy (ignore)*
  - Change on study treatment per protocol (dose reduction/interruption/allowed dose escalations): *treatment policy strategy (ignore)*
  - Dosing errors (e.g., missed dose): *treatment policy strategy (ignore)*
  - Deviation in any intake of concomitant medications: *treatment policy strategy (ignore)*
  - Intake of prohibited medications: *treatment policy strategy (ignore)*
  - Meeting any treatment failure criteria prior to Week 96 or treatment discontinuation due to any reason prior to Week 96: *composite (consider these as non-response)*
  - Handling of remaining intercurrent events: no other IE foreseen.
- **Treatment**:
  1. The randomized treatment arm (the investigational treatment asciminib 80 mg QD, or the Investigator selected TKI); with or without dose modifications (reductions/interruptions/allowed dose escalations); regardless of dosing errors, deviation in any intake of concomitant medications, intake of prohibited medication; and regardless of taking or not taking a TKI different from their pre-randomization selection of TKI in the comparator arm. Further details about the investigational treatment and control treatments are provided in Section 6.
  2. The randomized treatment arm (the investigational treatment asciminib 80 mg QD, or the Investigator selected TKI), within the stratum of participants that had imatinib as their pre-randomization selection of TKI; with or without dose modifications (reductions/interruptions/allowed dose escalations); regardless of dosing errors, deviation in any intake of concomitant medications, intake of prohibited medication; and regardless of taking or not taking a TKI different from their pre-randomization selection of TKI in the comparator arm. Further details about the investigational treatment and control treatments are provided in Section 6.
- **The summary measure:** stratum adjusted difference in the proportion of participants that are in MMR at Week 96 and corresponding 95% CI, between the

1. Randomized treatments (asciminib versus Investigator selected TKI).
2. Randomized treatments (asciminib versus Investigator selected TKI), within the stratum of participants that have imatinib as their pre-randomization selection of TKI.

2.2.2 Other secondary estimands

The **other secondary estimands** of interest, for the clinical questions below will be defined in the statistical analysis plan (SAP).

1. **A secondary clinical question of interest is:** what is the efficacy of asciminib (80 mg QD) compared to Investigator selected TKI within the stratum of participants that have a 2G TKI as their pre-randomization selection of TKI; with respect to **MMR at Week 48**, without meeting any treatment failure criteria and without treatment discontinuation, prior to Week 48, in newly diagnosed CML-CP patients; *regardless of* dose interruptions /reductions /allowed dose escalations; *regardless of* dosing errors, changes on concomitant medication, intake of prohibited medication; and *regardless of* taking a TKI different than the pre-randomization selection of TKI in the comparator arm.
2. **A secondary clinical question of interest is:** What is the efficacy of asciminib (80 mg QD) compared to Investigator selected TKI within the stratum of participants that have a 2G TKI as their pre-randomization selection of TKI; with respect to **MMR at Week 96**, without meeting any treatment failure criteria and without treatment discontinuation, prior to Week 96, in newly diagnosed CML-CP patients; *regardless of* dose interruptions/reductions/allowed dose escalations; *regardless of* dosing errors, changes on concomitant medication, intake of prohibited medication; and *regardless of* taking a TKI different than the pre-randomization selection of TKI in the comparator arm.
3. **A secondary clinical question of interest is:** What is the safety/tolerability of asciminib (80 mg QD) compared to 2G TKIs; with respect to the **time to discontinuation of study treatment due to AE (TTDAE)**, where prior treatment discontinuation due to other reasons is considered a competing risk event, in newly diagnosed CML-CP patients; *regardless of* dose interruptions/reductions/allowed dose escalations; *regardless of* dosing errors, changes on concomitant medication, intake of prohibited medication.

3 Study design

This study is a phase III, multi-center, open-label, randomized study of oral asciminib 80 mg QD versus Investigator selected TKI (imatinib, nilotinib, dasatinib, or bosutinib) in adult patients with newly diagnosed Ph+ CML-CP. All comparator TKIs will be made available, unless not permitted by local regulations or local Health Authority, or not approved for the treatment of CML in the country.

The study is designed to compare the efficacy of asciminib 80 mg QD with Investigator selected TKI for the treatment of newly diagnosed, previously untreated patients with Ph+ CML-CP. The Investigator selected TKI will be one of the treatment options approved by major Health Authorities (FDA/EMA) for first-line treatment of CML-CP - imatinib 400 mg QD or nilotinib 300 mg BID or dasatinib 100 mg QD or bosutinib 400 mg QD.

Approximately 402 participants will be randomized in a 1:1 ratio to asciminib or Investigator selected TKI.

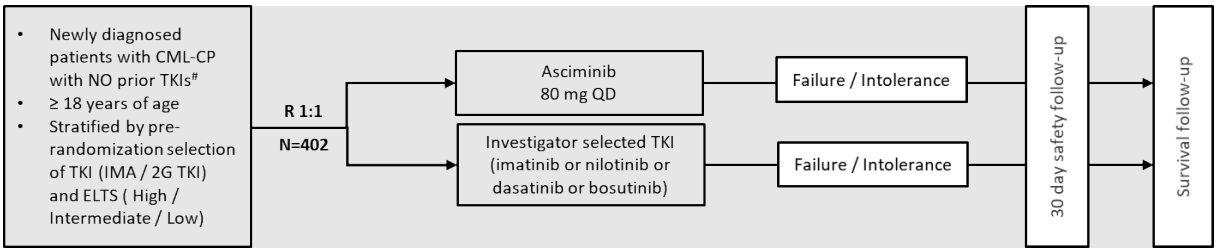
Randomization will be stratified based on the following two stratification factors:

- ELTS score (low versus intermediate versus high)
- Pre-randomization selected TKI (imatinib versus 2G TKI (nilotinib or dasatinib or bosutinib)).
    - Prior to randomization, the Investigator, in consultation with the patient, considering the current treatment paradigm and patient characteristics and comorbidities, will make a selection of preference for imatinib or 2G TKI (nilotinib or dasatinib or bosutinib) if the patient is randomized to the comparator arm. The selection should be made as close as possible to the randomization date once all relevant clinical information becomes available.

The stratified randomization based on these two stratification factors will help to achieve a balance across the treatment arms for the possible comorbidities and baseline characteristics of patients enrolled in the study.

To further ensure that the distribution of participants, between imatinib and 2G TKIs (nilotinib or dasatinib or bosutinib), in the Investigator selected TKI arm is reflective of the use of these agents in clinical practice, the enrollment into the strata of imatinib versus 2G TKI (nilotinib or dasatinib or bosutinib) based on the pre-randomization selection of TKI will be managed by Interactive Response Technology (IRT) to be approximately 50% versus 50%.

Figure 3-1 Study design



#: either imatinib, or nilotinib, or dasatinib or bosutinib for ≤ 2 weeks is allowed. No other treatment with TKIs (tyrosine kinase inhibitors) prior to randomization is permitted. 2G: 2nd generation; CML-CP: Chronic Myelogenous Leukemia – Chronic Phase; ELTS: EUTOS Long Term Survival; IMA: imatinib; R: randomized; TKI: tyrosine kinase inhibitor

Treatment arms: The study will have 2 treatment arms:

- Arm 1: Asciminib 80 mg QD under fasting conditions (as described in Section 6.7)
- Arm 2: Investigator selected TKI that will include one of the below treatments*:
    - Imatinib 400 mg QD administered with food
    - Nilotinib 300 mg BID (total daily dose of 600 mg) administered under fasting conditions (as described in Section 6.7)
    - Dasatinib 100 mg QD administered with or without a meal
    - Bosutinib 400 mg QD administered with food.

*Dose recommendations as per local label should be followed for participants with hepatic and renal impairment.

Dose escalation:

For participants randomized to the asciminib treatment arm, dose escalation beyond 80 mg QD for asciminib is not permitted.

In line with the label recommendations (FDA/ EMA approved labels) for the TKIs in the Investigator selected TKI arm, dose escalation will be allowed in the *Investigator selected TKI arm* for imatinib, dasatinib and bosutinib. The escalation in dose is not mandatory, but is at the discretion of the Investigator, if considered in the participant's best interest, and can only be done for participants that meet both the below criteria:

- Participants who do not experience Grade 3 toxicity
- Participants who meet the criteria for suboptimal response as per ELN treatment recommendation (Hochhaus et al 2020A)

The below dose escalation is allowed*:

- *Imatinib*: Dose escalation from a starting dose of 400 mg QD to 600 mg QD
- *Nilotinib*: Dose escalation beyond 300 mg BID for nilotinib is not permitted
- *Dasatinib*: Dose escalation from a starting dose of 100 mg QD to 140 mg QD
- *Bosutinib*: Up to two sequential dose escalations in increments of 100 mg QD from a starting dose of 400 mg QD to a maximum of 600 mg QD

*Dose recommendations as per local label should be followed for participants with hepatic and renal impairment.

For further details on study treatments refer to Section 6.

No crossover of study treatment across arms and no change of study treatment within the Investigator selected TKI will be allowed.

Duration of Study treatment: Participants on the study will continue to receive the assigned treatment until the End of Study, or until premature discontinuation due to treatment failure, disease progression or intolerance or due to Investigator or participant decision.

Duration of study: The End of Study will occur 5 years from the last participant first treatment in the study. Participants who discontinue study treatment prematurely due to any reason, will be followed up for survival and progression (to AP/BC) until the End of Study.

At the End of Study, for participants who in the opinion of the Investigator are continuing to benefit from the study drug, every effort will be made to continue to provide study treatment. The options may include switching to commercial supplies, where applicable.

End-points: In addition to the primary and key secondary end-points based on MMR, the study will also investigate secondary endpoints for efficacy, PK of single-agent asciminib, safety and tolerability of single-agent asciminib versus that of the Investigator selected TKI, and PRO assessment. Exploratory end-points for biomarkers and pharmacokinetics of asciminib will also be assessed.

Analysis time-points:

- The primary analysis will be performed when all randomized participants have been treated for at least 48 weeks or discontinued from study treatment prior to Week 48.

- The key secondary analysis will be performed when all randomized participants have been treated for at least 96 weeks or discontinued from study treatment prior to Week 96.
- The final analysis will be performed once the End of Study (i.e. 5 years from the last participant first treatment date in the study) is reached.

4 Rationale

4.1 Rationale for study design

The proposed study CABL001J12301 is a phase III, multi-center, open-label, randomized study of oral asciminib versus Investigator selected TKI in adult patients with CML-CP. This patient population includes adult participants ≥ 18 years of age with newly diagnosed CML-CP enrolled within 3 months of initial diagnosis. The study will include participants with a documented diagnosis of CML-CP as per ELN treatment recommendations (Hochhaus et al 2020A). Participants could have received treatment with hydroxyurea and/or anagrelide for disease control following initial diagnosis. Treatment with either imatinib, or nilotinib, or dasatinib or bosutinib for ≤ 2 weeks is allowed, as this may be initiated around the time of diagnosis for emergent disease control prior to randomization and is not expected to impact the safety or efficacy endpoints of this study. No other TKI therapy is permitted prior to study entry. This is in line with previous investigation of first-line therapy in CML-CP (Saglio et al 2010). The inclusion and exclusion criteria are expected to support enrollment of a patient population representative of adult patients with newly diagnosed CML-CP, while maintaining adequate safeguards for patient safety in view of the experimental nature of the study.

To evaluate the efficacy and safety of asciminib in this patient population, the study will have an active comparator arm- Investigator selected TKI. Approximately 402 participants will be randomized in a 1:1 ratio to receive either asciminib or the comparator arm, Investigator selected TKI.

Participants randomized to the Investigator selected TKI arm could be treated with either imatinib or 2G TKIs (nilotinib or dasatinib or bosutinib), all of which are treatment options approved by major Health Authorities (FDA/ EMA) for newly diagnosed CML-CP patients (Hochhaus et al 2020A, NCCN 2020). The TKI in the comparator arm is selected by the Investigator in consultation with the patient. Investigator discretion in selection of the TKI in comparator arm is allowed as the selection of first line treatment of patients with CML-CP is dependent on patient related factors such as age, lifestyle, comorbidities, and disease characteristics such as risk score at diagnosis, as well as on the regional treatment paradigm and clinical practice. Investigator choice in the selection of TKI for optimal treatment of patients with CML-CP in the comparator arm optimizes patient treatment and minimizes the risk of exclusion of any group of patients, any adult age group, risk category or patients with specific co-morbidity.

The randomized active comparator design, comparing asciminib with recommended treatment options in first-line (Hochhaus et al 2020A, NCCN 2020), minimizes the risk of operational bias and provides a rigorous tool to appropriately assess the efficacy and safety of asciminib vs Investigator selected TKI in this patient population.

Randomization will be stratified by EUTOS long-term survival (ELTS) risk group (low versus intermediate versus high) and pre-randomization selection of TKI of the control arm (imatinib versus 2G TKI [nilotinib or dasatinib or bosutinib]).

- ELTS score is a predictive and prognostic score used to estimate the risk of progression and survival risk in newly diagnosed patients with CML-CP. Similar to the historically used Sokal score, ELTS score also uses hematologic data, spleen size, and age, but is focused on CML –specific OS by reducing the negative prognostic value of age as applicable to TKI's. The ELTS score has been validated several times for its ability to significantly discriminate risk groups regarding long-term survival outcome and has been shown to provide better prognostic discrimination than Sokal, Hasford (Euro) or EUTOS score in CML (Geelen et al 2018, Pfirrmann et al 2020). The ELN and NCCN treatment guidelines recommend the use of the ELTS score as the preferred method to assess baseline CML risk and thus to inform the first-line treatment decisions for newly diagnosed patients with CML-CP (Hochhaus et al 2020A, NCCN 2020).
- Pre-randomization selection of the control treatment (imatinib vs 2G TKIs): Prior to randomization, the Investigator, in consultation with the patient and considering the current treatment paradigm and comorbidities presented by the patient, will make a selection of preference for one of imatinib, nilotinib, dasatinib or bosutinib, in the event that the patient is randomized to the control arm.

The randomization by these stratification factors will help achieve a balance across the treatment arms for the possible prognostic factors, comorbidities and baseline disease characteristics in the study. Stratification by geographic region is not considered as there is expected to be a high degree of overlap/correlation between geographic regions and our selected stratification factors; and also in order to limit the total number of strata.

In first line treatment of CML-CP approximately half of the patients are treated with imatinib and approximately half with 2G TKIs (Campbell et al 2019). Thus, in order to ensure that the distribution of patients between imatinib and 2G TKIs in the Investigator selected TKI arm is reflective of the use of these agents in clinical practice, the distribution of pre-randomization selection of imatinib versus 2G TKI will be managed by the IRT randomization system to be approximately 50% in imatinib and 50% in 2G TKI stratum.

The primary endpoint of the study is the proportion of participants that achieve MMR at Week 48 (MMR rate at Week 48). Assessment of the efficacy endpoint of MMR by molecular monitoring based on *BCR-ABL1* levels in International Scale (IS) by RQ-PCR with evidence of typical transcript is considered a sensitive and objective measure of response to treatment in CML-CP (Hochhaus et al 2020A, [FDA Guidance for Industry 2018], [EMA Anticancer guideline 2012]). A Novartis designated laboratory with validated PCR technology that has a sensitivity of at least MR4.5 will be used for molecular response assessment in the study.

MMR is predictive of superior long-term clinical outcomes in CML, namely PFS and OS. Strong evidence for MMR as a marker for survival comes from the German CML study IV where MMR at 12 months was associated with a better PFS (95.3% vs 86.8%) and OS (95.3% vs 89.8%) at 5 years (Hehlmann et al 2017). Long-term follow-up from the IRIS study also determined that imatinib-treated patients with MMR at 12 months had superior 10-year OS (91.1% vs 85.3%) with fewer CML-related deaths (97.8% vs 89.4%) compared with those failing this target Hochhaus et al 2017A. MMR is widely used as a surrogate marker of survival

in patient care and in clinical trials (Saussele et al 2018, Hochhaus et al 2020A, NCCN 2020). The [FDA Guidance for Industry: Hematologic Malignancies (2018)], [EMA Anticancer guideline (EMA/CHMP/703715/2012 Rev. 2)] supports the use of MMR as a measure of clinical benefit. Treatment guidelines for CML-CP consider achievement of MMR (*BCR-ABL1* levels IS $\leq$ 0.1% at 12 months (Week 48 of treatment) to be associated with a very low probability of subsequent disease progression and consider this an optimal response to treatment (Hochhaus et al 2020A, NCCN 2020). Thus, MMR rate at Week 48 of treatment is an objective, validated and standardized primary endpoint reflective of clinical benefit to the patient.

The study will be conducted as an open label study. The requirements of dose administration in relation to food and frequency of dosing are distinct for the two treatment arms and within the comparator arm; asciminib is to be administered once a day under fasting conditions, imatinib and bosutinib are to be administered once a day with food, dasatinib is to be administered once a day with or without food whereas nilotinib is to be administered twice a day under fasting conditions. Blinding of study treatment would be very complex and increase the likelihood of dosing errors in the study. Furthermore, as the efficacy endpoints are objectively measured standardized laboratory parameters, the open label nature of the study is not expected to introduce bias.

The End of Study will occur 5 years from the date the last participant receives the first treatment in the study. Participants who discontinue study treatment prematurely due to any reason, will be followed up for progression to AP/BC and survival up till the End of Study. The planned treatment duration of at least 5 years for all participants will be adequate to address both the multiple primary and key secondary objectives of the study, as well as the safety objectives.

4.2 Rationale for dose/regimen and duration of treatment

The investigational arm of study CABL001J12301 will evaluate asciminib at a continuous dose of 80 mg once-daily (QD).

In the FIH dose escalation study CABL001X2101, the MTD for single agent asciminib was not reached. Based on PK, safety and efficacy data available from study, a single agent dose of asciminib 40 mg BID was determined as the RDE for patients with CML-CP or CML-AP and further investigated in study CABL001A2301.

The asciminib dose of 80 mg QD for patients with newly diagnosed CML-CP is based on the clinical experience in patients with CML-CP in studies CABL001X2101 and CABL001A2301 and the PK/Pharmacodynamic (PD) modelling based exposure-response and exposure-safety analyses.

Clinical experience with asciminib single agent 80 mg total daily dose

Study CABL001X2101

The FIH dose escalation study CABL001X2101 evaluated single agent asciminib at a wide range of doses (10 mg – 200 mg BID, 80 mg – 200 mg QD). In the dose escalation part of the study, the MTD for single agent asciminib was not reached. Testing of escalating doses of asciminib showed that the 40 mg BID and the 80 mg QD dose were active and well tolerated in this heavily pretreated population of CML-CP patients.

As of cut-off date, study CABL001X2101 had enrolled 200 CML-CP/AP patients treated with single agent asciminib, where 53 (26.5%) patients were treated with a total daily dose of 80 mg and 132 (66%) patients were treated with a total daily dose higher than 80 mg. Data with asciminib single agent total daily dose of 80 mg and higher than 80 mg from study CABL001X2101 was analyzed to determine the efficacy and safety profile for asciminib across dose levels. The median duration of exposure to study treatment was 124.6 weeks (min- max: 0-302) and 123 (61.5%) patients are still on treatment. In these heavily pretreated patients with CML-CP/AP:

In study CABL001X2101 asciminib was well tolerated and its safety profile was similar across all doses explored; and no particular safety findings were observed for any specific dose level or regimen (QD/BID). (See Section 1.2.2.1 for further details).

Study CABL001A2301

Study CABL001A2301 is an ongoing Phase III, multi-center, active-controlled, open-label randomized study that compares the efficacy and safety of asciminib with that of bosutinib in the treatment of patients with CML-CP, who have received at least 2 prior ATP-binding site TKIs.

A total of 233 participants were randomized in a 2:1 ratio and stratified according to patients' cytogenetic response at screening (major or no major cytogenetic response) to receive either asciminib 40 mg twice daily (BID) (157 participants) or bosutinib 500 mg QD (76 participants).

The study met its primary objective: asciminib 40 mg BID was superior compared to bosutinib 500 mg QD, as demonstrated by the MMR rate at 24 weeks; the study showed significantly improved efficacy with favorable safety and tolerability of asciminib as compared to bosutinib in CML-CP patients treated with at least 2 prior TKIs. (See Section 1.2.2.2 for further details).

Exposure-safety and exposure-efficacy analyses

Data from study CABL001X2101 and CABL001A2301, with a cut-off date of respectively 25-May-2020 and 02-Apr-2020, was analyzed to evaluate the 80 mg QD vs 40 mg BID dose. Exposure-safety and exposure-efficacy analyses were performed using AUC, Cmax and Cmin as PK metrics. Exposure-safety and exposure-efficacy analyses were conducted using data from patients with CML-CP/AP treated with asciminib as single agent in doses ranging from 10 mg BID to 200 mg BID, 80 mg QD, 120 mg QD and 200 mg QD, and for whom PK data was available (N=353 for safety and N=303 for efficacy).

[redacted]

The exposure-safety analyses were based on PK-safety set included 199 participants from study CABL001X2101 and 154 participants from study CABL001A2301. The exposure-safety relationship was explored using various safety endpoints such as laboratory and vital signs abnormalities and AEs. The exposure metrics were based on daily predictions of AUC, Cmax and Cmin from the population PK model and a 5-day-average prior to safety event. In all safety endpoints analyzed (except Grade 2 or Higher Aspartate Aminotransferase (AST) increase), no

significant relationship was found between probability of safety events and increase in exposure within the range of dose levels and regimens investigated. For Grade 2 or higher AST increase, the increase in the probability of an event due to exposure was very small; for example, the increase was from 0.1% to 0.3% in study CABL001A2301 for a 5-fold increase in exposure. Regarding dose reduction due to an AE, it was found that the time to first such events was not associated with increasing exposure. Finally, analysis of change from baseline in serum creatinine was also found to be independent of exposure. In summary, asciminib has a similar safety profile across all dose regimens (and associated asciminib exposure) whether at 40 mg BID, 80 mg QD or 200 mg BID. The amount of safety data obtained at asciminib 80 mg QD may be considered small, however, the small sample size at the 80 mg QD dose (N=18) is more than counterbalanced by the total amount of data at 80 mg QD and higher total daily doses (N=150) with records collected over several years of treatment. Despite the increase in Cmax (by about 60% based on popPK) with the 80 mg QD compared to that of the 40 mg BID, in view of the lack of association between the chance of AEs with increasing exposure (by 5-fold), the 80 mg QD regimen was considered to have a similar safety profile to that of 40 mg BID.

To characterize the exposure-response relationship based on data from the two studies, semi-mechanistic drug response models for the effect of asciminib on %*BCR-ABL1* levels were developed. The exposure response efficacy analyses included data of 303 CML-CP participants from study CABL001A2301 (n=154) and study CABL001X2101 (n=149). A total of 267 participants received twice-daily (BID.) dosing, while 36 participants received once-daily (QD) dosing. At baseline, majority of the patients had >10% BCR-ABL1 transcript levels. The exposure-response models in efficacy highlighted the existence of a slightly positive exposure-efficacy relationship, which did not translate into clinically meaningful difference in median predicted MMR rates across the doses tested. Direct comparisons provided evidence that the efficacy is similar between asciminib 80 mg QD and 40 mg BID.

The totality of evidence from the various exposure response models indicate a similar efficacy between 80 mg QD and 40 mg BID. In the light of the good safety profile of asciminib, and lack of association between the probability of AEs and increase in asciminib exposure, e.g. Cmax, the 80 mg QD is considered to offer an alternative dosage regimen option. Given the food effect of asciminib and its consequent fasting restrictions, the dose regimen of 80 mg QD provides a convenient regimen that may improve adherence to treatment.

Participant benefit

In the study CABL001J12301, in view of decreasing participant burden and increasing compliance in the first line setting, a once-daily dose (QD) of asciminib 80 mg will be evaluated. As presented above, the safety and efficacy of 80 mg QD is not expected to differ from the 40 mg BID dose that was tested in study CABL001A2301 in patients with CML-CP who received at least 2 prior ATP-binding site TKIs.

Requiring participants to take asciminib twice-daily in fasting conditions poses practical challenges for many participants with regard to managing their daily meals and schedules, and it may impact treatment adherence and long-term compliance. According to Geissler et al 2017, 35.8% of patients taking their medication once-daily were highly adherent, whereas patients taking their medication twice-daily were highly adherent only in 24.9% of patients and 26.7%

were in the low adherence group. Consequently, QD dosing is likely to be associated with better adherence and patient convenience.

In conclusion, based on the current efficacy and safety data available and safety-exposure and efficacy–exposure analyses, asciminib 80 mg QD has been selected as the dose and regimen to be used in this phase III study in newly diagnosed patients with CML-CP. Additionally, the once daily regimen is patient-centric and is likely to support better patient adherence to treatment in this patient population.

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

Rationale for choice of comparator

The comparator arm for this study is defined as Investigator selected TKI. For participants randomized to the Investigator selected TKI arm, the Investigator can choose to treat with either imatinib 400 mg QD treatment, or a 2G TKI (i.e. either nilotinib 300 mg BID, or dasatinib 100 mg QD, or bosutinib 400 mg QD). Ponatinib is not included as a TKI option in the comparator arm, as it is not approved for first-line use and would therefore not be reflective of current clinical practice.

Therefore, it is clinically relevant to compare asciminib with the proposed options of Investigator selected TKI, which is a comparator reflective of the current treatment paradigm. Moreover, imatinib remains the primary choice of first line treatment for many patients and its use is further boosted by its availability as a generic drug (Hochhaus et al 2020A). Additionally imatinib also served as the control arm in the pivotal studies (ENESTnd: Saglio et al 2010, DASISION: Kantarjian et al 2010B, BFORE: Cortes 2018) which were the basis of approval for the use of nilotinib, dasatinib and bosutinib, respectively, for treatment of patients with newly diagnosed CML-CP. Therefore, it is also important to compare asciminib versus imatinib (i.e. compare asciminib versus Investigator selected TKI, within the stratum of patients with imatinib as their pre-randomization selection of TKI).

In the Investigator selected TKI arm, dose escalation will be allowed, by Investigator decision, for imatinib, dasatinib and bosutinib for patients who do not have AEs of Grade 3 or higher and who meet the criteria for suboptimal response as per ELN 2020 treatment recommendation (Hochhaus et al 2020A).

For patients being treated with imatinib, dose escalation to imatinib 600 mg QD and for those being treated with dasatinib, dose escalation to dasatinib 140 mg QD is allowed. Similarly, for patients being treated with bosutinib, up to two sequential dose escalations in increments of 100 mg QD to a maximum of bosutinib 600 mg QD is allowed. No dose escalation beyond 300 mg BID is permitted for patients being treated with nilotinib. Escalation of dose for these TKIs is based on approved labels (FDA/EMA) of the respective TKI and is reflective of the management of patients with CML-CP in clinical practice. Locally applicable approved prescribing information should be consulted prior to any dose escalation.

To ensure that the distribution of patients between imatinib and 2G TKIs (nilotinib or dasatinib or bosutinib) in the Investigator selected TKI arm is reflective of the use of these agents in clinical practice, the patients' enrollment in the two strata (based on the pre-randomization

selection of imatinib versus a 2G TKI) will be approximately 50% versus 50%. This distribution is considered to be reflective of the current treatment paradigm and will allow for analyses comparing asciminib versus imatinib (i.e. asciminib versus Investigator selected TKI within the stratum of patients with imatinib as their pre-randomization selection of TKI), and asciminib versus 2G TKIs (i.e. asciminib versus Investigator selected TKI within the stratum of patients with a 2G TKI as their pre-randomization selection of TKI).

The treatment selection for newly diagnosed adult patients with CML-CP is complex and guided by several factors including age, risk score, comorbidities and treatment goals. Imatinib has lower rates of efficacy responses as compared to 2G TKIs (nilotinib, dasatinib or bosutinib), however imatinib remains a widely used treatment option with a very favorable safety and tolerability profile. Thus an additional sub-population of interest will include the patients with newly diagnosed CML-CP within the stratum of patients with imatinib as the pre-randomization selection of TKI.

4.4 Purpose and timing of interim analyses/design adaptations

No formal interim analysis is planned in the study. Safety outputs will be prepared for the data monitoring committee (DMC) as outlined in Section 10.2.3.

4.5 Risks and benefits

Appropriate eligibility criteria, as well as specific dose modification and stopping rules in the event of expected toxicities, are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities; including management of study drug induced AEs, are provided in Section 6.5.

Overall, asciminib (as monotherapy or in combination with other TKIs) has shown a favorable benefit-risk profile in two independent clinical studies. Results from the phase I study ([CABL001X2101]) showed positive responses with asciminib in a heavily pretreated population who had resistance to or unacceptable side effects from TKIs. In the ASCEMBL study ([CABL001A2301]) asciminib demonstrated superiority in the molecular response over bosutinib in participants treated with two prior TKIs (Hochhaus et al 2020B).

In the current protocol asciminib will be a first line treatment and this will allow for a population with a newly diagnosed condition and lower risk of progression to enter the trial, who may potentially benefit from a better response to asciminib. In addition, the tolerability of asciminib may allow for a more long-standing treatment with less side effects and lower risk of treatment discontinuation in this population.

Efficacy of the drug is assessed through molecular monitoring in central lab standardized to the international scale. With the exception of the bone marrow assessment required in the case of treatment failure, the protocol does not include invasive examination. Participant visits are aligned with the safety monitoring requirements as well as with current treatment recommendations and represent a common schedule that is also required in clinical practice outside of the study. It is therefore anticipated that the protocol will take every precaution to allow for the best possible safety of the patients while at the same time carefully managing the additional burden of the trial to patients.

Management of side effects represent a significant challenge with TKIs, in particular as patients may achieve a normal life expectancy. Data from ASCEMBL Hochhaus et al 2020B support a more favorable safety profile of asciminib compared with bosutinib. Patients may benefit from the treatment with asciminib and the improved quality of life. The most frequently reported AEs in both the clinical studies (CABL001X2101 and CABL001A2301) are listed in Section 1.2.2.

In this trial, the risks are managed through detailed information provided in the [Asciminib Investigator's Brochure] and requirements delineated in the study protocol. Other risks to subjects in this trial will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, and adherence to dose modification and interruption guidance provided in the protocol.

Recommended guidelines for prophylactic or supportive treatment for expected toxicities; including management of study drug induced AEs are provided in Section 6.5. Moreover, close follow up for evidence of efficacy, based on molecular response data, will permit rapid decision making, and discontinuation of therapy if necessary (see Section 9.1.1 data analysis).

Female participants 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 participant will not reliably comply, they should not be entered or continue in the study.

The local labels for imatinib, bosutinib, dasatinib and nilotinib characterize both efficacy and safety of each compound and provide guidance to maximize the efficacy and minimize the risks to patients.

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

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

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. At the Investigator's discretion and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial assessment/procedures according to Table 8-1 Assessment schedule performed at a remote location. Assessment/procedures will be performed remotely under the oversight of the Investigator, who

retains accountability for the oversight. The Investigator retains accountability for all efficacy and safety decisions with delegation of tasks to an off-site healthcare professional. The off-site healthcare professionals will be provided by a third-party vendor sourced by Novartis. Where a site wishes to use off-site healthcare professionals that are not provided by Novartis this must be agreed with Novartis before use.

In addition to procedures performed by the off-site healthcare professional, the on-site staff might perform certain procedures remotely using tele-visits.

5 Study Population

The study CABL001J12301 will randomize approximately 402 adult participants (≥ 18 years of age) with newly diagnosed CML-CP (diagnosed within 3 months prior to enrollment) in a 1:1 fashion to receive either asciminib or Investigator selected TKI (imatinib, nilotinib, dasatinib or bosutinib).
Participants could have received treatment with hydroxyurea and/or anagrelide for disease control following initial diagnosis. Continuation of hydroxyurea which had been administered for urgent control of high cell counts prior to randomization is allowed during the first two weeks of study, and should be tapered. Treatment with any TKIs prior to randomization is not allowed, except for a period of ≤ 2 weeks of either imatinib, or nilotinib, or dasatinib or bosutinib. No TKI other than the study treatment should be used post-randomization. The definition of CML-CP will be according to the European Leukemia Network (ELN) criteria (Hochhaus et al 2020A), and is outlined below in the inclusion criteria.

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

5.1 Inclusion criteria

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

1. Male or female participants ≥ 18 years of age.
2. Participants with CML-CP within 3 months of diagnosis.

3a. Diagnosis of CML-CP (ELN 2020 criteria) with cytogenetic confirmation of the Philadelphia chromosome

- Documented chronic phase CML will meet all the below criteria (Hochhaus et al 2020A):
  - < 15% blasts in peripheral blood and bone marrow,
  - < 30% blasts plus promyelocytes in peripheral blood and bone marrow,
  - < 20% basophils in the peripheral blood,
  - PLT count ≥ 100 x 10^9/L (≥ 100,000/mm^3),
  - No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly.

4. ECOG performance status of 0, or 1.
5. Adequate end organ function as defined by:
   - Total bilirubin (TBL) < 3 x ULN; participants with Gilbert's syndrome may only be included if TBL ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN

- CrCl ≥ 30 mL/min as calculated using Cockcroft-Gault formula,
- 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

6a. Participants must have the following laboratory values within normal limits 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 CrCl* ≥ 90 mL/min)
- 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 CrCl* ≥ 90 mL/min)
- Magnesium (magnesium increase of up to 3.0 mg/dL or 1.23 mmol/L if associated with CrCl* ≥ 90 mL/min)
- For participants with mild to moderate renal impairment (CrCl* ≥ 30 mL/min and < 90 mL/min) - potassium, total calcium (corrected for serum albumin) and magnesium should be ≥ LLN or corrected to within normal limits with supplements prior to randomization.

*CrCl as calculated using Cockcroft-Gault formula

7. Signed informed consent must be obtained prior to any study related screening procedures being performed.
8. Evidence of typical *BCR-ABL1* transcript [e14a2 and/or e13a2] at the time of screening which are amenable to standardized RQ-PCR quantification.

5.2 Exclusion criteria

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

1a. Previous treatment of CML with any other anticancer agents including chemotherapy and/or biologic agents or prior stem cell transplant, with the exception of hydroxyurea and/or anagrelide. Treatment with either imatinib, or nilotinib, or dasatinib or bosutinib for ≤ 2 weeks is allowed. No treatment with other tyrosine kinase inhibitors prior to randomization is permitted.

2. Known cytopathologically confirmed CNS infiltration (in absence of suspicion of CNS involvement, lumbar puncture not required).
3. Impaired cardiac function or cardiac repolarization abnormality including but not limited to any one of the following:

- History within 6 months prior to starting study treatment of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG).
- Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block).
- QTc ≥ 450 ms (male participants), ≥460 ms (female participants) on the average of three serial baseline ECG (using the QTcF formula) as determined by central reading. If QTcF ≥ 450 ms and electrolytes are not within normal ranges, electrolytes should be corrected and then the participant re-screened for QTc.

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

4. 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 arterial or pulmonary hypertension, uncontrolled clinically significant hyperlipidemia).
5. History of significant congenital or acquired bleeding disorder unrelated to cancer.
6. Major surgery within 4 weeks prior to study entry or who have not recovered from prior surgery.
7. History of other active malignancy within 3 years prior to study entry with the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively.
8. History of acute pancreatitis within 1 year prior to randomization or medical history of chronic pancreatitis.
9. History of chronic liver disease leading to severe hepatic impairment, or ongoing acute liver disease.

10a Known history of chronic Hepatitis B (HBV), or chronic Hepatitis C (HCV) infection. Testing for Hepatitis B surface antigen (HBs Ag) and Hepatitis B core antibody (HBc Ab/anti HBc) will be performed at screening. If anti-HBc is positive, HBV-DNA evaluation must be carried out at screening. Patients having positive HBV-DNA must not be enrolled in the study. Also, patients with positive HBsAg must not be enrolled in the study. For details on the criteria see Appendix 16.4.

11. History of Human Immunodeficiency Virus (HIV) unless well-controlled on a stable dose of anti-retroviral therapy at the time of screening.
12. 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).
13. Participation in a prior investigational study within 30 days prior to randomization or within 5 half-lives of the investigational product, whichever is longer.

14a. If local regulations deviate from the contraception methods listed below to prevent pregnancy, local regulations apply and will be described in the ICF.

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 a period of time after stopping study medication. For asciminib, this period of time is 3 days after the last dose; if local regulations or locally approved

prescribing information differ from the protocol required duration of contraception, the longer duration must be followed and the same requirements will be described in the ICF. Participants taking Investigator selected TKI should be willing to follow contraception requirements in the locally-applicable prescribing information for the TKI received in the study.

Highly effective contraception methods include:

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

  iii. Sexually active males taking Investigator selected TKI should be willing to follow contraception requirements in the locally-applicable prescribing information for the TKI received in the study. Sexually active males taking asciminib do not require contraception.

15. Known hypersensitivity to the study treatment.

6 Treatment

6.1 Study treatment

The investigational treatments in this study includes asciminib (80 mg QD) and an Investigator selected TKI that include imatinib (400 mg QD); nilotinib (300 mg BID); dasatinib (100 mg QD) and bosutinib (400 mg QD).

The term "investigational drug" refers to the Novartis investigational drug, asciminib.

The "Investigator selected TKIs" could be considered as Investigational Medicinal Product (IMP) as well depending on local regulations. Dose recommendations as per local label should be followed for participants with hepatic and renal impairment.

For any component of the investigational treatment, all dosages prescribed and administered to the subject and all dose changes during the study (including the reason for change) must be recorded on the appropriate electronic Case Report Form (eCRF).

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drugs*

Investigational/ Control Drug (Name and Strength)	Treatment form or Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
Asciminib (ABL001) 40 mg	Tablet	Oral use	Open label	Sponsor (global)
Imatinib 400 mg	Tablet	Oral use	Open label	Locally sourced
Imatinib 100 mg	Tablet	Oral use	Open label	Locally sourced
Dasatinib 100 mg	Tablet	Oral use	Open label	Locally sourced
Dasatinib 70 mg	Tablet	Oral use	Open label	Locally sourced
Dasatinib 50 mg	Tablet	Oral use	Open label	Locally sourced
Dasatinib 20 mg	Tablet	Oral use	Open label	Locally sourced
Nilotinib 150 mg	Capsule	Oral use	Open label	Locally sourced
Nilotinib 200 mg	Capsule	Oral use	Open label	Locally sourced
Bosutinib 400 mg	Tablet	Oral use	Open label	Locally sourced
Bosutinib 100 mg	Tablet	Oral use	Open label	Locally sourced

*Please note: Locally available generic equivalents or strength are permitted for all TKIs included in the comparator arm. Investigator will select from the locally available appropriate TKIs option.

Refer to Section 6.7 for preparation and dispensation.

Dose recommendations as per local label should be followed for participants with hepatic and renal impairment.

6.1.2 Additional study treatments

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

6.1.3 Supply of study treatment

Novartis Global Clinical Supplies will supply asciminib to the investigational site as 40 mg tablets. Medication will be packaged as open label, with a 2 part label (base plus peel-off or tear-off). A unique medication number will be added on the label.

Investigator selected TKIs (nilotinib, dasatinib, bosutinib, imatinib) will be provided locally by the study site, subsidiary or designee as commercially available unless not permitted by local regulations or local Health Authority; or not approved for the treatment of CML in the country.

6.1.4 Treatment arms/group

Arm 1: Asciminib 80 mg QD under fasting conditions (as described in Section 6.7)

Arm 2: Investigator selected TKI that will include one of the below treatments as per the pre-randomized selection of TKI (imatinib or the 2G TKI (nilotinib or dasatinib or bosutinib))*.

- Imatinib 400 mg QD administered with food
- Nilotinib 300 mg BID (total daily dose of 600 mg) administered under fasting conditions (as described in Section 6.7)
- Dasatinib 100 mg QD administered with or without meal
- Bosutinib 400 mg QD administered with food

*Dose recommendations as per local label should be followed for participants with hepatic and renal impairment.

6.1.5 Post-trial access to treatment

Participants who complete participation in this trial and continue to derive clinical benefit from the treatment based on the Investigator's evaluation will receive post-trial access based on the criteria for post-trial access being satisfied.

Post Trial Access (PTA) means the provision of treatment to trial participants following their completion of trial participation. PTA will be provided until one of the following is met: participant no longer derives clinical benefit, Investigator discontinues treatment, launch or reimbursement (where applicable), treatment fails to achieve registration in the trial participant's country, or the clinical program is discontinued for any other reason.

Mechanisms for provision of PTA may include an extension phase to this study, a separate extension protocol, a rollover protocol, provision of the Novartis/Sponsor investigational product in a non-trial setting (known as post-study drug supply [PSDS]) when no further safety or efficacy data are required, or any other mechanism appropriate for the country.

The PTA mechanism must comply with local laws and regulations in the participating trial countries. If Novartis/Sponsor discontinues the PTA for this trial, Novartis/Sponsor will work with Investigators to transition participants into locally available alternative treatment, or standard of care.

6.1.6 Treatment duration

There is no fixed duration of treatment planned per participant. The participants are treated in the study up to end of study treatment period (defined as 5 years from the randomization date the last participant received the first treatment in the study), unless participants have discontinued treatment earlier. Participants may be discontinued from treatment with the study drug at any time due to unacceptable toxicity, disease progression, treatment failure and/or at the discretion of the Investigator or the participant. Participants who discontinue study treatment prematurely due to any reason, will be followed up for progression to AP/BC and survival up till End of Study.

6.1.6.1 Treatment beyond disease progression

Should a disease progression occur during study, the participant must be discontinued and will be treated at Investigator's discretion outside of the study.

6.2 Other treatment(s)

Anti-emetics

Use of anti-emetics is allowed. Prophylactic anti-emetics should be started only once the participant experiences nausea or vomiting, at the discretion of the Investigator. It is recommended that participants use drugs that do not cause QT prolongation. Please note that some anti-emetics have a known risk for Torsade de Pointes and should be used with caution (refer to Section 6.2.1.1 and Section 16.1).

Contraceptives

Hormonal contraceptives are allowed as contraception methods.

Anticoagulation agents

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

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

Caution is also advised when asciminib is co-administered with anti-PLT pro-drugs such as clopidogrel, ticlopidine and prasugrel, which require metabolic activation by CYP3A4 and CYP2C9. Participants using anti-PLT pro-drugs should still be carefully monitored.

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

Drugs that affect gastric pH

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

6.2.1 Concomitant therapy

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

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

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

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

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the participant are allowed, provided their use is documented in the participant records and on the appropriate case report form, including the medication's duration (start and end dates or if continuing at final exam). These include blood and PLT transfusions for participants with anemia and with thrombocytopenia. Concomitant use of hydroxyurea for urgent control of high cell counts during the first 2 weeks of study treatments is allowed.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

For participants treated with asciminib:

Following drugs should be used with caution (see Table 16-1 for examples):

- CYP3A4/5 substrates with narrow therapeutic index
- CYP2C9 substrates with narrow therapeutic index
- Strong CYP3A4 inducers
- Substrates of OATP1B, BCRP or both transporters, including, but not limited to sulfasalazine, methotrexate, pravastatin, atorvastatin, pitavastatin, rosuvastatin and simvastatin. 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 (ABL001 IB v10 – Section 1.4.2). As far as possible avoid co-administering drugs with a "Known", "Possible" or "Conditional" risk of Torsades de Pointes/QT prolongation (per Table 16-1) during the course of the study.

If during the course of the study, concomitant administration of a drug with "Known risk", "Possible risk" or "Conditional risk of Torsades de Pointes" is required, based on the Investigator assessment and clinical need, study treatment may be continued under close ECG monitoring to ensure participant safety.

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

For participants treated with the Investigator selected TKI:

The Investigator must follow the respective **local label** for specific directions regarding restrictions in the use of concomitant therapy for each of the comparator TKIs.

6.2.1.2 Use of bisphosphonates

The use of bisphosphonates regardless of indication is allowed.

6.2.2 Prohibited medication

For all participants in the study:

Other anticancer agents

The administration of any other anticancer agents including chemotherapy and biologic agents is not permitted except for anti-cancer treatments of newly diagnosed solid cancers (e.g. prostate cancer) that would not impact the level of minimal residual disease of participants. These participants may remain in the current study after consultation with Novartis. The administration of other tyrosine kinase inhibitors indicated for treatment of CML is **not** allowed.

Use of hydroxyurea for urgent control of high cell counts during the first 2 weeks of study treatments is allowed.

For participants treated with the Investigator selected TKI:

The Investigator must follow the respective **local label** for specific directions regarding other drugs that are contraindicated with the assigned study treatment.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a subject Number (subject No.) that is assigned when the participant is first enrolled for screening and is retained as the primary identifier for the participant 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 participant is numbered uniquely across the entire database. Upon signing the informed consent form (ICF), the site will use the electronic data capture (EDC) system to assign the participant the next sequential subject No.

Once assigned, the subject No. must not be reused for any other participant and the subject No. for that individual must not be changed **even if the participant is rescreened.**

Re-screening is allowed once for participants that were initially screen failures for reasons which are amenable to correction, such as abnormal laboratory values and/ or concurrent medical conditions after reaching an adequate level of control. If a patient is a screen failure due to not meeting the laboratory levels for electrolytes under Inclusion criterion 6a, and rescreened after correction of these levels, the time since diagnosis could exceed 3 months, provided all other inclusion/ exclusion criteria continue to be met. All eligibility criteria must be re-checked and met prior to enrollment of the participant into the study. A new ICF will need to be signed if the Investigator chooses to re-screen the participant.

If the participant fails to be randomized or start treatment for any reason, the reason will be entered into the appropriate eCRF page, and the Interactive Response Technology (IRT) system should be notified as soon as possible that the participant was not randomized.

6.3.2 Treatment assignment, randomization

In this randomized, open label trial, participants will be randomized in a 1:1 ratio to one of the two treatment arms. Randomization will be stratified into 6 groups based on the two stratification factors at screening:

- The participants ELTS score (low versus intermediate versus high) – the score based on the values recorded at diagnosis will be recorded at screening. The score will be calculated using the European LeukemiaNet calculator available at: leukemia-net.org/leukemias/cml/elts_score/
- The pre-randomization selection of TKI (imatinib versus 2G TKI)

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of participant 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 Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to medication packs containing only the study treatments packaged and labelled under global sponsor.

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

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

6.4 Treatment blinding

This study is a randomized open label study. Treatment will be open to participants, investigator staff, persons performing the assessments, and the Novartis Clinical Trial Team (CTT).

However, in order to minimize the potential impact of the knowledge of treatments, the randomization list will be kept strictly confidential. No aggregate statistical analyses by treatment arm shall be performed prior to the database lock.

6.5 Dose escalation and dose modification

Asciminib:

The investigational arm of study CABL001J12301 will evaluate asciminib at a dose of 80 mg once-daily (QD). Dose escalation beyond 80 mg QD for asciminib is ***not permitted***.

Investigator selected TKI:

Dose escalation will be allowed in the Investigator selected TKI arm for imatinib, dasatinib and bosutinib in participants who do not experience Grade 3 toxicity and who meet the criteria for suboptimal response as per ELN 2020 treatment recommendation (Hochhaus et al 2020A)

Imatinib: Dose escalation from a starting dose of 400 mg QD to 600 mg QD

Dasatinib: Dose escalation from a starting dose of 100 mg QD to 140 mg QD

Bosutinib: Up to two sequential dose escalations in increments of 100 mg QD from a starting dose of 400 mg QD to a maximum of 600 mg QD.

Nilotinib: Dose escalation beyond 300 mg BID for nilotinib is not permitted.

Dose recommendations as per local label should be followed for participants with hepatic and renal impairment.

No crossover of study treatment across arms and no change of study treatment within the Investigator selected TKI will be allowed.

6.5.1 Dose modifications

In both treatment arms, if a participant requires a dose interruption more than 28 days for a non-hematologic toxicity, then the participant must be discontinued from the study treatment. If a hematologic toxicity (cytopenia Grade 3 or 4) lasts for more than 42 days without recovery to at least a Grade 2, despite the study treatment interruption and adequate management (including hematopoietic growth factors), then the participant must be discontinued from the study treatment.

For participants treated with asciminib

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

Dose modifications for asciminib are summarized in Table 6-2. The dose reduction indicated as "recommendations" are provided to assist Investigators in the event the participant experiences toxicity. However, deviations from "mandatory" dose interruptions and/or reductions are not allowed and mandatory interruptions or reductions must be strictly followed. Re-escalation to asciminib 80 mg QD is permitted if a change in the participant's individual benefit/risk assessment at the lower dose level is seen. Re-escalation will be allowed only once for any participant for any specific event per protocol. Further re-escalation to a maximum of 80 mg QD may be allowed in case the event is considered to be significantly different than the one(s) experienced previously and must be based on discussion with and approval by the Novartis medical monitor. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-2.

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

A participant must discontinue treatment with asciminib if, after treatment is resumed at a lower dose level, the toxicity recurs with the same or worse severity, except for recurrence of

cytopenias (Table 6-2). If a participant requires a dose interruption more than 28 days for a non-hematologic toxicity, then the participant must be discontinued from the study treatment. If a hematologic toxicity (cytopenia Grade 3 or 4) lasts for more than 42 days without recovery to at least a Grade 2, despite the study treatment interruption and adequate management (including hematopoietic growth factors), then the participant must be discontinued from the study treatment.

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

Dose modifications for asciminib	
Worst toxicity CTCAE Grade (version 5)	**Asciminib**
Investigations (Hematologic) If a hematologic toxicity (cytopenia Grade 3 or 4) lasts for more than 42 days without recovery to at least a Grade 2, despite the study treatment interruption and adequate management (including hematopoietic growth factors), then the participant must be discontinued from the study treatment.	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L)	**Recommendation**: Maintain dose level
Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	**Recommendation**: Maintain dose level
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L)	**Mandatory**: Omit dose until resolved to ≤ Grade 2, (recheck Complete Blood Count (CBC) 2x/week), then: if resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, then reduce dose ↓1 dose level
Grade 4 (ANC < 0.5 x 10^9/L)	**Mandatory**: Omit 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
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	**Mandatory**: Omit dose until resolved, then ↓ 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L)	**Recommendation**: maintain dose level
Grade 2 (PLT < 75- 50 x 10^9/L)	**Recommendation**: maintain dose level
Grade 3 (PLT < 50 - 25 x 10^9/L)	**Mandatory**: Omit dose until resolved to ≤ Grade 2, (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, then reduce dose ↓1 dose level
Grade 4 (PLT < 25 x 10^9/L)	**Mandatory**: Omit 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**: Omit dose until resolved to ≤ Grade 2, then maintain current dose level. For recurrent Grade 3-4 cytopenias
Non-hematologic adverse reactions except where further specified in individual sections	
Grade 1	**Recommendation**: Maintain dose level

Dose modifications for asciminib	
Grade 2	**Recommendation:** Omit dose until resolved to ≤ Grade 1, then maintain dose level
Grade 3	**Mandatory:** Omit dose until resolved to ≤ Grade 1, then reduce dose ↓ 1 dose level
Grade 4	**Mandatory**: Permanently discontinue participant from study drug treatment
Investigations (Renal)	
Serum creatinine	
>ULN - 1.5 x ULN	**Recommendation**: maintain dose level
>1.5 - 3.0 x baseline; > 1.5 - 3.0 x ULN	**Recommendation**: Omit dose until resolved to ≤ 1.5 x ULN or baseline, then maintain dose level
>3.0 x baseline; > 3.0 - 6.0 x ULN)	**Mandatory**: Permanently discontinue participant from study drug treatment
> 6.0 x ULN	**Mandatory**: Permanently discontinue participant from study drug treatment
Investigations (Hepatic)	
Isolated TBL elevation	
> ULN – 1.5 x ULN irrespective of baseline levels	**Recommendation**: Maintain dose level
> 1.5 - 3.0 x ULN irrespective of baseline levels	**Recommendation:** Omit dose. Repeat liver tests[b] within 48-72 hours then monitor weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN or baseline: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓1 dose level
> 3.0 - 10.0 x ULN irrespective of baseline levels	**Mandatory:** Omit dose. Repeat liver tests[b] within 48-72 hours then monitor weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN or baseline: if resolved in ≤ 14 days, then reduce dose ↓1 dose level if resolved in > 14 days, then discontinue participant from study drug treatment. The participant should be monitored weekly (including liver tests[b]), or more frequently if clinically indicated, until TBL have resolved to baseline or stabilization over 4 weeks
> 10.0 x ULN irrespective of baseline levels	**Mandatory:** Permanently discontinue participant from study drug treatment. The participant should be monitored weekly (including liver tests[b]), or more frequently if clinically indicated, until TBL have resolved to baseline or stabilization over 4 weeks
Isolated Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) elevation	
If normal at baseline	
> ULN - 3.0 x ULN	**Recommendation**: Maintain dose level
> 3.0 - 5.0 x ULN	**Recommendation:** Maintain dose level. Repeat liver tests[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results;

Dose modifications for asciminib	
	if abnormal lab values are confirmed upon the repeat test, then monitor Lliver tests[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN
> 5.0 - 10.0 x ULN	**Mandatory:** Omit dose. Repeat liver tests[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor liver tests[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN If resolved in ≤ 14 days resume at prior dose level If resolved in > 14 days, resume with reduced dose ↓1 dose level
> 10.0 - 20.0 x ULN	**Mandatory:** Omit dose. Repeat liver tests[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor liver tests[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN Then resume with reduced dose ↓1 dose level.
> 20.0 x ULN	**Mandatory: Permanently discontinue**
If elevated at baseline:	
> Baseline - 3.0 x Baseline AND ≤ 5 x ULN	Recommendation: Maintain dose level
> 3.0 x Baseline AND > 5.0 x ULN (duration less than 2 weeks)	Recommendation: Maintain dose level. Repeat liver tests[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 liver tests[b] weekly, or more frequently if clinically indicated, until resolved to ≤ ULN or baseline
> 3.0 x Baseline AND > 5.0 x ULN (duration more than 2 weeks):	Mandatory: Omit dose. Repeat liver tests[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 liver tests[b] weekly, or more frequently if clinically indicated, until resolved to ≤ ULN or baseline. If resolved, resume with reduced ↓ 1 dose level.
> 5.0 x Baseline AND > 8.0 x ULN (irrespective of the duration):	Mandatory: Omit dose. Repeat liver tests[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 liver tests[b] weekly, or more frequently if clinically indicated, until resolved to ≤ ULN or baseline. If resolved, resume with reduced ↓ 1 dose level.
> 20.0 x ULN	Permanently discontinue
Combined [c] elevations of AST or ALT and TBL	
For participants with normal baseline ALT and AST and TBL value: AST or ALT >3.0xULN combined with TBL >2.0 x ULN without evidence of cholestasis[d] For participants with elevated baseline AST or ALT or TBL value AST or ALT> 3 x baseline OR [> 8.0 x ULN], whichever is lower, combined with TBL >2x baseline AND >2.0 x ULN **Note: For participants with Gilbert's syndrome, at least 2-fold increase in direct bilirubin.	**Mandatory:** Interrupt treatment and adjudicate for DILI: Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of liver tests[b], or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Refer to Section 6.5.2.1 for additional follow-up evaluations as applicable. Mandatory: If causality assessment indicates DILI is probable: Permanently discontinue participant from treatment. If not DILI: Treat the identified cause according to institutional guidelines. Once resolved, reduce by one dose level if cause is treatment related.

Investigation (metabolic)	
Asymptomatic amylase and/or lipase elevation	
> ULN - 1.5 x ULN	**Recommendation**: Maintain dose level, measure 2x week
> 1.5 - 5.0 x ULN	**Recommendation**: Maintain dose level, measure 2x week
>5.0 x ULN	**Mandatory:** Omit dose until resolved to ≤ 1.5 x ULN 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., Magnetic resonance imaging (MRI), CT scan or ultrasound).
> 5.0 x ULN and with signs or symptoms	**Mandatory:** Permanently discontinue participant from study drug treatment. Obtain appropriate imaging (i.e., MRI, Computed tomography (CT) scan or ultrasound).
Vascular disorders	
Hypertension	
Systolic BP 140-159 mm Hg or Diastolic BP 90-99 mm Hg	**Recommendation**: Maintain dose level. Initiate antihypertensive drug/ increase the dose of existing antihypertensive drug or change treatment plan as per Investigator's assessment
Systolic BP ≥160 mm Hg or Diastolic BP ≥100 mm Hg	**Mandatory**: Omit dose until resolved ≤ Grade 1/baseline, then reduce dose ↓ 1 dose level. Initiate anti-hypertensive drug/ increase the dose of existing anti-hypertensive drug or change treatment plan as per Investigator's assessment
CTCAE Grade 4	**Mandatory**: Permanently discontinue participant from study drug treatment
Gastro intestinal	
Pancreatitis	
Grade 2 (enzyme elevations with radiologic findings for pancreatitis as per CTCAE v5.0.. For isolated increased enzymes please see table for asymptomatic amylase and/or lipase elevation)	**Mandatory**: If radiologic findings, hold treatment until resolved to ≤ Grade 1 or baseline. If treatment delay is ≤ 21 days, then reduce dose ↓ 1 dose level. If treatment delay > 21 days, discontinue treatment and keep monitoring with appropriate imaging (i.e., MRI, CT scan or ultrasound)**.
Grade ≥ 3	**Mandatory**: Permanently discontinue participant from study drug treatment. Obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).
Diarrhea* **	
Grade 1	**Recommendation:** Maintain dose level but, initiate anti-diarrhea treatment
Grade 2	**Recommendation**: Omit dose until resolved (initiate anti-diarrhea treatment) to ≤ grade 1, then maintain dose level. If diarrhea returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then reduce dose ↓ 1 dose level
Grade 3	**Recommendation**: Omit dose, initiate anti-diarrhea treatment and discontinue participant from study drug treatment

Grade 4	**Mandatory:** Initiate anti- diarrhea treatment and permanently discontinue participant from study drug treatment
Nausea/vomiting	
Grade 1	**Recommendation:** Maintain dose level but, may initiate anti-nausea treatment
Grade 2	**Recommendation:** Omit dose until resolved (initiate anti-nausea and other supportive treatment) to ≤ grade 1, then maintain dose level. If nausea/vomiting returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then reduce dose ↓ 1 dose level
Grade 3	**Mandatory:** Omit dose until resolved (initiate anti-nausea and other supportive treatment) to ≤ grade 1, then reduce dose ↓ 1 dose level. **Recommendation:** Omit dose for ≥ grade 3 vomiting or grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic (as per local practice)
Grade 4	**Mandatory**: Permanently discontinue participant 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**: Omit dose until resolved to Grade ≤ 1, then: If resolved in ≤ 7 days, reduce dose ↓ 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then discontinue participant from study drug treatment
Grade 4, despite skin toxicity therapy	**Mandatory**: Permanently discontinue participant from study drug treatment
General disorders and administration site conditions	
Fatigue/ Asthenia (General disorders and administration site conditions)	
Grade 1 or 2	**Recommendation**: Maintain dose level
Grade 3	**Recommendation**: Omit 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 AEs (CTCAE Version 5.0). [b] Core liver tests consist of ALT, AST, TBL (fractionated [direct and indirect], if TBL > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN). [c] "Combined" defined as TBL increase to the defined threshold concurrently with ALT/AST increase to the defined threshold. If combined elevations of AST or ALT and TBL do not meet the defined thresholds, please follow the instructions for isolated elevation of TBL and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when 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 Alkaline Phosphatase (ALP) elevation (>2.0 x ULN and R value <2) in participants without bone metastasis or elevation of ALP liver fraction in participants with bone metastasis.
Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury.
* Note: If TBL > 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, participants will be discontinued permanently from study treatment.
*** Note: Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools, or overt diarrhea.

Table 6-3 Dose reduction steps for asciminib

Dose reduction*	Starting dose level – 0	Dose level – 1
Asciminib	Two 40 mg tablet QD (once daily) (total daily dose 80 mg)	One 40 mg tablet QD (total daily dose 40 mg)

*Dose reduction should be based on the worst toxicity demonstrated at the last dose.
Asciminib dose reduction below a total daily dose of 40 mg is not allowed.

For participants treated with the Investigator selected TKI:

Dose modifications of the Investigator selected TKI are at Investigator's discretion and in accordance with institutional practice and local labels.

The Investigator must follow the respective **local label** for specific directions regarding dose modifications.

If a participant requires a dose interruption more than 28 days for a non-hematologic toxicity, then the participant must be discontinued from the study treatment. If a hematologic toxicity (cytopenia Grade 3 or 4) lasts for more than 42 days without recovery to at least a Grade 2, despite the study treatment interruption and adequate management (including hematopoietic growth factors), then the participant must be discontinued from the study treatment.

6.5.1.1 Dose adjustments for QTcF prolongation

In case of QTcF >500 ms (or QTcF prolongation >60 ms from baseline)

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

- Assess the quality of the ECG recording and the QT value and repeat if needed
- Interrupt asciminib treatment until confirmed resolution of QTcF and as per dose reduction guidelines for non-hematological AEs.
- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming asciminib treatment.
- Review concomitant medication associated with QT prolongation, including drugs with a "Known", "Possible", or "Conditional risk of Torsades de Pointes" (refer to Table 16-1),

and drugs with the potential to increase the risk of study drug exposure related QT prolongation.

- Check the dosing schedule and treatment compliance.

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

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

6.5.2 Follow-up for toxicities

Participants 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 participants must be followed up for AEs and SAEs for 30 days following the last dose of study treatment.

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

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

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

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

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

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

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

Evaluate status of liver metastasis (new or exacerbation) or vascular occlusion – e.g. using CT, MRI, or duplex sonography.

Perform relevant examinations (Ultrasound or MRI, Endoscopic retrograde cholangiopancreatography (ERCP)) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis (is defined as an Alkaline Phosphatase (ALP) elevation > 2.0 x ULN with R value < 2 in participants without bone metastasis, or elevation of the liver-specific ALP isoenzyme in participants with bone metastasis).

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury.

Table 6-4 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed Liver test abnormalities.

Table 6-4 Clinical and diagnostic assessments to rule out possible alternative causes of observed Liver Test abnormalities.

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

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

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

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

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

6.5.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced AEs, i.e., hematological, hepatic, renal, metabolic, vascular, gastrointestinal, skin toxicity and general disorders are provided in Table 6-2. Refer to preclinical toxicity and or clinical data found in the current [Asciminib Investigator's Brochure] or locally applicable (imatinib, nilotinib, dasatinib, and bosutinib labels).

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The Investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the Investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the Investigator and/or study personnel at each visit using tablets counts (if applicable at the visit) and information provided by the participant. 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.

Remote treatment administration compliance will be assessed by the off-site healthcare professional, and information provided to the Investigator and/or study personnel (as per Section 4.6).

6.6.2 Emergency breaking of assigned treatment code

Not applicable as this is an open-label study.

6.7 Preparation and dispensation

Asciminib (investigational drug):

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

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

A unique medication number is printed on the label of the investigational drug. Investigator staff will identify the investigational drug kits to administer to the participant by contacting the IRT and obtaining the medication number(s). The investigational drug has a 2-part label (base plus tear-off label), immediately before administering the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

Other study drugs (imatinib, nilotinib, dasatinib, bosutinib):

The other study drugs (imatinib, nilotinib, dasatinib, bosutinib) will be supplied locally as commercially available by the site pharmacy or by Novartis, if so, the drugs will be labeled accordingly to comply with the country legal requirements. Preparation and dispensation should follow the locally approved label and local practice.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of investigational treatments directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of investigational treatments from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 12 weeks supply. In this case, regular phone calls or virtual contacts (every 4 weeks until 12 weeks, then every 12 weeks or more frequently if needed), will occur between the site and the participant for instructional purposes, safety monitoring, drug accountability, investigation of any AEs, ensuring participants continue to benefit from treatment and discussion of the participant´s health status until the participants can resume visits at the study site. Please refer to Section 10.1.1 and Section 6.5 where assessment of suitability for continued investigational treatments administration may be needed.

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

The Investigator or designated site staff 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. If study treatment is administered at home e.g. oral medication, participants will be asked to return all unused study treatment and packaging and at the end of the study or at the time of discontinuation of study treatment.

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, 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.

The treatment for remote administration will be shipped from the pharmacy to the participants' home in accordance with the local practice.

6.7.2 Instruction for prescribing and taking study treatment

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

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 Table 6-5 and Table 6-1 and all the information about the administration of the investigational drug are described in the Section 6.1.3 and Section 6.1.4. Dose reductions can be performed as described in Table 6-3. Dose escalation information can be found in Section 6.5.

Table 6-5 Dose and treatment schedule*

	Dose	Frequency
Investigational Drug		
Asciminib (ABL001)	80 mg	once daily
Other Study Drugs		
Imatinib	400 mg	once daily
Nilotinib	300 mg (total daily dose of 600 mg)	twice daily
Dasatinib	100 mg	once daily
Bosutinib	400 mg	once daily

* Dose recommendations as per local label should be followed for participants with hepatic and renal impairment.

At baseline visit (Week 1) the participants will be randomized into one of the 2 treatment arms (stratified by pre-randomization selection of TKI and ELTS score), and the responsible site personnel will identify the study treatment package(s) to dispense by the medication number(s) assigned by IRT to the participant.

Asciminib arm:

Asciminib two 40 mg tablets will be administered orally daily on a continuous schedule (i.e. 80 mg QD). Asciminib should be ingested as follows:

- Participants should take asciminib daily at approximately the same time each day in the morning.
- Participants should take asciminib under fasting conditions (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.
- On days that PK samples are obtained, the participant should take asciminib during the clinic visit after the pre-dose PK samples, when instructed by the study staff.
- Participants 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 participant 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.

Investigator selected TKI arm:

The Investigator must follow the respective **local label** for specific directions for the administration of imatinib, dasatinib, bosutinib, and nilotinib. For all drugs taken QD, morning dosing is required in the study in order to allow compliance with key study requirements such as ECG collection. Dose recommendations as per local label should be followed for participants with hepatic and renal impairment.

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

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

7 Informed consent procedures

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the patient and/or their legally authorized representative and answer all questions regarding the study. Participants must be informed that their participation is voluntary.

Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

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

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

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

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

The following informed consents are included in this study:

- Main study consent, which also includes
- A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants

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

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic 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 Heath Authority.

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

Moreover, as per Section 4.6, qualifying participants may be offered the option to have certain clinical trial procedures performed at a remote location. In this case, informed consent must be obtained before conducting any study-specific procedures. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

The Assessment Schedule Table 8-1 lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule, Table 8-1, or as close to the designated day/time as possible. In case unscheduled assessments of any type are required, they may be performed as per Investigator's decision and will be recorded in the appropriate eCRF. The visit **"Baseline/Week 1"** is the **day 1** of the study, meaning the first day of dosing; all subsequent visits refer to end of the week, meaning for example that the visit **"Week 2"** is performed 2 weeks after the day 1 at **day 14** of the study (**"Week 4"** at **day 28** and so on).

The randomization and assessments (see Table 8-1) for the **Visit Name "Baseline/Week 1"**, except for the one specified as pre-dose, can be done with a window of -3 days from first dose (study day 1).

For the other visits, a visit window of +/- 3 days will be allowed. For PROs the collection window is described in Section 8.5.1, ECG will be performed before the PK sample collections. Missed or rescheduled visits should not lead to automatic discontinuation.

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

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

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

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic 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 allowed by 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 participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant 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.

Where multiple assessments are required to be performed at the same time point, and where the order of assessments is important for the evaluation of data, the order is based on study priorities and assessment needs. PRO measure(s) must be completed before any clinical assessments are performed at any given visit. PK sampling is prioritized, and other assessments are arranged around the collection of this sample.

Table 8-1 Assessment Schedule

Period	**Screening[4]**	**Treatment***											**End of Treatment**	**30 Days Safety follow-up**	**Survival follow-up Phase (Every 12 weeks)**
Visit Name	**Screening**	**Baseline/ Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Every 12 weeks to EOT**	**EOT/ Early Discontinuation**	**30 Days Safety follow-up**	**Survival follow-up**
Visit Numbers[1]	**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240**
Days (+/- 3 days, when applicable as per Section 8)	**-21 to -1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**168**	**252**	**336**	**420**	**-**	**-**	**-**
Pre-randomization selection discussion	S														
Obtain Informed consent	X														
IWRS/IRT Registration	X	X[5]	X	X	X	X	X	X	X	X	X	X	X		
Pre-randomization selection of TKI	X[3]														
Randomization		X[5]													

Period	**Screening[4]**	**Treatment***											**End of Treatment**	**30 Days Safety follow-up**	**Survival follow-up Phase (Every 12 weeks)**
Visit Name	**Screening**	**Baseline/ Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Every 12 weeks to EOT**	**EOT/ Early Discontinuation**	**30 Days Safety follow-up**	**Survival follow-up**
Visit Numbers[1]	**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240**
Days (+/- 3 days, when applicable as per Section 8)	**-21 to -1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**168**	**252**	**336**	**420**	**-**	**-**	**-**
Review eligibility	X														
Demography	X														
Inclusion / Exclusion criteria	X														
Medical history/current medical conditions	X														
Smoking History	X														
Charlson Comorbidity Index (CCI)	X														
Disease History	X														

Period	**Screening[4]**	**Treatment***											**End of Treatment**	**30 Days Safety follow-up**	**Survival follow-up Phase (Every 12 weeks)**
Visit Name	**Screening**	**Baseline/ Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Every 12 weeks to EOT**	**EOT/ Early Discontinuation**	**30 Days Safety follow-up**	**Survival follow-up**
Visit Numbers[1]	**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240**
Days (+/- 3 days, when applicable as per Section 8)	**-21 to -1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**168**	**252**	**336**	**420**	**-**	**-**	**-**
Prior Antineoplastic Therapy	X														
Prior/Concomitant Medications	X	Ongoing basis												X	
Physical Examination	S														
Extramedullary involvement	X	X[5]	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs	X	X[5]	X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance status	X														
Body Height	X														
Body Weight	X	X[5]	X	X	X	X	X	X	X	X	X	X	X		

Period	**Screening[4]**	**Treatment***											**End of Treatment**	**30 Days Safety follow-up**	**Survival follow-up Phase (Every 12 weeks)**
Visit Name	**Screening**	**Baseline/ Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Every 12 weeks to EOT**	**EOT/ Early Discontinuation**	**30 Days Safety follow-up**	**Survival follow-up**
Visit Numbers[1]	**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240**
Days (+/- 3 days, when applicable as per Section 8)	**-21 to -1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**168**	**252**	**336**	**420**	**-**	**-**	**-**
Blood collection for BCR-ABL1 quantification by RQ-PCR	X			X		X		X	X	X	X	X	X		
Bone marrow assessment for cytogenetic assessment	If no previous result <3 months old available		if clinically indicated												
PK sampling (asciminib arm only)			X (as per Table 8-6)	X (as per Table 8-6)				X (as per Table 8-6)	X (as per Table 8-6)		X (as per Table 8-6)				

Period	**Screening[4]**	**Treatment***											**End of Treatment**	**30 Days Safety follow-up**	**Survival follow-up Phase (Every 12 weeks)**
Visit Name	**Screening**	**Baseline/ Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Every 12 weeks to EOT**	**EOT/ Early Discontinuation**	**30 Days Safety follow-up**	**Survival follow-up**
Visit Numbers[1]	**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240**
Days (+/- 3 days, when applicable as per Section 8)	**-21 to -1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**168**	**252**	**336**	**420**	**-**	**-**	**-**
[redacted]															
Hematology	X	X[5]	X	X	X	X	X	X	X	X	X	X	X		
Clinical Chemistry	X	X[5]	X	X	X	X	X	X	X	X	X	X	X		
HbA1c	X							X	X	X	X	X	X		
Coagulation	X	if clinically indicated													
Other Hepatic Tests for suspected DILI		If clinically indicated													

Period	**Screening[4]**	**Treatment***											**End of Treatment**	**30 Days Safety follow-up**	**Survival follow-up Phase (Every 12 weeks)**
Visit Name	**Screening**	**Baseline/ Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Every 12 weeks to EOT**	**EOT/ Early Discontinuation**	**30 Days Safety follow-up**	**Survival follow-up**
Visit Numbers[1]	**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240**
Days (+/- 3 days, when applicable as per Section 8)	**-21 to -1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**168**	**252**	**336**	**420**	**-**	**-**	**-**
Hepatitis screen	X														
Pregnancy Test (serum)	X	X[5]		X		X		X	X	X	X	X	X		
Pregnancy Test (urine)		S (Every 4 weeks if serum pregnancy test is not performed)													
Electrocardiogram (ECG)	X	X	X	X				X	X		X	X (Week 96 only)	X		
Adverse Events/SAE	Ongoing basis													X	X[2]
Study drug dispensation		S						S	S	S	S	S			
Study drug administration		Ongoing basis													

Period	Screening[4]	Treatment*											End of Treatment	30 Days Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name	Screening	Baseline/ Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 24	Week 36	Week 48	Every 12 weeks to EOT	EOT/ Early Discontinuation	30 Days Safety follow-up	Survival follow-up
Visit Numbers[1]	1	110	120	130	140	150	160	170	180	190	200	210	220	230	240
Days (+/- 3 days, when applicable as per Section 8)	-21 to -1	1	14	28	42	56	70	84	168	252	336	420	-	-	-
[redacted]															

Period	Screening[4]	Treatment*											End of Treatment	30 Days Safety follow-up	Survival follow-up Phase (Every 12 weeks)
Visit Name	Screening	Baseline/ Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 24	Week 36	Week 48	Every 12 weeks to EOT	EOT/ Early Discontinuation	30 Days Safety follow-up	Survival follow-up
Visit Numbers[1]	1	110	120	130	140	150	160	170	180	190	200	210	220	230	240
Days (+/- 3 days, when applicable as per Section 8)	-21 to -1	1	14	28	42	56	70	84	168	252	336	420	-	-	-
[redacted]															
EORTC QLQ-C30 plus CML24		X		X		X		X	X		X	X (Week 96 only)	X (Every 4 weeks until 12 weeks after EOT)		
[redacted]															

Period	**Screening[4]**	**Treatment***											**End of Treatment**	**30 Days Safety follow-up**	**Survival follow-up Phase (Every 12 weeks)**
Visit Name	**Screening**	**Baseline/ Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Every 12 weeks to EOT**	**EOT/ Early Discontinuation**	**30 Days Safety follow-up**	**Survival follow-up**
Visit Numbers[1]	**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240**
Days (+/- 3 days, when applicable as per Section 8)	**-21 to -1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**168**	**252**	**336**	**420**	**-**	**-**	**-**
[redacted]															
Trial Feedback Questionnaires (TFQ)		X[6]							X[6]				X[6]		
Disposition													X		
Survival follow-up															X

Period	**Screening[4]**	**Treatment***											**End of Treatment**	**30 Days Safety follow-up**	**Survival follow-up Phase (Every 12 weeks)**
Visit Name	**Screening**	**Baseline/ Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Every 12 weeks to EOT**	**EOT/ Early Discontinuation**	**30 Days Safety follow-up**	**Survival follow-up**
Visit Numbers[1]	**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240**
Days (+/- 3 days, when applicable as per Section 8)	**-21 to -1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**168**	**252**	**336**	**420**	**-**	**-**	**-**
Antineoplastic therapies since discontinuation of study treatment														X	X
Stem Cell Transplant status															X
Progression status															X

* "Baseline/Week 1" is the day 1 of the study; all subsequent visits refer to end of the week, meaning for example that the visit "Week 2" is performed 2 weeks after the day 1 at day 14 of the study

[X] Assessment to be recorded in the clinical database or received electronically from a vendor

[S] Source document

[1] Visit structure given for internal programming purpose only

Period	**Screening[4]**	**Treatment***											**End of Treatment**	**30 Days Safety follow-up**	**Survival follow-up Phase (Every 12 weeks)**
Visit Name	**Screening**	**Baseline/ Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Every 12 weeks to EOT**	**EOT/ Early Discontinuation**	**30 Days Safety follow-up**	**Survival follow-up**
Visit Numbers[1]	**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240**
Days (+/- 3 days, when applicable as per Section 8)	**-21 to -1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**168**	**252**	**336**	**420**	**-**	**-**	**-**

[2] Any SAEs experienced after the 30 day safety FU should be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment unless otherwise specified by local law/regulations

[3] The selection should be made as close as possible to the randomization date once all relevant clinical information is available

[4] The central reading of the screening ECGs as well as the results of the BCR-ABL1 RQ-PCR, hematology, chemistry and hepatitis screen must be available prior to randomization to evaluate eligibility

[5] Baseline assessments that can be done with a - 3 days window. The other assessments should be done on day 1

[6] TFQ is not considered study data and will be received electronically outside the clinical database

8.1 Screening

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

All screening 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, coagulation, hemoglobin A1c (HbA1c), Hepatitis screen, serum pregnancy test, peripheral blood collection for *BCR-ABL1* RQ-PCR for evidence of typical transcripts), evaluation of all relevant medical history including smoking history and other cardiovascular risk factors and other comorbidities including an assessment of the Charlson comorbidity index (CCI), CML disease history, including prior TKI therapy, antineoplastic medication, prior and concomitant medication and must be performed prior to randomization. ELTS score should be based on the variables recorded at the time of initial diagnosis of CML. The score will be calculated using the European LeukemiaNet calculator available at //.leukemia-net.org/leukemias/cml/elts_score/ 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.

Participants 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* RQ-PCR, hematology, chemistry and hepatitis screen must be available prior to randomization to evaluate eligibility.

A participant 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 participant will not be required to sign another ICF, and the original participant 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 participant 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 participant after a participant has screen failed. All required screening activities must be performed when the participant is re-screened for participation in the study. An individual participant may only be re-screened once for the study. Once the number of participants screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the participants who screen failed will not be permitted to re-screen.

8.1.1 Eligibility screening

Following registering in the IRT for screening, participant 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

Participants who sign an informed consent and are subsequently are found to be ineligible prior to randomization will be considered as screen failures. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a SAE during the screening period (see SAE Section 10.1.3 for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized. Data and samples collected from participants prior to screen failure may still be analyzed. The reason for screen failure should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

Participant demographic and baseline characteristic data to be collected on all participants include: age, gender, race, ethnicity, height, weight, 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.

Participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities. The collection of race and ethnicity is performed to enable the Sponsor to evaluate the potential influence of baseline factors such as age, race/ethnicity, risk group (eg: ELTS), cytogenetic response at baseline etc. on the effect of asciminib with respect to the study endpoints. Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

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

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 participant's eCRF.

8.3 Efficacy

8.3.1 Molecular response

- Molecular response (MR) will be assessed in all participants. Peripheral blood samples will be collected from all participants at screening and at every 4 weeks until Week 12 and then every 12 weeks till end of study treatment for analysis of *BCR-ABL1* level via RQ-PCR by a Novartis designated laboratory. Levels of *BCR-ABL1* transcripts will be determined by

real-time quantitative PCR (RQ-PCR) testing of peripheral blood. Log reduction in *BCR-ABL1* transcripts levels from the standardized baseline value, or the percent ratio of *BCR-ABL1* transcripts versus control gene (ABL1) transcripts converted to a reference standard, international scale Hughes and Branford 2006, will be calculated for each sample. MMR is defined as *BCR-ABL1* IS ≤0.1%.

MMR and related variables are defined as the following:

- MMR criteria is defined as a ≥ 3.0 log reduction in *BCR-ABL1* transcripts compared to the standardized baseline equivalent to ≤ 0.1 % *BCR-ABL1/ABL1* % by international scale as measured by RQ-PCR, confirmed by duplicate analysis of the same sample
- MR4.0 criteria is defined as *BCR-ABL1* IS levels ≤ 0.01%
- MR4.5 criteria is defined as *BCR-ABL1* IS levels ≤ 0.0032%
- Loss of MMR is defined as *BCR-ABL1* IS > 0.1% in association with a ≥ 5-fold rise in BCR-ABL1 from the lowest value achieved on study treatment and replicated by a second analysis of the same sample.
- Confirmed Loss of MMR is defined as a loss of MMR confirmed by analysis of another sample taken after an interval of not less than 4 weeks and not more than 6 weeks unless associated with confirmed loss of CHR or loss of CCyR or progression to AP/BC or CML related death.
- Loss of MR4.0 is defined as *BCR-ABL1* IS > 0.01% confirmed by subsequent sample analysis within 12 weeks showing loss of MR4 associated with a ≥ 5-fold rise in BCR-ABL1 from the lowest value achieved on study treatment, unless it is associated with confirmed loss of CHR or loss of CCyR or progression to AP/BC or CML-related death.
- Loss of MR4.5 is defined as *BCR-ABL1* IS > 0.0032% confirmed by subsequent sample analysis within 12 weeks showing loss of MR4.5 associated with a ≥ 5-fold rise in BCR-ABL1 from the lowest value achieved on study treatment, unless it is associated with confirmed loss of CHR or loss of CCyR or progression to AP/BC or CML-related death.

The blood samples will be taken as described in Table 8-2. Additional unscheduled blood sample may be taken at the discretion of the Investigator at any time during the study as clinically indicated.

For participants who discontinue treatment for reasons other than death, lost to follow-up, or withdrawal of consent (WoC)/opposition to use data/biological samples, disease status and survival status must continue to be monitored as in Table 8-1.

Participants who discontinue from study treatment for documented disease progression must continue to be followed up for survival as outlined within the schedule of assessments (Table 8-1).

Table 8-2 Blood samples (Molecular response)

Sample Type	Volume	Visit*	Time Point
Peripheral Blood for *BCR-ABL1* RQ-PCR	15 mL	Screening	Anytime
		Week 4	Pre-dose
		Week 8	Pre-dose
		Week 12	Pre-dose
		Week 24	Pre-dose

Sample Type	Volume	Visit*	Time Point
		Week 36	Pre-dose
		Week 48	Pre-dose
		Every 12 weeks visits up to EOT	Pre-dose
		EOT	Anytime
		Confirmed Loss of MMR	Within 4 to 6 weeks from detection of loss of MMR
		Unscheduled sample	Anytime

* As per Section 8, a visit window +/- 3 days might be allowed

8.3.2 Cytogenetic Response

Bone marrow aspirate for cytogenetic analyses will be performed at screening and upon treatment failure (for definition of treatment failure, see Section 9.1.1). These exams will be performed and analyzed locally. Fluorescent In-situ hybridization (FISH) analysis will not be accepted. The results will be recorded on the Bone Marrow eCRF.

If results from a recent bone marrow analysis, done in the past 3 months, are available, bone marrow aspiration at screening need not be redone and results can be reported on the Bone Marrow eCRF.

Cytogenetic analysis of bone marrow should include 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. CCyR is defined as 0% Ph+ metaphases in a review of at least 20 metaphases.

8.3.3 Hematological Response

Hematologic response will be assessed by CBC and physical examination at each visit.

Complete Hematological Response (CHR) will be defined as all of the following present for ≥ 4 weeks:

- white blood cell(s) (WBC) count < 10 x 10^9/L
- PLT count < 450 x 10^9/L
- Basophils < 5%
- No blasts and promyelocytes in peripheral blood
- Myelocytes + metamyelocytes < 5% in peripheral blood
- No evidence of extramedullary disease, including spleen and liver

8.3.4 Appropriateness of efficacy assessments

Assessment of hematologic response is a standard measure of assessing the return of blood counts to normal values, in response to treatment for CML (Cortes et al 2011). Regular assessment of hematologic response is recommended by treatment guidelines (NCCN 2020). Assessing molecular response with RQ-PCR is considered as standard in CML therapy and recommended in treatment guidelines (Hochhaus et al 2020A, NCCN 2020). It is acknowledged that response can be assessed using only standardized results via International

Scale (IS) as *BCR-ABL*%. Mutational testing for treatment decisions can be done at Baseline, Week 24, Week 48, Week 96 and EOT, and any additional timepoint on Investigator discretion as clinically indicated is required in case of treatment failure. Cytogenetic assessment is required in case of treatment failure (Hochhaus et al 2020A, NCCN 2020).

8.4 Safety

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 or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur if needed for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-3 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, with the exception of extramedullary involvement as described below, including the spleen size if extramedullary involvement is detected. 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 investigational drug 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 centimeters (cm) and body weight (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, coagulation, 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 [ABL001J12301 laboratory manual]. The time windows

granted for laboratory evaluations are identical with the corresponding visit time windows for each visit (see Section 8). As per Table 8-4, each sample for the analysis of Glucose and Triglycerides needs to be collected under fasting condition: [ideally] 8 hours fasting is required with only water being allowed to be consumed.

Abnormal laboratory values or test results constitute AEs 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.

If at any time a participant has laboratory parameters obtained from a local laboratory due to inability to have an on-site visit, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory. The results of the local laboratory will be recorded in the eCRF if any the following criteria are met:

- A treatment decision was made based on the local results, or
- There are no concomitant central results available, or
- Local lab results document an AE not reported by the central lab, or
- Local lab results document an AE where the severity is worse than the one reported by the central lab.

Table 8-4 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Mean Corpuscular Hemoglobin Concentration (MCHC), Ery Mean Corpuscular hemoglobin Concentration, Ery.Mean Corpuscular Volume, PLTs, Erythrocytes, Leukocytes, Erythrocyte Cell Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Blasts, Promyelocytes, Myelocytes, Metamyelocytes,)
Coagulation	**International normalized ratio (INR) and Activated Partial Thromboplastin Time (APTT)**
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Total Calcium, Magnesium, Phosphate, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin (TBL), Total Cholesterol, Low Density Lipoprotein (LDL Cholesterol), High Density Lipoprotein (HDL Cholesterol), Total Protein, Triglycerides (fasting), Urea Nitrogen or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting), Hemoglobin A1c
Hepatitis markers	Hepatitis B Virus DNA, Hepatitis B Virus Surface Antigen, Hepatitis B Virus Surface Antibody, Hepatitis B Virus Core Antibody, Hepatitis C Virus RNA
Pregnancy Test*	Serum / Urine pregnancy test

* For details on pregnancy testing, please refer to Section 8.4.3

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, if participants cannot visit the site for protocol specified safety lab assessments conducted through central labs, an alternative lab (local) collection site may be used.

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, e.g., at the Screening and/or Baseline visit(s) (as applicable) to assess eligibility. The Investigator must calculate QTcF if it is not auto-calculated by the ECG machine.

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 participant 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 , for details please refer to Table 8-5 and Table 8-6.

These three sequential 12-lead ECGs are to be collected with ECG machines supplied by the central ECG laboratory and all three ECGs for each time point should be sent to central reading. All ECGs performed will be independently reviewed. Instructions for the collection and transmission of these ECGs to the independent central reader will be provided in the [CABL001J12301 ECG Manual].

Dose adjustments in case of QT prolongation should be performed per Section 6.5.1 (Refer to section Dose adjustments in case of QTcF prolongation).

Readings for QTc prolongation will be based on the average seen in the scans for each time point. The enrollment of participants 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 $\geq$ 450 ms (male) or $\geq$ 460 ms (female) by automated reading, an immediate manual central reading must be requested by calling Central cardiac safety reading center IQVIA. The participant may not be dosed if the average of the manually read ECGs confirms a QTcF $\geq$ 450 ms (male) or $\geq$ 460 ms (female).

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

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

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

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

- At screening and baseline
- At Week 2, 4, 12, 24, 48, 96
- At the EOT

Table 8-5 Central ECG collection plan in all randomized arms

Week	Study 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	12 Lead, triplicate
		Post-dose 2 hours, 3 hours, 4 hours	
Week 4	28	Pre-dose	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
Weeks 96	672	Pre-dose	12 Lead, triplicate
EOT	-	Pre-dose	12 Lead, triplicate
Unscheduled sample	-	Anytime	12 Lead, triplicate

* As per Section 8, a visit window +/- 3 days will be allowed

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 ms 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 6.5.1.1.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the Investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. 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.

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

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

All women of childbearing potential have to complete a serum pregnancy test (Serum ß-HCG) as indicated in Table 8-1 and Table 8-4. Pregnancy testing is not required for participants 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 8-4, during the following time points:

- Randomized treatment: screening, baseline (Week 1), Week 4 (if applicable), Week 8 (if applicable), and at each visit from Week 12 onwards until the EOT.

Urine pregnancy tests have to be performed at home every 4 weeks if serum pregnancy test is not performed. This also includes the timepoints at EOT and 30-days safety follow-up where required. Information for urine pregnancy test must be included in the source documentation at the study site at the next participant visit as unique source data, this information will not be captured in the CRF. If a test result indicates a pregnancy, the participant must contact the Investigator immediately to stop the study medication, including Investigator selected TKIs.

All pregnancies of study participants 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 treatment phase of the 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 medical documentation, confirming permanent sterilization, or if the 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.

If participants cannot visit the site to have serum pregnancy tests during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants 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 participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

8.4.4 Appropriateness of safety measurements

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

8.5 Additional assessments

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

- Patient Reported Outcomes
- Pharmacokinetics
- Biomarkers
- Resource Utilization

8.5.1 Clinical Outcome Assessments (COAs)

Patient Reported Outcomes (PRO)

A PRO is a measurement based on a report that comes from the study participant about the status of a participant's health condition without interpretation of the participant's report by anyone else. Symptoms or other unobservable concepts known only to the participant (e.g. pain severity or fatigue) can only be assessed using PRO measures. PRO measures can also assess the participant's perspective on functioning or activities that may also be observable by others.

For this study, the PRO measures listed below will be used to evaluate patient-reported measures of health-related quality-of-life (HRQoL), disease symptoms, functioning and treatment-related side effects.

- European organization for research and treatment of cancer - quality of life questionnaire (EORTC QLQ-C30)
- European organization for research and treatment of cancer CML module (EORTC QLQ-CML24)
- [redacted]

Collection of ePRO

All PRO data will be collected using an electronic patient reported outcomes (ePRO) device. The ePRO device will be programmed for collection as described in Table 8-1 and for at-home PRO data collection by the participant.

[redacted]

Provision of ePRO devices will occur at the Baseline/Week 1 visit. Site will ensure set up of ePRO device is completed according to ePRO vendor training. Participants will be trained by the site on how to use the ePRO device. The baseline PRO assessment at the Baseline/Week 1 visit will be completed at the site prior to all other study assessments and administration of study treatment. Participants will also be provided instructions to continue PRO assessments at home after baseline assessment at the Baseline/Week 1 visit. Study participants should be given sufficient space and time to complete all PRO questionnaires. In addition, sites will be provided further instructions to support participants if technical problems should arise with ePRO devices. PRO measures should be provided in the participant's language. In case any PRO questionnaire

is not available in a language the participant is familiar with, the PRO questionnaire must be omitted. If additional information or further instructions are needed, participants can receive additional technical support when they bring the ePRO device to the site during all scheduled visits.

In order to minimize missing data, compliance must be checked frequently and early on to identify any problems with PRO data reporting.

Participant's refusal to complete all or any part of a PRO measures should not be captured as a protocol deviation.

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

All questionnaires should be administered in the language most familiar to the participant 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 participant's perspective. This is to avoid potentially biasing participants or their responses to study questionnaires.

Study Investigators must follow reporting instructions outlined in Section 10 (AEs section) of the study protocol.

PRO assessments have to be performed from all participants during the treatment period and up to 12 weeks after EOT.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, COA data may be collected remotely (e.g. web portal, telephone interviews utilizing, a tablet provided by a third party vendor) depending on local regulations, technical capabilities, and following any applicable training in the required process.

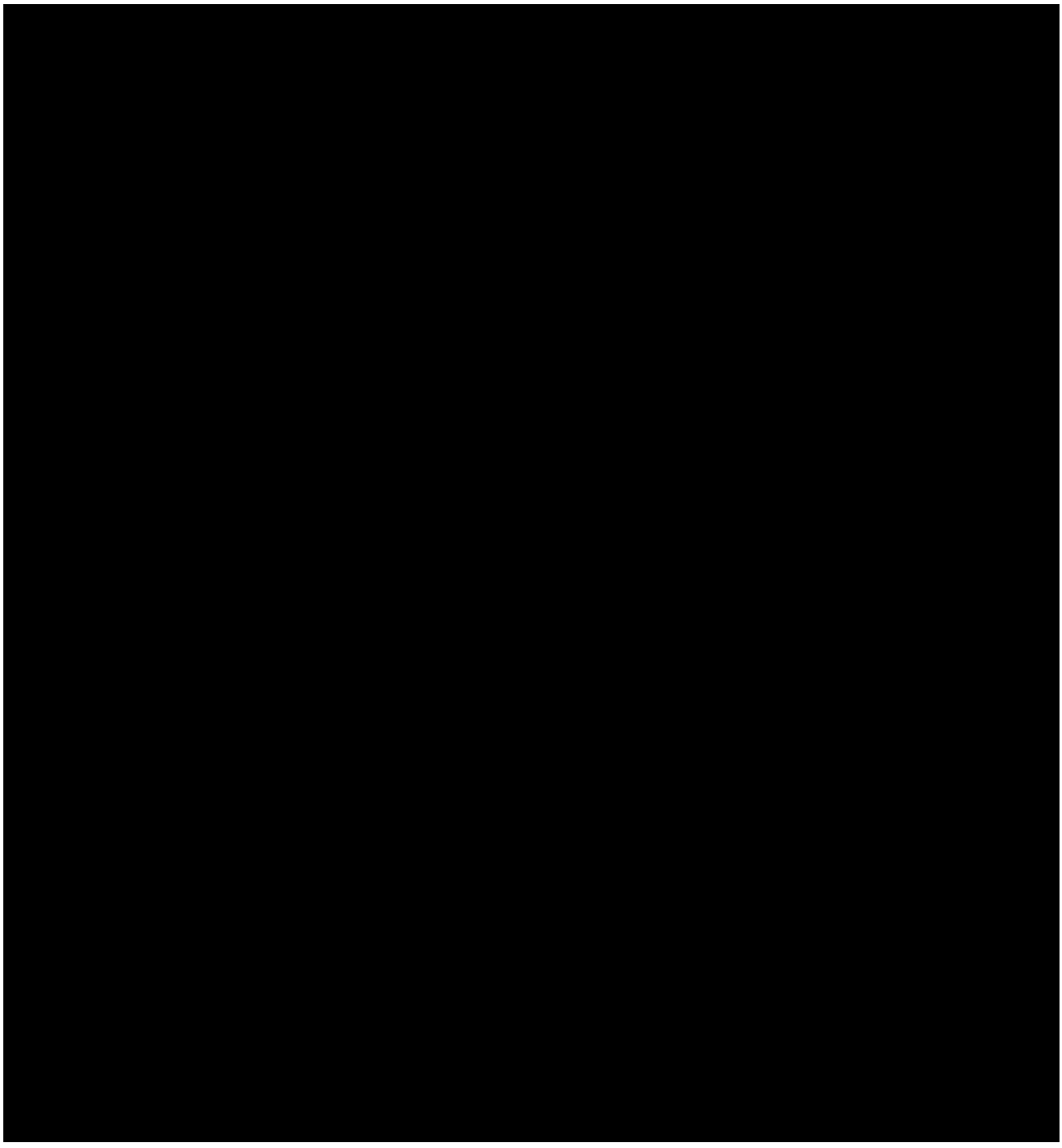
EORTC QLQ-C30 and QLQ-CML24

The European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC-QLQ-C30) and the CML specific module, the QLQ-CML24 will be used to evaluate patient-reported outcome measures of health-related quality-of-life, functioning, colorectal cancer symptoms, treatment-related side effects, and global health status (Anderson et al 1993).

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer participants and used frequently in cancer clinical trials. The questionnaire contains 30 items and is composed of both multi-item scales and single-item measures based on the participant's experience over the past week. These include five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/QoL scale (Anderson et al 1993). 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).

The EORTC QLQ-CML24 assesses specific concepts relevant to the experience of participants with CML. The QLQ-CML24 has 24 items which assess symptom burden, impact on daily life and on worry/mood, body image problems, and satisfaction with care and with social life based on the participant's experience over the past week (Efficace et al 2014). The QLQ-CML24 items are scored on a 4 point Likert scale, with a range of ‘not at all’ to ‘very much’.



[redacted]

Trial Feedback Questionnaire

This study is including an optional questionnaire, the "Trial Feedback Questionnaire" for trial participants to provide feedback on their clinical trial experience. Individual trial participant responses will not be reviewed by Investigators. Responses may be used by the sponsor to understand where improvements can be made in the clinical trial process. This questionnaire does not ask questions about the trial participant's disease, symptoms, treatment effect, or AEs, and, therefore is not considered as trial data and will be received electronically outside the clinical database.

8.5.2 Pharmacokinetics

8.5.2.1 Pharmacokinetic blood collection and handling

Blood samples for asciminib pharmacokinetics will be collected from all study participants allocated to the asciminib treatment arm. Blood samples for full PK profiles will be collected from approximately 25 participants Table 8-6. These participants will be identified sequentially at selected sites that are capable of serial PK sampling over 12 hours. Asciminib should be taken for at least 3 consecutive days without interruption or dose modification prior to full PK day on Week 2/Day 14. All other participants allocated to the asciminib treatment arm will undergo a sparse PK sampling scheme on Week 2/Day 14 (Sparse PK-group). Subsequent trough PK samples will be taken from all participants.

See Table 8-6 for the time-points of sample collection.

Refer to the [CABL001J12301 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

Plasma samples will be obtained to characterize the disposition of the study drug asciminib after oral administration.

Table 8-6 Pharmacokinetic blood collection log

Week	Study Day*	Scheduled Time Point	Dose Reference ID	PK Sample No	Blood Volume (mL)
2	14	0 h (Pre-dose)[a]	1	1	2
	14	1 h (± 10 min)[b]	1	2[b]	2
	14	2 h (± 10 min)	1	3	2
	14	3 h (± 15 min)	1	4	2
	14	4 h (± 15 min)	1	5	2
	14	6 h (± 30 min)[b]	1	6[b]	2
	14	8 h (± 60 min)[b]	1	7[b]	2
	14	12 h (± 60 min)[b]	1	8[b]	2
4	28	0 h (Pre-dose)[a]	3	9	2
12	84	0 h (Pre-dose)[a]	4	10	2
24	168	0 h (Pre-dose)[a]	5	11	2
48	336	0 h (Pre-dose)[a]	6	12	2
		Unscheduled		2001+	

[a] Pre-dose PK sample should be taken immediately prior to the next administration of asciminib.
[b] Full PK-group only.
* As per Section 8, a visit window +/- 3 days might be allowed

8.5.2.2 Analytical method

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

8.5.2.3 Pharmacogenomics

A 3 mL blood sample will be obtained [redacted] for pharmacogenomics analysis from all study participants allocated to the asciminib treatment arm as specified in Table 8-1. Genetic variant analysis of the [redacted] may be performed to investigate the effect of enzyme variations on asciminib exposure. Other genetic analyses on genes that are related to the asciminib metabolism and action or disease may also (or instead) be performed using these samples. In addition, this sample collection is required on the study. It is included in the main consent and is not optional, unless otherwise indicated by local IRB/EC or Health Authority requirements.

The sample collection must be captured on appropriate eCRF and requisition form(s).

8.5.3 Biomarkers

Exploratory biomarker analysis will be used for characterizing resistance mechanisms and association with kinetics of molecular response (duration of response, time to achieve MR). All biomarker analysis will be performed at a Novartis designated laboratory. Mutations in [redacted]

[redacted], and can be conducted at Investigator discretion if clinically indicated, to monitor for the emergence of BCR-ABL1 mutations, including T315I which requires participant discontinuation from the study. Exploratory analysis of [redacted] tests should be performed only if approval has been obtained from all relevant health authorities, as applicable.

Biomarkers assessments include:

- **Mutational analysis:** Mutations in [redacted] will be evaluated in association with response to treatment, allowing increased understanding of CML biology and help evaluate markers of resistance. Sequencing of [redacted] will assess both individual mutations as well as characterize the participant mutational profile. Samples will be sequenced to monitor the emergence of mutations during treatment and explore if early detection of mutations or dynamics of a mutation profile can predict participant response to treatment or disease progression. Sequencing analysis of BCR-ABL1 will also be used to monitor the emergence of detectable T315I mutation to support discontinuation criteria for the study.
- **Cellular Markers:** CML bone marrow is characterized by lymphoid lineage immunosuppression (Brück et al 2018). Immunophenotyping via flow cytometry to assess expression of cellular markers such as those [redacted] Assessments will be run in bone marrow if available, and on peripheral blood samples to determine if this less invasive sampling can be used to detect changes in the tumor microenvironment and immune cell populations in response to TKI.
- **Markers by Gene Expression Profiling:** Blood samples will be collected for gene expression profiling. There is evidence that differential expression of multiple genes and pathways, especially those associated with immune response may be predictive response to TKI treatment. This analysis will aim to identify a gene expression signature that is predictive of depth and/or duration of response to 1L asciminib and to explore prognostic or predictive expression biomarkers in CML.
- **Leukemia cells from whole blood (Drug sensitivity profiling)**: to explore sensitivity of participant leukemic cells to a panel of TKIs or other drugs relevant to CML treatment to guide identification of a potential second line treatment for participants who fail 1L asciminib.

Remaining plasma may also be used to look for markers that may be associated with treatment response or predict response to treatment.

[redacted]

8.5.3.1 Additional biomarker assessments

Optional additional biomarker studies

If the participant agrees, the biological samples collected in this trial (e.g. blood, plasma, serum) may be kept for up to 15 years to be used for additional studies related to the study drug(s) or cancer, including research to help develop ways to detect, monitor or treat cancer. A decision to perform such exploratory biomarker research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as assay availability

8.5.4 Resource utilization

The measures of HCRU to be collected include: hospitalization (H), emergency room (ER) visit, general practitioner (GP) visits, specialist (Sp) visit and urgent care (UC) visit. These measures will be used to derive the economic impact of treatment. Hospitalization visits will also record the number of days in ward and the type of ward (hospital unit) and the discharge status. At each RU collection, the reason for the visit (i.e. related to CML, AE or other reason) will be collected in order to quantify the impact of asciminib, Investigator selected TKI and imatinib within the stratum of Investigator selected TKI on healthcare resources. The RU assessment will be completed at each scheduled clinical trial visit; the RU will be completed by the Investigator however information with respect to the number of GP, UC, Sp or ER visits will be ascertained from the participant. All attempts to collect as much information from the participant as possible should be made in order to minimize selection bias.

9 Discontinuation and completion

The Investigator should discontinue study treatment for a given participant and/or withdraw the participant from the study if he/she believes that continuation would be detrimental to the participant's well-being, or that the participant is unable or unwilling to comply with protocol requirements.

A participant will be considered to have completed the study when the participant has completed the last visit planned in the protocol.

The Investigator and/or referring physician will recommend the appropriate follow-up medical care, if needed, for all participants who are prematurely withdrawn from the study.

9.1 Discontinuation from study treatment and from study

Completion of the study will be when the last participant has completed end of study follow up.

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and can be initiated by either the participant or the Investigator.

The Investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being. Participants who discontinue study treatment should undergo an EOT visit.

Discontinuation from study treatment is required under the following circumstances：

- Participant/guardian decision
- Use of prohibited treatment as per recommendations in the prohibited treatment Section 6.2.2
- Any situation in which continued study participation might result in a safety risk to the participant

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

- In the event of detection of T315I mutation at any time the participant **must** be discontinued from the study treatment.
- In the event of confirmed loss of MMR (in 2 consecutive tests, Section 12.7) at any time during the study treatment the participant **must** be discontinued from the study treatment.
- In the event of treatment failure (as per ELN criteria, Hochhaus et al 2020A) the participant must be discontinued from the study treatment.The following events will constitute ‘treatment failure’ based on ELN criteria (Hochhaus et al 2020A)
    - *BCR-ABL1 transcript level* > 10% IS at 3 months if confirmed within the next 1–3 months
    - *BCR-ABL1 transcript level* > 10% IS at 6 months
    - *BCR-ABL1 transcript level* > 1% IS at 12 months
    - *BCR-ABL1 transcript level* >1% IS after 12 months,
    - Detection of a BCR-ABL1 mutation which can potentially cause resistance to study treatment (asciminib or Investigator selected TKI) or high-risk additional chromosome abnormalities in Ph+ cells at any time after initiation of study treatment. [Per ELN treatment recommendations for known mutations resistant to specific TKI and high-risk additional chromosome abnormalities Hochhaus et al 2020A].

- In the event of disease progression, the participant must be discontinued from the study treatment.
  - The following events are considered disease progression
    - CML-related death (any death during treatment or follow-up if the principal cause of death is marked as "study indication" in the eCRF by the Investigator, or if the death occurred subsequent to documented progression to AP/BC and the cause of death is reported as "unknown" or not reported by the Investigator)
    - Accelerated phase (AP) as defined by any of the following:
      - ≥ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate
      - ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate
      - ≥ 20% basophils in the peripheral blood
    - Thrombocytopenia (< 100 x 10^9/L) that is unrelated to therapy
    - Blast crisis (BC) as defined by any of the following:
      - ≥ 30% blasts in peripheral blood or bone marrow aspirate
      - Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma).
      - Any value of AP or BC within the first 4 weeks of study treatment is not considered as progression to AP/BC unless the patient discontinues study treatment due to progression or unsatisfactory therapeutic effect within the first 8 weeks.
- In the event of a pregnancy during study, if a participant wants to pursue the pregnancy then participant **must** be discontinued from the study treatment. However, in the event of a spontaneous miscarriage or in the event of elective abortion, the participant is permitted to continue study treatment.

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

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

Participants who discontinue from study treatment agree to return for the EOT and follow-up visits indicated in the Assessment Schedule (refer to Section 8), every effort should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

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

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

- New / concomitant treatments

- AEs / SAEs

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

Participants who discontinue from study treatment for reasons other than death, lost to follow-up, or WoC/opposition to use data/biological samples, must continue to be followed up for disease progression and survival as outlined within the schedule of assessments (Table 8-1).

Participants who discontinue from study treatment for documented disease progression must continue to be followed up for survival as outlined within the schedule of assessments (Table 8-1).

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason. If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

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

WoC/opposition to use data/biological samples occurs when a participant:

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

and

- No longer wishes to receive study treatment

and

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

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

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

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

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

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

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

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

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 ICF.

For EU and Rest of World (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.

9.1.4 Lost to follow-up

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

9.1.5 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.

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

In taking the decision to terminate, Novartis will always consider the participant's welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant’s interests. The Investigator 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

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

Participants on the study will continue to receive the assigned treatment until End of Study, or until premature discontinuation due to treatment failure, disease progression or intolerance or due to Investigator or participant decision.

The End of Study will occur 5 years from the randomization date of the last participant first treatment in the study. Participants who discontinue study treatment prematurely due to any reason, will be followed up for survival until the End of Study.

The primary analysis cut-off date will be when all randomized participants have been treated for at least 48 weeks or discontinued from study treatment prior to Week 48. Subsequent to this analysis, the primary Clinical study report (CSR) will be developed. Following the cut-off date for the primary CSR, the study will remain open. Participants who are ongoing at the time of the primary analysis will continue to receive the assigned study treatment.

The key secondary analysis cut-off date will be when all randomized participants have been treated for at least 96 weeks or discontinued from study treatment prior to Week 96.

The final analysis cut-off date will be once the End of Study (i.e. 5 years from the randomization date of the last participant enrolled into the study) is reached.

The end of study treatment analysis will be conducted with a cut-off date 30 days after the end of study treatment period to ensure all available treatment data from all participants in the study is analyzed and summarized in a CSR.

After the end of the study treatment period the study treatment will be made available to participants who in the opinion of the Investigators are still deriving clinical benefit. This may be outside of this study through alternative options including, but not limited to participant rollover program.

Participants will be followed for survival and progression to AP/BC for up to 5 years from the randomization date of the last participant enrolled into the study. Information on subsequent treatments will also be collected. An updated analysis of OS and PFS will be performed at the end of the follow-up period in the final study CSR.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

During any pandemic such as COVID-19 that limits or prevents on-site study visits regular phone calls will occur for safety monitoring and discussion of the participant's health status until the participant can again visit the site. This telephone contact should preferably be done according to the study visit schedule or more frequently if needed. Please refer to Section 4.6 for further information.

10.1.1 Adverse events

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

The Investigator has the responsibility for managing the safety of individual participant and identifying AEs.

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

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

AEs must be recorded in the AEs 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 participant
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 AEs must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/permanently discontinued

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 AEs only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

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

AEs (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 not recovered/not resolved (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 AP or BC), should not be reported as a serious adverse event.

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

Information about adverse drug reactions for the investigational drug can be found in the [Asciminib Investigator Brochure].

Abnormal laboratory values or test results constitute AEs 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 participants with the underlying disease.

10.1.2 Serious adverse events

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

- Fatal
- Life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E15D Guidelines).

- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect

- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the participant's general condition
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- Is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room (ER) or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E15D Guidelines).

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

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

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

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after participant 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 event (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. Information about all SAEs is collected and recorded on the eSAE with paper backup Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

All follow-up information for the SAE including 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 should be reported separately as a new event.

The following SAE reporting timeframes apply:

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

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 unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported 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, participant 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 recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and (until transition to the EU CTR) reported to Safety only if associated with an SAE. Misuse or abuse (and upon transition to the 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.

10.1.6 Adverse events of special interest

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

AEs of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the [Asciminib Investigator's Brochure].

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

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

The following two categories of abnormalities/AEs 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 16-2 in Section 16.2 for complete definitions of liver laboratory triggers and liver events.

Once a participant is exposed to study treatment, 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 16-3 . 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 participant. 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 participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant 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 16-4 should be followed up by the Investigator or designated personnel at the trial site as summarized in Section 16.3.

10.2.3 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site Investigators participating in the study. The DMC will be constituted prior to the first participant randomization. The DMC will assess the safety data at defined intervals, beginning approximately 6 months after the first randomized participant has started treatment. Subsequent reviews of the safety data will be conducted approximately every 6 months. Additional meetings may be scheduled in the event of unexpected new data or events on an as needed basis (eg. if significant safety findings).

This includes but does not limit the role of the DMC to evaluate these data and to provide recommendations to the sponsor to continue, modify or stop the study early. The DMC will be in place at least until the conduct of the primary analysis. It is expected that the DMC will consist at a minimum of two physicians with appropriate disease area qualifications and one statistician. There will be a meeting with the DMC describing their roles and responsibilities and discussing potential data format and process issues prior to the finalization of DMC charter.

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

- No safety concerns, ethical to continue the study as planned

- Serious safety concerns precluding further study treatment, regardless of efficacy
- Recommendation to continue the study but proposing an amendment to the protocol (e.g., incorporate an additional safety assessments)

If the study is recommended to continue by the DMC, no details about the safety results will be revealed.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

10.2.4 Steering Committee

The Steering Committee (SC) will be established comprising Investigators participating in the trial, i.e. not being members of the DMC and Novartis representatives from the Clinical Trial Team.

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 EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

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

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

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 CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and

requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant 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. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/delegated CRO representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the Investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/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 15 years for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The Investigator must also keep the original ICF signed by the participant (a signed copy is given to the participant) for 15 years.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the

study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

The primary analysis cut-off date will be when all randomized participants have been treated for at least 48 weeks or discontinued from study treatment prior to Week 48.

The key secondary analysis cut-off date will be when all randomized participants have been treated for at least 96 weeks or discontinued from study treatment prior to Week 96.

The final analysis cut-off date will be once the End of Study (i.e. 5 years from the randomization date of the last participant enrolled into the study) is reached.

Participants who discontinue study treatment prematurely due to any reason (e.g.: treatment failure, disease progression or intolerance or due to Investigator or participant decision), will be followed up for survival and progression to AP/BC until the End of Study.

The data will be analyzed by Novartis and/or designated CRO. The data from all participating centers in this protocol will be combined, so that an adequate number of participants will be available for analyses. Study data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant PK and PD measurements. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum, and maximum as well as 25th and 75th percentiles will be presented.

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 participants to whom study treatment has been assigned by randomization.

The **IMA Full Analysis Set (FAS_{IMA})** comprises all from the FAS, whose pre-randomization selection of TKI is imatinib.

The **2G TKI Full Analysis Set (FAS_{2GTKI})** comprises all participants from the FAS, whose pre-randomization selection of TKI is a 2G TKI (nilotinib, dasatinib or bosutinib).

According to the intent to treat principle (reflecting the treatment policy estimands approach), participants in the FAS, FAS_{IMA}, FAS_{2GTKI} will be analyzed according to the treatment and stratum they have been assigned to during the randomization procedure.

The main primary and key secondary estimands that are based on the treatment policy and composite approach and will analyze participants according to the treatment and stratum they have been assigned to during the randomization procedure.

As described in Section 12.4.6 and Section 12.5.6; the supplemental estimands based on a combination of the treatment policy and hypothetical approach will also analyze participants according to the treatment and stratum they have been assigned to during the randomization

procedure. The difference will be that that data after occurrence of an intercurrent event will be imputed when the hypothetical approach is used.

The **Safety Set** comprises all participants who received at least one dose of any study treatment. Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the participant took at least one dose of that treatment, or the first treatment received if the randomized treatment was never received.

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

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

Other analysis sets

For duration of MMR, the **MMR Responder Set** will be used, which comprises the subset of participants from the FAS (or FAS_{IMA}or FAS_{2GTKI}) who achieve MMR at any time.

For duration of MR4.0, the **MR4.0 Responder Set** will be used, which comprises the subset of participants from the FAS (or FAS_{IMA} or FAS_{2GTKI}) who achieve MR4.0 at any time.

For duration of MR4.5, the **MR4.5 Responder Set** will be used, which comprises the subset of participants from the FAS (or FAS_{IMA} or FAS_{2GTKI}) who achieve MR4.5 at any time.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment arm for the FAS, FAS_{IMA} and FAS_{2GTKI}. Categorical data will be presented as frequencies and percentages. For continuous data, mean, SD, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

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

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, SD, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in days to asciminib and Investigator selected TKI (overall and by strata of pre-randomization selection of TKI), as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose

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

The number of participants with dose adjustments (reductions, interruption, or permanent discontinuation, allowed dose escalations for comparator arm drugs, dosing errors) and the reasons will be summarized by study drug components and by study treatment. All dosing data will be listed.

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

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

12.4 Analysis of the primary endpoint(s)/estimand(s)

12.4.1 Definition of primary endpoint(s)/estimand(s)

The study has **multiple primary objectives** which are to compare the efficacy of:

1. Asciminib versus Investigator selected TKI, in participants with newly diagnosed CML-CP, with respect to the proportion of participants that are in MMR at Week 48.
2. Asciminib versus that of Investigator selected TKI, within the stratum of participants with imatinib as their pre-randomization selection of TKI, in participants with newly diagnosed CML-CP, with respect to the proportion of participants that are in MMR at Week 48.

The study will be declared positive if either of the two primary objectives is met.

The **primary endpoint** of the study is defined as the binary outcome (Yes/No) of whether a participant meets the criteria for **MMR at Week 48.**

Only participants with MMR at Week 48 visit are considered responders. In other words, any participant who achieves MMR before Week 48 visit, but is no longer in MMR at Week 48 visit, will be considered as a non-responder for the primary analyses. A participant will be considered to have met the primary endpoint if the result of *BCR-ABL1* analysis from the Novartis designated laboratory by RQ-PCR meets the MMR criteria (*BCR-ABL1* IS levels $\leq$ 0.1%) at Week 48. Participants discontinuing the randomized treatment due to any reason (e.g. intolerance, death, etc., i.e. having performed an end of study treatment (EOT)) prior to Week 48, or participants meeting any treatment failure criteria prior to Week 48, will be counted as not being in MMR at Week 48.

The **primary estimands** corresponding to the multiple primary objectives will address the following clinical questions of interest:

1. What is the efficacy of asciminib (80 mg QD) compared to Investigator selected TKI; with respect to MMR at Week 48, without meeting any treatment failure criteria and without treatment discontinuation prior to Week 48, in participants with newly diagnosed CML-CP; *regardless of* dose interruption/ reduction/ allowed escalations, dosing errors, changes on

concomitant medication, intake of prohibited medication , and *regardless of* taking a TKI different from their pre-randomization selection of TKI in the comparator arm.

2. What is the efficacy of asciminib (80 mg QD) compared to Investigator selected TKI within the stratum of participants that have imatinib as their pre-randomization selection of TKI; with respect to MMR at Week 48, without meeting any treatment failure criteria and without treatment discontinuation prior to Week 48, in participants with newly diagnosed CML-CP; *regardless of* dose interruption/ reduction/ allowed escalations, dosing errors, changes on concomitant medication, intake of prohibited medication , and *regardless of* taking a TKI different from their pre-randomization selection of TKI in the comparator arm.

The primary estimands strategy (based on the treatment policy and composite approaches), their attributes, handling of intercurrent events are described in detail in Section 2.1.

12.4.2 Statistical model, hypothesis, and method of analysis

The hypotheses corresponding to the multiple primary objectives are as follows:

- **H1**
  - **$H1_0$**: the proportion of participants that achieve MMR at Week 48 in the asciminib arm is less than or equal to the proportion of participants that achieve MMR at Week 48 in the Investigator selected TKI arm.
  - **$H1_a$**: the proportion of participants that achieve MMR at Week 48 in the asciminib arm is higher than the proportion of participants that achieve MMR at Week 48 in the Investigator selected TKI arm.
- **H2**
  - **$H2_0$**: within the stratum of participants that have imatinib as their pre-randomization selection of TKI, the proportion of participants that achieve MMR at Week 48 in the asciminib arm is less than or equal to the proportion of participants that achieve MMR at Week 48 in the Investigator selected TKI arm.
  - **$H2_a$**: within the stratum of participants that have imatinib as their pre-randomization selection of TKI, the proportion of participants that achieve MMR at Week 48 in the asciminib arm is higher than the proportion of participants that achieve MMR at Week 48 in the Investigator selected TKI arm.

The analyses of the primary endpoints will be performed using the FAS for the comparison of asciminib versus the Investigator selected TKI; or the FAS_{IMA} for the comparison of asciminib versus Investigator selected TKI, within the stratum of participants that have imatinib as their pre-randomization selection of TKI. Following the intent to treat principle (which is reflective of the primary estimands approach based on the treatment policy and composite strategy), participants will be analyzed according to the treatment arm and stratum they were assigned to at randomization.

The primary comparisons of proportions of participants that are in MMR at Week 48 for:

1. Asciminib versus Investigator selected TKI, will be performed using a one-sided stratified Mantel-Haenszel test, stratified by both randomization stratification factors (ELTS risk score and pre-randomization selection of TKI (imatinib versus 2G TKI)).
2. Asciminib versus Investigator selected TKI, within the stratum of participants that have imatinib as their pre-randomization selection of TKI, will be performed using a one-sided

stratified Mantel-Haenszel test, stratified by only the ELTS risk score randomization stratification factor.

The family wise error rate will be controlled at 2.5% level via the graphical gatekeeping procedure which is described Section 12.7

The study will be considered positive if the null hypothesis for either of the two primary objectives can be rejected.

The response rates and corresponding two sided 95% CIs for the primary endpoints, based on the Pearson-Clopper method will be presented by the:

1. Treatment arms (asciminib or Investigator selected TKI).
2. Treatment arms (asciminib or Investigator selected TKI) within the stratum of participants that have imatinib as their pre-randomization selection of TKI.

The stratified Mantel-Haenszel estimate of the common risk difference (for the proportion of participants that are in MMR at Week 48) between:

1. Asciminib and Investigator selected TKI arm, stratified by randomization stratification factors of the ELTS risk score and pre-randomization selection of TKI (imatinib versus 2G TKI),
2. Asciminib and Investigator selected TKI arm, within the stratum of participants that have imatinib as their pre-randomization selection of TKI, stratified by only randomization stratification factor of the ELTS risk score, will be provided, together with the corresponding two sided 95% confidence interval.

All the confidence intervals (CIs) reported will be nominal 95% CIs which are unadjusted for multiple testing and will be presented for descriptive purposes.

12.4.3 Handling of remaining intercurrent events of primary estimand

The handling of intercurrent events for the primary estimands are described in detail in Section 2.1. No other intercurrent events are foreseen.

12.4.4 Handling of missing values not related to intercurrent event

Only participants with MMR at Week 48 visit are considered responders for the primary analyses. In other words, any participant who achieves MMR before Week 48 visit, but is no longer in MMR at Week 48 visit, will be considered as a non-responder (as is the case for participants who never achieve MMR at or before Week 48 visit).

Handling of missing values/censoring/discontinuations:

- Participants discontinuing the randomized treatment due to any reason (e.g. intolerance, death, etc., i.e. having performed an EOT) prior to Week 48, or participants meeting any treatment failure criteria prior to Week 48, will be counted as not being in MMR at Week 48.
- Participants with missing PCR evaluation at Week 48 visit, will be imputed as MMR, if they have non-missing PCR evaluations at Week 36 and Week 60 visits, and both of these meet the MMR criteria (*BCR-ABL1* IS levels $\leq 0.1\%$).

If PCR evaluations are performed at unscheduled visits, these will be mapped to non-overlapping analysis time windows and will be taken into consideration. The analysis time windows will be described in detail in the SAP.

12.4.5 Sensitivity analyses for primary endpoint/estimand

Sensitivity analysis for the primary end-points may be performed and will be described in the statistical analyses plan.

12.4.6 Supplementary analysis

Supplemental estimands for the end-point of MMR at Week 48 based on the treatment policy, composite and hypothetical strategies as described below will be produced. The supplemental estimand differs from the primary estimand in the way in which it handles the intercurrent event of *taking a TKI different from the pre-randomization selection TKI in the comparator arm*. These estimands will be presented for descriptive purposes.

Additional **supplemental clinical questions of interest** are:

1. What is the efficacy of asciminib (80 mg QD) compared to Investigator selected TKI, with respect to MMR at Week 48, without meeting any treatment failure criteria prior to Week 48 or discontinuing treatment due to any reason prior to Week 48, in participants with newly diagnosed CML-CP; *regardless of* dose interruption/reduction/allowed escalations, dosing errors, changes on concomitant medication, intake of prohibited medication; *if participants did not take a TKI different from their pre-randomization selection TKI in the comparator arm*.
2. What is the efficacy of asciminib (80 mg QD) *compared to imatinib as the Investigator selected TKI*, with respect to MMR at Week 48, without meeting any treatment failure criteria prior to Week 48 or discontinuing treatment due to any reason prior to Week 48, in participants with newly diagnosed CML-CP, within the stratum of participant that have imatinib as their pre-randomization selection of TKI; *regardless of* dose interruption/reduction/allowed escalations, dosing errors, changes on concomitant medication, intake of prohibited medication; *if participants did not take a TKI different from their pre-randomization selection of imatinib the comparator arm*.

The supplemental estimands for the end-point of MMR at Week 48 are described by the following attributes:

Population: Newly diagnosed adult Ph+ CML-CP participants, as defined by Inclusion/Exclusion criteria; (1) overall and (2) within the stratum with imatinib as their pre-randomization selection of TKI.

Endpoint: the composite end-point of MMR at Week 48 visit, without meeting any treatment failure criteria prior to Week 48 and without discontinuing treatment due to any reason prior to Week 48. A participant will be counted as being in MMR at Week 48 visit if he/she meets the MMR criterion (BCR-ABL IS $\leq$ 0.1%) at Week 48 visit, unless the participant met any treatment failure criteria prior to Week 48 or discontinued the randomized treatment due to any reason prior to Week 48.

Intercurrent events (IE):

- **Set 1 (IE1)**

  - Taking a TKI different from the pre-randomization selection of TKI (i.e. the *first dose of TKI is different from pre-randomization selection of TKI)*: *hypothetical strategy (impute)*
- **Set 2 (IE2)**
  - Change of study treatment per protocol (dose reduction/interruption/allowed dose escalations): *treatment policy strategy (ignore)*
  - Dosing errors (e.g.: missed dose): *treatment policy strategy (ignore)*
  - Deviation in any intake of concomitant medications: *treatment policy strategy (ignore)*
  - Intake of prohibited medications : *treatment policy strategy (ignore)*
- **Set 3 (IE3)**
  - Meeting any treatment failure criteria prior to Week 48 or treatment discontinuation due to any reason prior to Week 48: *composite (consider this non-response).*
- *If a participant only experience IE2s' these will be handled as per treatment policy approach and ignored. If a participant experiences IE1, these are handled as per the hypothetical policy approach and the data for MMR after the occurrence of the IE1 will be imputed (by hypothetical values from a model based on participants from the comparator arm that take a TKI at randomization that is the same as their pre-randomization selection of TKI).*
- *The IE1 if it occurs, will always occur before any other IE2 events. If a participant experiences both IE1 and IE2s, the hypothetical strategy will take precedence over the treatment policy strategy and all the data for MMR after the occurrence of IE1 will be imputed.*
- *Further details on the imputation model will be specified in the SAP.*

Handling of remaining intercurrent events: no other IE foreseen

Treatment:

1. The randomized treatment arm (the investigational treatment asciminib 80 mg QD, or *the Investigator selected TKI*); with or without dose modifications (reduction/interruption/allowed escalation), dosing errors, deviation in any intake of concomitant medications, intake of prohibited medication, *if taking a TKI different from the pre-randomization selection of TKI in the comparator arm would not be possible.*
2. The randomized treatment arm (the investigational treatment asciminib 80 mg QD, or *imatinib as the Investigator selected TKI*), *within the stratum of participants that have imatinib as their pre-randomization selection of TKI*; with or without dose modifications (reduction/interruption/allowed escalation), dosing errors, deviation in any intake of concomitant medications, intake of prohibited medication, *if taking a TKI different from the pre-randomization selection of imatinib in the comparator arm would not be possible.*

The summary measure:

1. stratum adjusted difference in the proportion of participants that are in MMR at Week 48 and corresponding 95% CI, between the two treatments (asciminib versus Investigator selected TKI).

2. stratum adjusted difference in the proportion of participants that are in MMR at Week 48 and corresponding 95% CI, between the two treatments (asciminib versus imatinib), within the stratum of participants that have imatinib as their pre-randomization selection of TKI.

12.4.7 Supportive analyses

If either of the primary objectives is met, subgroup analyses to assess the homogeneity of the treatment effect (for MMR at Week 48) across subgroups (eg: based on demographic and baseline disease characteristics, ELTS prognostic categories, geographic regions etc.) will be performed.

Details will be provided in the SAP.

12.5 Analysis of the key secondary endpoint(s)/estimand(s)

12.5.1 Definition of key secondary endpoint(s)/estimand(s)

The study has **multiple key secondary objectives** which are:

1. To compare the efficacy of asciminib versus Investigator selected TKI, in patients with newly diagnosed CML-CP, with respect to the proportion of participants that are in MMR at Week 96.
2. To compare the efficacy of asciminib versus that of Investigator selected TKI, within the stratum of participants with imatinib as their pre-randomization selection of TKI, in patients with newly diagnosed CML-CP, with respect to the proportion of participants that are in MMR at Week 96.

The two key secondary objectives will be formally tested only if either (i) $H1_0$ and $H2_0$ are both rejected or (ii) if only $H2_0$ is rejected, as described in the testing strategy in Section 12.7.

The **key secondary endpoint** is defined as the binary outcome (Yes/No) of whether a participant meets the criteria for **MMR at Week 96.**

Only participants with MMR at Week 96 visit are considered responders. In other words, any participant who achieves MMR before Week 96 visit, but is no longer in MMR at Week 96 visit, will be considered as a non-responder for the key secondary analyses. A participant will be considered to have met the key secondary endpoint if the result of *BCR-ABL1* analysis from the Novartis designated laboratory by RQ-PCR meets the MMR criteria (BCR-ABL1 IS levels $\leq$ 0.1%) at Week 96. Participants discontinuing the randomized treatment due to any reason (e.g. intolerance, death, etc., i.e. having performed an end of study treatment (EOT)) prior to Week 96, or participants meeting any treatment failure criteria prior to Week 96, will be counted as not having being in MMR at Week 96.

The **key secondary estimands** corresponding to the multiple key secondary objectives will address the following clinical questions of interest:

1. What is the efficacy of asciminib (80mg QD) compared to Investigator selected TKI; with respect to MMR at Week 96, without meeting any treatment failure criteria and without treatment discontinuation prior to Week 96, in patients with newly diagnosed CML-CP; *regardless of* dose interruption/ reduction/ allowed escalations, dosing errors, changes on

concomitant medication, intake of prohibited medication , and *regardless of* taking a TKI different from their pre-randomization selection of TKI in the comparator arm.

2. What is the efficacy of asciminib (80mg QD) compared to Investigator selected TKI within the stratum of participants that have imatinib as their pre-randomization selection of TKI; with respect to MMR at Week 96, without meeting any treatment failure criteria and without treatment discontinuation prior to Week 96, in patients with newly diagnosed CML-CP; *regardless of* dose interruption/ reduction/ allowed escalations, dosing errors, changes on concomitant medication, intake of prohibited medication , and *regardless of* taking a TKI different from their pre-randomization selection of TKI in the comparator arm.

The key secondary estimands strategy (based on the treatment policy and composite approaches), their attributes, handling of intercurrent events are described in detail in Section 2.2.1.

12.5.2 Statistical model, hypothesis and methods of analysis

The hypotheses corresponding to the **multiple key secondary objectives** are as follows:

- **H3**
  - **$H3_0$**: the proportion of participants that are in MMR at Week 96 in the asciminib arm is less than or equal to the proportion of participants that achieve MMR at Week 96 in the Investigator selected TKI arm.
  - **$H3_a$**: the proportion of participants that achieve MMR at Week 96 in the asciminib arm is higher than the proportion of participants that are in MMR at Week 96 in the Investigator selected TKI arm.
- **H4**
  - **$H4_0$**: within the stratum of participants that have imatinib as their pre-randomization selection of TKI, the proportion of participants that are in MMR at Week 96 in the asciminib arm is less than or equal to the proportion of participants that achieve MMR at Week 96 in the Investigator selected TKI arm.
  - **$H4_a$**: within the stratum of participants that have imatinib as their pre-randomization selection of TKI, the proportion of participants that achieve MMR at Week 96 in the asciminib arm is higher than the proportion of participants that are in MMR at Week 96 in the Investigator selected TKI arm.

The analyses of the key secondary endpoints will be performed using the FAS for the comparison of asciminib versus the Investigator selected TKI; or the FAS_{IMA} for the comparison of asciminib versus Investigator selected TKI, within the stratum of participants that have imatinib as their pre-randomization selection of TKI. Following the intent to treat principle (which is reflective of the key secondary estimands approach based on the treatment policy and composite strategy), participants will be analyzed according to the treatment arm and stratum they were assigned to at randomization.

The key secondary comparisons of the proportions of participants are in MMR at Week 96 for:

1. Asciminib versus Investigator selected TKI, will be performed using a one-sided stratified Mantel-Haenszel test, stratified by both randomization stratification factors (ELTS risk score and pre-randomization selection of TKI (imatinib versus 2G TKI)).

2. Asciminib versus Investigator selected TKI, within the stratum of participants that have imatinib as their pre-randomization selection of TKI, will be performed using a one-sided stratified Mantel-Haenszel test, stratified by only the ELTS risk score randomization stratification factor.

The family wise error rate will be controlled at 2.5% level via the graphical gatekeeping procedure which is described Section 12.7.

The response rates and corresponding two sided 95% CIs for the key secondary endpoints, based on the Pearson-Clopper method will be presented by the:

1. Treatment arms (asciminib or Investigator selected TKI).
2. Treatment arms (asciminib or Investigator selected TKI) within the stratum of participants that have imatinib as their pre-randomization selection of TKI.

The stratified Mantel-Haenszel estimate of the common risk difference (in the proportion of participants that are in MMR at Week 96) between:

1. Asciminib and Investigator selected TKI arm, stratified by randomization stratification factors of the ELTS risk score and pre-randomization selection of TKI (imatinib versus 2G TKI),
2. Asciminib and Investigator selected TKI arm, within the stratum of participants that have imatinib as their pre-randomization selection of TKI, stratified by only randomization stratification factor of the ELTS risk score, will be provided, together with the corresponding two sided 95% CI.

All the confidence intervals (CIs) reported will be nominal 95% CIs which are unadjusted for multiple testing and will be presented for descriptive purposes.

12.5.3 Handling of remaining intercurrent events of key secondary estimand

The handling of intercurrent events for the key secondary estimands are described in detail in Section 2.2.1. No further intercurrent events are foreseen.

12.5.4 Handling of missing values not related to intercurrent event

Only participants with MMR at Week 96 visit are considered responders for the key Secondary analyses. In other words, any participant who achieves MMR before Week 96 visit, but is no longer in MMR at Week 96 visit, will be considered as a non-responder.

Handling of missing values/censoring/discontinuations:

- Participants discontinuing the randomized treatment due to any reason (e.g. intolerance, death, etc., i.e. having performed an EOT) prior to Week 96, or participants meeting any treatment failure criteria prior to Week 96, will be counted as not being in MMR at Week 96.
- Participants with missing PCR evaluation at Week 96, will be imputed as MMR, if they have non-missing PCR evaluations at Week 84 and Week 108, and both of these meet the MMR criteria (*BCR-ABL1* IS levels $\leq 0.1\%$).

  If PCR evaluations are performed at unscheduled visits, these will be mapped to non-overlapping analysis time windows and will be taken into consideration. The analysis time windows will be described in detail in the SAP.

12.5.5 Sensitivity analysis for key secondary endpoint/estimand

Sensitivity analyses for the key secondary end-points may be performed and will be described in the SAP.

12.5.6 Supplementary analysis

Supplemental estimands for the end-point of MMR at Week 96 based on the treatment policy, composite and hypothetical strategies as described below will be produced. The supplemental estimand differs from the key secondary estimand in the way in which it handles the intercurrent event of *taking a TKI different from the pre-randomization selection TKI in the comparator arm.* These estimands will be presented for descriptive purposes.

Additional **supplemental clinical questions of interest** are:

1. What is the efficacy of asciminib (80 mg QD) compared to Investigator selected TKI, with respect to MMR at Week 96, without meeting any treatment failure criteria prior to Week 96 or discontinuing treatment due to any reason prior to Week 96, in patients with newly diagnosed CML-CP; *regardless of* dose interruption/reduction/allowed escalations, dosing errors, changes on concomitant medication, intake of prohibited medication; *if participants did not take a TKI different from their pre-randomization selection TKI in the comparator arm*.
2. What is the efficacy of asciminib (80 mg QD) *compared to imatinib as the Investigator selected TKI*, with respect to MMR at Week 96, without meeting any treatment failure criteria prior to Week 96 or discontinuing treatment due to any reason prior to Week 96, in patients with newly diagnosed CML-CP, within the stratum of participant that have imatinib as their pre-randomization selection of TKI; *regardless of* dose interruption/reduction/allowed escalations, dosing errors, changes on concomitant medication, intake of prohibited medication; *if participants did not take a TKI different from their pre-randomization selection of imatinib the comparator arm*.

The supplemental estimands for the end-point of MMR at Week 96 are described by the following **attributes**:

Population: Newly diagnosed adult Ph+ CML-CP participants, as defined by Inclusion/Exclusion criteria; (1) overall and (2) within the stratum with imatinib as their pre-randomization selection of TKI.

Endpoint: the composite end-point of MMR at Week 96 visit, without meeting any treatment failure criteria prior to Week 96 and without discontinuing treatment due to any reason prior to Week 96. A participant will be counted as being in MMR at Week 96 visit if he/she meets the MMR criterion (BCR-ABL IS $\leq$ 0.1%) at Week 96 visit, unless the participant met any treatment failure criteria prior to Week 96 or discontinued the randomized treatment due to any reason prior to Week 96.

Intercurrent events (IE):

- **Set 1 (IE1)**
  - Taking a TKI different from the pre-randomization selection of TKI (i.e. the first dose of TKI is different from pre-randomization selection of TKI): *hypothetical strategy (impute)*

- **Set 2 (IE2)**
  - Change of study treatment per protocol (dose reduction/interruption/allowed dose escalations): *treatment policy strategy (ignore)*
  - Dosing errors (e.g.: missed dose): *treatment policy strategy (ignore)*
  - Deviation in any intake of concomitant medications: *treatment policy strategy (ignore)*
  - Intake of prohibited medications : *treatment policy strategy (ignore)*
- **Set 3 (IE3)**
  - Meeting any treatment failure criteria prior to Week 96 or treatment discontinuation due to any reason prior to Week 96: *composite (consider this non-response).*
- *If a participant only experience IE2s' these will be handled as per treatment policy approach and ignored. If a participant experiences IE1, these are handled as per the hypothetical policy approach and the data for MMR after the occurrence of the IE1 will be imputed (by hypothetical values from a model based on participants from the comparator arm that take a TKI at randomization that is the same as their pre-randomization selection of TKI).*
- *The IE1 if it occurs, will always occur before any other IE2 events. If a participant experiences both IE1 and IE2s, the hypothetical strategy will take precedence over the treatment policy strategy and all the data for MMR after the occurrence of IE1 will be imputed.*
- *Further details on the imputation model will be specified in the SAP.*

Handling of remaining intercurrent events: no other IE foreseen

Treatment:

1. The randomized treatment (the investigational treatment asciminib 80 mg QD, or *the Investigator selected TKI*); with or without dose modifications (reduction/interruption/allowed escalation), dosing errors, deviation in any intake of concomitant medications, intake of prohibited medication, *if taking a TKI different from the pre-randomization selection of TKI in the comparator arm would not be possible.*
2. The randomized treatment (the investigational treatment asciminib 80 mg QD, or *imatinib as the Investigator selected TKI*), *within the stratum of participants that have imatinib as their pre-randomization selection of TKI*; with or without dose modifications (reduction/interruption/allowed escalation), dosing errors, deviation in any intake of concomitant medications, intake of prohibited medication, *if taking a TKI different from the pre-randomization selection of imatinib in the comparator arm would not be possible.*

The summary measure:

1. stratum adjusted difference in the proportion of participants that are in MMR at Week 96 and corresponding 95% CI, between the two treatments (asciminib versus Investigator selected TKI).
2. stratum adjusted difference in the proportion of participants that are in MMR at Week 96 and corresponding 95% CI, between the two treatments (asciminib versus imatinib), within the stratum of participants that have imatinib as their pre-randomization selection of TKI.

12.5.7 Supportive analyses

If either of the key secondary objectives is met, subgroup analyses to assess the homogeneity of the treatment effect (for MMR at Week 96) across subgroups (eg: based on demographic and baseline disease characteristics, ELTS prognostic categories, geographic regions etc.) will be performed.

Details will be presented in the SAP.

12.6 Analysis of the secondary safety end-point of Time to Discontinuation of Study Treatment due to AE (TTDAE)

The study has **one secondary safety objective**, which will be formally tested at the Week 96 analysis timepoint.

The secondary safety objective is to compare the safety/tolerability of asciminib versus 2G TKIs, in patients with newly diagnosed CML-CP, with respect to the time to discontinuation of study treatment due to AE (TTDAE).

This secondary safety objective will be formally tested only if both key secondary objectives are met. i.e if $H4_0$ and $H3_0$ are both rejected, as described in the testing strategy in Section 12.7.

The **secondary endpoint** of TTDAE is defined as the time from the date of first dose of study treatment to the date of discontinuation of study treatment due to AE. For participants ongoing without study treatment discontinuation, on or prior to the analysis cut-off date, the time will be censored at the at the analysis cut-off date.

The secondary safety objective estimand strategy, its attributes, handling of intercurrent events will be described in detail in the SAP.

Statistical model, hypothesis and methods of analysis

The hypotheses corresponding to the **secondary safety objective for TTDAE** is as follows:

H5:

- **$H5_0$**: the cause-specific hazard for the event of discontinuation of study treatment due to AE, for participants that received asciminib is greater than or equal to that for participants that received a 2G TKI.
- **$H5_a$**: the cause-specific hazard for the event of discontinuation of study treatment due to AE, for participants that received asciminib is less than that for participants that received a 2G TKI.

Competing risk analysis of TTDAE will be performed using the safety set. The 'discontinuation of study treatment due to AE' will be considered as the event of interest, while discontinuation from study treatment due to other reasons that are not due AEs will be considered as competing risk events.

The estimated cumulative incidence rates and 95% CIs at specified scheduled visits will be presented for each treatment group (asciminib and the 2G TKI). The cumulative incidence curve will be plotted.

The comparison of TTDAE for asciminib versus the 2G TKIs will be implemented via the log-rank test of the cause-specific hazard for the event of interest.

The family wise error rate will be controlled at 2.5% level via the graphical gatekeeping procedure which is described in Section 12.7.

Supplementary analysis

The competing risk analysis for the cause-specific hazard for the competing risk events will also be performed; as will the analysis via the sub-distribution hazard approach. These supplementary analyses will be provided for information purpose only.

12.7 Testing Strategy and Type-I Error Control for the multiple primary and key secondary objectives; and for the secondary safety objective

The overall family wise type-I error (1-sided level of significance $\alpha = 2.5\%$) control for testing the multiple primary and key secondary hypotheses, is achieved through the graphical gate-keeping multiple testing procedure (Bretz et al 2009, Bretz et al 2011) as shown in in Figure 12-1 .

The multiple hypotheses are grouped into three families; those associated with the primary objectives (H1, H2), those associated with the key secondary objectives (H3, H4) and those associated with the secondary safety objective (H5).

The **primary end-point (MMR at Week 48) family of hypotheses F_1**, are:

- **$H1_0$**: the proportion of participants that achieve MMR at Week 48 in the asciminib arm is less than or equal to the proportion of participants that achieve MMR at Week 48 in the Investigator selected TKI arm.

versus

- **$H1_a$**: the proportion of participants that achieve MMR at Week 48 in the asciminib arm is greater than the proportion of participants that achieve MMR at Week 48 in the Investigator selected TKI arm.

and

- **$H2_0$**: within the stratum of participants that have imatinib as their pre-randomization selection of TKI, the proportion of participants that achieve MMR at Week 48 in the asciminib arm is less than or equal to the proportion of participants that achieve MMR at Week 48 in the Investigator selected TKI arm.

versus

- **$H2_a$**: within the stratum of participants that have imatinib as their pre-randomization selection of TKI, the proportion of participants that achieve MMR at Week 48 in the asciminib arm is greater than the proportion of participants that achieve MMR at Week 48 in the Investigator selected TKI arm.

The **key secondary end-point (MMR at Week 96) family of hypotheses F_2**, are:

- **$H3_0$**: the proportion of participants that achieve MMR at Week 96 in the asciminib arm is less than or equal to the proportion of participants that achieve MMR at Week 96 in the Investigator selected TKI arm.

versus

- **$H3_a$**: the proportion of participants that achieve MMR at Week 96 in the asciminib arm is greater than the proportion of participants that achieve MMR at Week 96 in the Investigator selected TKI arm.

and

- **$H4_0$**: within the stratum of participants that have imatinib as their pre-randomization selection of TKI, the proportion of participants that achieve MMR at Week 96 in the asciminib arm is less than or equal to the proportion of participants that achieve MMR at Week 96 in the Investigator selected TKI arm.

versus

- **$H4_a$**: within the stratum of participants that have imatinib as their pre-randomization selection of TKI, the proportion of participants that achieve MMR at Week 96 in the asciminib arm is greater than the proportion of participants that achieve MMR at Week 96 in the Investigator selected TKI arm.

The secondary safety end-point (TTDAE) family of hypotheses F3 is:

- H50: the cause-specific hazard for the event of discontinuation of study treatment due to AE, for participants that received asciminib is greater than or equal to that for participants that received a 2G TKI.

versus

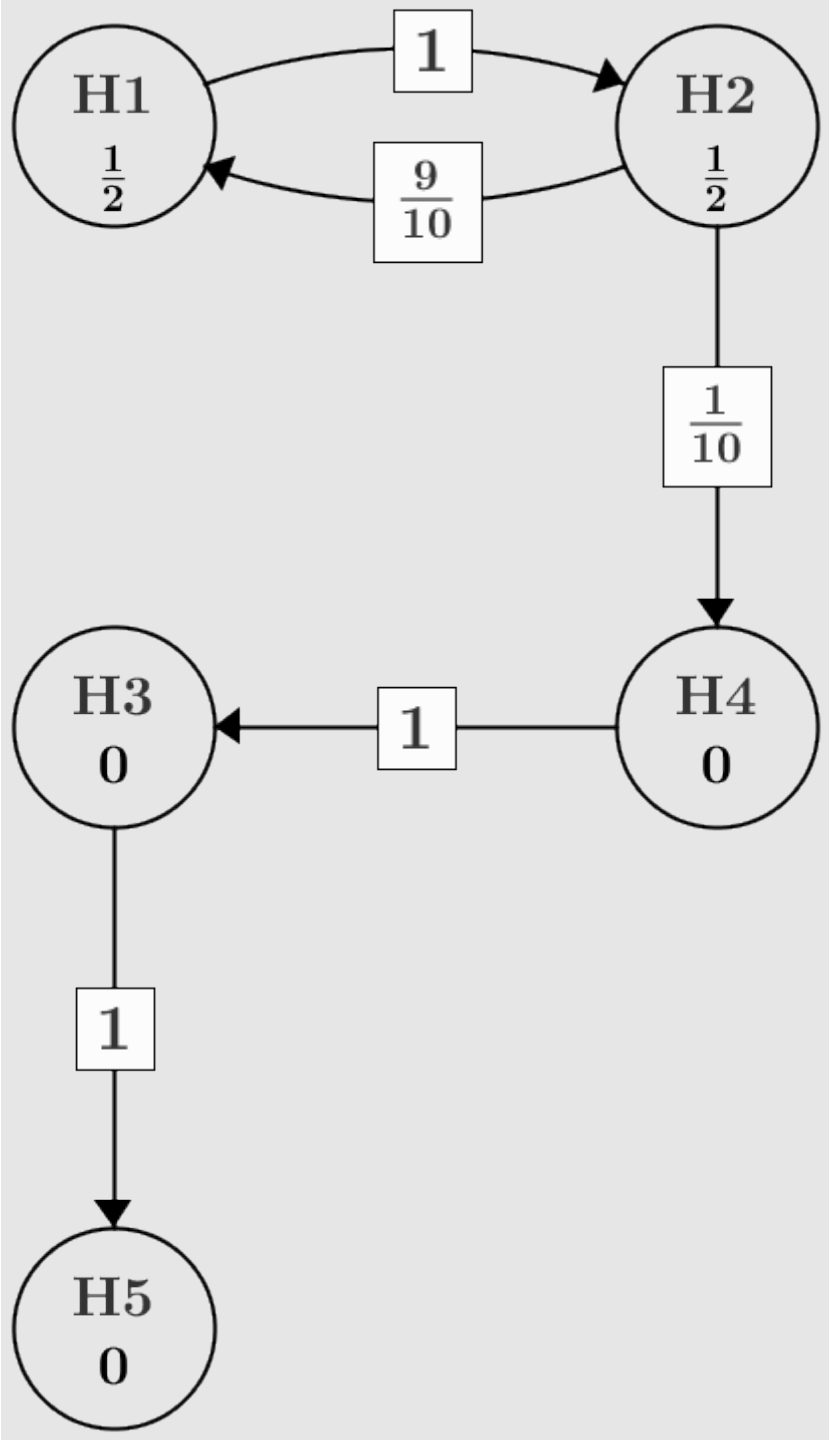
- H5a: the cause-specific hazard for the event of discontinuation of study treatment due to AE, for participants that received asciminib is less than that for participants that received a 2G TKI.

The analyses cut-off date for testing H1 and H2 will be when all randomized participants have been treated for at least 48 weeks or discontinued from study treatment prior to Week 48.

The analyses cut-off date for testing H3 and H4 will be when all randomized participants have been treated for at least 96 weeks or discontinued from study treatment prior to Week 96.

The analyses cut-off date for testing H5 will be when all randomized participants have been treated for at least 96 weeks or discontinued from study treatment prior to Week 96.

Figure 12-1 Testing hierarchy (graphical gatekeeping procedure)



The primary and key secondary hypotheses, H1, H2, H3, H4 and H54, are represented by nodes in the graph; with the associated local weights (i.e. proportion of total alpha (1- sided α=2.5%) available to test that hypothesis). A directed edge from one hypothesis Hi, to another one Hj, means that when the null hypothesis associated with Hi is rejected, its local weight (i.e. the local alpha) can be transferred to Hj. The weight associated with that edge quantifies the proportion of the local alpha of Hi that is transferred to Hj.

The three families of hypotheses will be tested in the following manner. The null hypotheses in family F_1 (H1 and H2) will be examined first and tested using the weighted parametric tests (Bretz et al 2011); the hypotheses in family F_2 (H3 and H4) will be tested using the fixed-sequence testing approach; followed by the hypothesis in family F_3 (H5) will be tested using the fixed-sequence testing approach. The null hypotheses in key secondary end-point family F_2 can be tested if the null hypothesis for H2 (or for both H1 and H2) in the primary end-point family F_1 is rejected. The null hypotheses in secondary safety end-point family F_3 can be tested if the null hypothesis for both H4 and H3 in the key secondary end-point family F_2 are rejected.

The weighted parametric test for the primary end-points family also exploits the correlation between the test statistics for H1 and H2, which arises because the population for testing H2 is a stratum from within the population for testing H1. Let T1 and T2 be the test statistics for H1 and H2 respectively, then the correlation is computed as shown in the figure below:

where n_1, n_1* are the number of participants in asciminib arm, overall and within the stratum of participants with imatinib as their pre-randomization selection of TKI; and n_0, n_0* are the number of participants in Investigator selected TKI arm, overall and within the stratum of participants with imatinib as their pre-randomization selection of TKI respectively.

Let $\alpha_1 = w_1*\alpha$ and $\alpha_2 = w_2*\alpha$ be primary end-point specific alphas for H1 and H2 respectively, let α_3 and the α_4 be key secondary end-point specific alphas for H3 and H4 respectively, and the α_5 be secondary safety end-point specific alpha for H5. To begin with, we distribute the overall global alpha level (1-sided α=0.025) such that the two primary hypotheses get equal weights (i.e. w_1=0.5 and w_2=0.5), as each of the multiple primary objectives is considered equally important. In addition, to begin with, the two key secondary hypotheses are not given any weight since achieving these objectives is not relevant if we cannot meet the primary objective H2, or meet both H1 and H2. Similarly, the secondary hypothesis H5 is also not given any weight to begin with.

Within the primary end-point family F_1:

- The testing of H1 and H2 can be performed simultaneously at the split levels of $\alpha_1 = w_1*\alpha$ and $\alpha_2 = w_2*\alpha$ respectively.
  - When using the correlation between the test statistics for H1 and H2, the test of the intersection hypothesis H1 and H2 would be done at levels that are slightly larger than w1*alpha and w2*alpha (for details please refer to Bretz et al 2011).
- If $H1_0$ is rejected at an alpha of α_1, then this w_1 is passed on to test H2 which can then be tested at the alpha of $w_1*\alpha+w_2*\alpha = \alpha$ (i.e. H2 can be tested at the full alpha).
- If $H2_0$ is rejected at an alpha of α_2, then 0.9 of w_2 is passed onto testing H1, which can then be tested at an alpha of $(w_1 + 0.9*w_2)*\alpha$

Within the key secondary end-point family F_2:

- If only $H2_0$ is rejected in the primary family, then H4 can be tested at an alpha of $\alpha_4 = 0.1*w_2*\alpha$
- If both $H1_0$ and $H2_0$ are rejected in the primary family, then H4 can be tested at the full alpha of α_4=0.025.
- If $H4_0$ is rejected at an alpha of α_4, then this α_4 is passed on to test H3

- if only $H2_0$ from the primary family and $H4_0$ from the key secondary family are rejected, then H3 is tested at an alpha level $\alpha_3=0.1*w_2*\alpha$
- if both $H1_0$ and $H2_0$ from the primary family, and $H4_0$ from the key secondary family are rejected, then H3 is tested at the full alpha level $\alpha_3=0.025$.

Within the secondary safety end-point family F_3:

- If both $H4_0$ and $H3_0$ are rejected in the key secondary family, then H5 can be tested at the full alpha of $\alpha_5=0.025$.

The raw p-value rejection boundaries:

Let p_1 and the p_2 be the raw p-values for H1 and H2 respectively; let p_3 and the p_4 be the raw p-values for H3 and H4 respectively and let p_5 be the raw p-values for H5.

Assuming that the number of participants enrolled into the imatinib stratum based on pre-randomization selection of TKI is 50% of the total number of participant enrolled into the study, **the raw p-value rejection boundaries for the primary end-point family F1 are:**

H1 and H2 are simultaneously tested, each at local alpha= 0.01469289 (which is greater than 0.025/2 due to the positively correlated test statistics with a correlation of sqrt (0.5)).

- If $p_1 > 0.01469289$ and $p_2 > 0.01469289$ then $H1_0$ is not rejected and $H2_0$ is not rejected, and testing stops
- If $p_1 \leq 0.01469289$ and $p_2 \leq 0.01469289$ then $H1_0$ is rejected and $H2_0$ is rejected
- if $p_1 \leq 0.01469289$ and $p_2 > 0.01469289$ then $H1_0$ is rejected and H2 can be retested at the local alpha level of 0.025. If $0.01469289 < p_2 \leq 0.025$ then we can also reject $H2_0$
- If $p_1 > 0.01469289$ and $p_2 \leq 0.01469289$ then $H2_0$ is rejected and H1 can be retested at the local alpha level of 0.02375 = (1+0.9)*0.0125. If $0.01469289 < p_1 \leq 0.02375$ then we can also reject $H1_0$

The raw p-value rejection boundaries for the key secondary end-point family F2:

- If both $H1_0$ and $H2_0$ are rejected in the primary family, then H4 can be tested at the full alpha of 0.025. If $p_4 \leq 0.025$ then we can reject $H4_0$. If $H4_0$ is rejected and $p_3 \leq 0.025$, then we can reject $H3_0$.
- If only $H2_0$ is rejected in the primary family, then H4 will be tested at an alpha of 0.00125. If $p_4 \leq 0.00125$ then we can also reject $H4_0$. If $H4_0$ is rejected and $p_3 \leq 0.00125$, then we can reject $H3_0$.
- If only $H1_0$ is rejected in the primary family, or none of the null hypotheses in the primary family are rejected, then the secondary family cannot be tested.

The raw p-value rejection boundaries for the secondary safety end-point family F3:

If both $H4_0$ and $H3_0$ are rejected in the key secondary family, then H5 can be tested at the full alpha of 0.025. If $p_5 \leq 0.025$ then we can reject $H5_0$.

Equivalently, the raw p-values from the Mantel-Haenszel tests (as described in Section 12.4.2 and Section 12.5.2) and from the log-rank test (as described in Section 12.6) will be adjusted for the multiple testing (alpha control as described in the above graphical gatekeeping procedure), to obtain the adjusted p-values, using the "gMCP" package (Rohmeyer K, Klinglmueller F (2020)) in R. The adjusted p-values will be used to perform the 1-sided 2.5% level test for each of the hypotheses. i.e. if the *adjusted p-value* for a hypothesis is ≤0.025 we will reject the corresponding null hypothesis. The adjusted p-values for the primary end-points family will be computed as per the weighted parametric test using the correlation estimated from the observed study data.

12.8 Analysis of secondary endpoints/estimands

This section describes the analyses for other secondary end-points related to efficacy, PK, safety and tolerability and PROs. No confirmatory statistical testing of other secondary endpoints, that are described in this section, will be performed.

12.8.1 Efficacy and/or Pharmacodynamic endpoint(s)

This section describes definitions and the analyses methods for other secondary end-points related to efficacy. No confirmatory statistical testing of other secondary efficacy endpoints will be performed, however, nominal p-values when presented will be provided for descriptive purposes.

Additional details such as handling of missing values, sensitivity analyses, supportive analyses etc. will be described in detail in the SAP.

12.8.1.1 Other Efficacy Endpoints

The other secondary objectives related to efficacy in this study are:

- To estimate the efficacy of asciminib versus Investigator selected TKI, within the strata of participants with a 2G TKI as their pre-randomization selected TKI, with respect to MMR **at** Week 48.
- To estimate the efficacy of asciminib versus Investigator selected TKI, within the strata of participants with a 2G TKI as their pre-randomization selected TKI, with respect to MMR **at** Week 96.
- To compare the efficacy of asciminib versus Investigator selected TKI with respect to the additional efficacy endpoints listed below.
- To compare the efficacy of asciminib versus Investigator selected TKI, within the stratum of participants with imatinib as their pre-randomization selected TKI, with respect to the additional efficacy endpoints listed below.
- To estimate the efficacy of asciminib versus Investigator selected TKI, within the strata of participants with a 2G TKI as their pre-randomization selected TKI, with respect to the additional efficacy endpoints listed below.

The other efficacy endpoints are:

- MMR **at** all scheduled data collection time points (except Week 48 and Week 96).
- MMR **by** all scheduled data collection time points.

- MR4.0 and MR4.5 **at** and **by** all scheduled data collection time points.
- BCR-ABL1 ≤1% **at** and **by** all scheduled data collection time points.
- Complete Hematological response (CHR) **at** and **by** all scheduled data collection time points.
- Complete Cytogenetic response (CCyR) **by** Week 48 and Week 96.
- Time to first MMR, first MR4.0, first MR4.5.
- Duration of MMR, MR4.0, MR4.5.
- TTF.
- FFS.
- EFS.
- PFS.
- OS.

Unless otherwise stated, the analysis of all other secondary efficacy endpoints for the comparison of:

- Asciminib versus Investigator selected TKI arm will be based on the FAS
- Asciminib versus Investigator selected TKI, within the strata of participants with imatinib as their pre-randomization selected TKI will be based on the FAS_{IMA}
- Asciminib versus Investigator selected TKI, within the strata of participants with a 2G TKI as their pre-randomization selected TKI will be based on the FAS_{2GTKI}

The exceptions are using the Molecular Responder Set, MR4.0 Responder Set and MR4.5 Responder Set for the analysis of durations of MMR, MR4.0 and MR4.5 respectively.

Definitions of MMR/ MR4.0/MR4.5/CHR/CCyR at and by a scheduled visit:

The **rates "at"** a scheduled visit are defined as the proportion of participants who meet the criteria for the end-point (MMR/MR4.0/MR4.5/CHR/CCyR) *at* the specified visit. Participants discontinuing the randomized treatment due to any reason or participants meeting failure criteria, prior to the specific visit will be considered as non-responder for the end-point at the specified visit.

I.e. If a participant achieves the end-point earlier, but then loses it at the visit, he/she will be classified as a non-responder the end-point at that visit.

For the end-point of MMR and CCyR, an exception to the rule is if the evaluation at the specified visit is missing, but both evaluations from the preceding and following scheduled visits meet the criteria for the end-point, the assessment at the specified visit is imputed as a responder for the end-point (Yes).

If PCR evaluations are performed at unscheduled visits, these will be mapped to non-overlapping analysis time windows and will be taken into consideration. The analysis time windows will be described in detail in the SAP.

The **rates "by"** scheduled visits are defined as the proportion of participants who meet the criteria for having achieved the end-point (MMR/MR4.0/MR4.5/CHR/CCyR) *at or before* the specified visit, i.e. if a participant achieves the end-point, but then loses it before or at the visit,

he/she will still be classified as achieving the end-point by that specified visit. Participants discontinuing the randomized treatment prior to the specific time point due to any reason or participants meeting failure criteria, without having achieved the end-point *at or before* that visit will be considered as not achieving the end-point by the specified visit.

Definitions of Duration of MMR/ MR4.0/MR4.5:

Duration of a specified molecular end-point (MMR/ MR4.0/ MR4.5) is defined as the time between the date of the first documented achievement of the specified molecular end-point and the earliest date of loss of the specified molecular end-point, treatment failure, progression to AP/BC, or CML-related death for participants in the specified molecular end-point Responder Set. The duration will be censored at the last molecular assessment (RQ-PCR) date while on treatment for participants who have not experienced any of the above events.

In case of duration of MMR, loss of MMR must be a confirmed loss (confirmed by 2 consecutive tests).

Confirmed loss of MMR is the loss of MMR that must be confirmed by subsequent sample analysis within 4 to 6 weeks showing loss of MMR associated with a ≥ 5-fold rise in BCR-ABL1 from the lowest value achieved on study treatment, unless it is associated with confirmed loss of CHR or loss of CCyR or progression to AP/BC or CML-related death.

Confirmed loss of MR4.0 or MR4.5 is the loss of MR4.0 or MR4.5, respectively, that must be confirmed by subsequent sample analysis within 12 weeks showing loss of MR4 or MR4.5 as applicable, associated with a ≥ 5-fold rise in BCR-ABL1 from the lowest value achieved on study treatment, unless it is associated with confirmed loss of CHR or loss of CCyR or progression to AP/BC or CML-related death.

Definitions of Time to first MMR/ MR4.0/ MR4.5:

Time to first specified molecular end-point (MMR/MR4.0/MR4.5) is defined as the time from the date of randomization to the date of the first documented occurrence of the end-point.

In the time to event analysis, time will be censored at the last molecular assessment (RQ-PCR) date while on treatment, or the EOT (whichever comes first) for participants who have not experienced the event (i.e. not achieved the end-point).

In the competing risk analysis, time to MMR will be censored at the last molecular assessment (RQ-PCR) date on treatment, or the EOT (whichever comes first) prior to or at the analysis cut-off date; for participants who have not experienced an event (MMR/ MR4.0/ MR4.5) or a competing risk event (as described in Section 12.8.1.2).

Definitions of Time to Treatment Failure (TTF):

TTF is defined as the time from date of randomization to the first/earliest documented date of any of the following events:

- Treatment failure as defined below based on ELN criteria (Hochhaus et al 2020A),
- Confirmed loss of MMR (in 2 consecutive tests, Section 12.8.1.1) at any time while on study treatment,

- Discontinuation from study treatment due to any reason (e.g.: discontinuation due to AE, Investigator/participant decision, unsatisfactory treatment response, progression to AP/BC, death due to any cause etc.)

For participants that have not experienced an event prior to or at the analysis cut-off date, the time will be censored at the last study assessment (RQ-PCR, cytogenetic, hematologic etc.) date while on treatment, or the EOT (whichever comes first).

Definitions of Failure Free Survival (FFS):

FFS is defined as the time from the date of randomization to the earliest occurrence of the following events:

- Treatment failure as defined below based on ELN criteria (Hochhaus et al 2020A),
- confirmed loss of MMR (in 2 consecutive tests, Section 12.8.1.1) at any time while on study treatment,
- progression to AP/BC (including progressions observed during the survival follow-up period),
- death from any cause (including deaths observed during the survival follow-up period).

For participants that have not experienced an event prior to or at the analysis cut-off date, the time will be censored at the date of last study treatment assessment (PCR, cytogenetic, hematologic or extramedullary) or last post-treatment follow-up.

Definitions of Event Free Survival (EFS):

EFS is defined as the time from the date of randomization to the earliest occurrence of the following events:

- Treatment failure as defined below based on ELN criteria (Hochhaus et al 2020A),
- confirmed loss of MMR (in 2 consecutive tests, Section 12.8.1.1) at any time while on study treatment,
- discontinuation of study treatment due to AE,
- progression to AP/BC (including progressions observed during the survival follow-up period),
- death from any cause (including deaths observed during the survival follow-up period).

For participants that have not experienced an event prior to or at the analysis cut-off date, the time will be censored at the date of last study treatment assessment (PCR, cytogenetic, hematologic or extramedullary) or last post-treatment follow-up.

Definitions of Progression Free Survival (PFS):

PFS is defined as the time from the date of randomization to the earliest occurrence of the following events:

- progression to AP/BC (including progressions observed during the survival follow-up period),
- death from any cause (including deaths observed during the survival follow-up period).

For participants that have not experienced an event prior to or at the analysis cut-off date, the time will be censored at the date of last study treatment assessment (PCR, cytogenetic, hematologic or extramedullary) or last post-treatment follow-up.

Definition of Overall Survival (OS):

OS is defined as the time from the date of randomization to the date of death from any cause (including deaths observed during the survival follow-up period). For participants that have not experienced an event prior to or at the analysis cut-off date, the time will be censored at the date of last contact before the cut-off date.

Molecular Response Criteria:

Please refer to Section 8.3.1

Complete Haematological Response (CHR) Criteria:

Please refer to Section 8.3.3

Complete Cytogenetic Response Criteria

- Please refer to Section 8.3.2

Treatment Failure Criteria:

The following events will constitute 'treatment failure' based on ELN criteria (Hochhaus et al 2020A)

- *BCR-ABL1 transcript level* > 10% IS at 3 months if confirmed within the next 1–3 months
- *BCR-ABL1 transcript level* > 10% IS at 6 months
- *BCR-ABL1 transcript level* > 1% IS at 12 months
- *BCR-ABL1 transcript level* >1% IS after 12 months,
- Detection of a BCR-ABL1 mutation which can potentially cause resistance to study treatment (asciminib or Investigator selected TKI) at any time after initiation of study treatment. [Per ELN treatment recommendations for known mutations resistant to specific TKI Hochhaus et al 2020A].

Intolerance is defined as:

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

12.8.1.2 Statistical hypothesis, models and methods of analyses of other efficacy endpoints

Analyses of the other secondary efficacy endpoints will not adjusted for multiple testing and, nominal p-values when presented will be provided for descriptive purposes.

Analyses for (MMR/ MR4.0/ MR4.5 / CHR/ CCyR) rates at and by scheduled visits:

Frequency and percentage of participants in the molecular response categories will be presented for each scheduled visit. For the **by** visits summary, the within-participant best molecular response category up to the specific time points is used to calculate the frequency and percentage. The response rate for each endpoint and the associated two sided 95% CI based on the Pearson-Clopper method will be presented by the:

- Treatment arms (asciminib or Investigator selected TKI).
- Treatment arms (asciminib or Investigator selected TKI) within the stratum of participants that have imatinib as their pre-randomization selection of TKI.
- Treatment arms (asciminib or Investigator selected TKI) within the stratum of participants that have a 2G TKI as their pre-randomization selection of TKI.

Comparisons of proportion of participants achieving the end-points (at and by scheduled visits) for:

- Asciminib versus Investigator selected TKI, will be performed using a one-sided stratified Mantel-Haenszel test, stratified by both randomization stratification factors (ELTS risk score and pre-randomization selection of TKI (imatinib versus 2G TKI)).
- Asciminib versus Investigator selected TKI, within the stratum of participants that have imatinib as their pre-randomization selection of TKI, will be performed using a one-sided stratified Mantel-Haenszel test, stratified by only the ELTS risk score randomization stratification factor.

The stratified Mantel-Haenszel estimate of the common risk difference (for the proportion of participants achieving the end-point) between:

- Asciminib and Investigator selected TKI arm, stratified by randomization stratification factors of the ELTS risk score and pre-randomization selection of TKI (imatinib versus 2G TKI),
- Asciminib and Investigator selected TKI arm, within the stratum of participants that have imatinib as their pre-randomization selection of TKI, stratified by only randomization stratification factor of the ELTS risk score,
- Asciminib and Investigator selected TKI arm, within the stratum of participants that have a 2G TKI as their pre-randomization selection of TKI, stratified by only randomization stratification factor of the ELTS risk score,

will be provided, together with the corresponding two sided 95% CI.

Analyses for Duration of MMR/ MR4.0/ MR4.5

Duration of MMR/ MR4.0/ MR4.5 will be analyzed by Kaplan-Meier (KM) method and presented by KM plots. The estimated median duration along with the 95% CIs

Brookmeyer and Crowley 1982 , along with the proportion of participants who are still in still responders at specified scheduled visits and the associated 95% CIs, will be presented for each treatment arm (overall and within the stratum defined by pre-randomization selection of TKI).

The cumulative incidence of MMR/ MR4.0/ MR4.5 will be graphically displayed by an increasing step function. This curve will increase each time (after randomization) at which a new responder is observed and thus will increase up to the best observed response rate (e.g. up to 50% if half of the participants in the analysis population are able to achieve response).

Analyses for Time to First MMR/ MR4.0/ MR4.5

Competing risk analysis of time to first MMR/ MR4.0/ MR4.5 will be performed. Discontinuation from study treatment due to any reason (treatment failure, death etc.), without prior achievement of the end-point (MMR/ MR4.0/ MR4.5) will be considered as competing risk. The estimated cumulative incidence rates and 95% CIs at specified scheduled visits will be presented for each treatment arm (overall and within the stratum defined by pre-randomization selection of TKI). The cumulative incidence curve will be plotted. For this competing risk analysis, time to first achievement of the end-point (MMR/ MR4.0/ MR4.5) will be censored at the last molecular assessment (RQ-PCR) date on treatment, or the EOT (whichever comes first) prior to or at the analysis cut-off date, for participants who have not experienced an event (MMR/ MR4.0/ MR4.5) or a competing risk event.

Analyses for Failure Free Survival (FFS) and Event Free Survival (EFS)

Competing risk analysis of FFS and EFS will be performed. The estimated cumulative incidence rates and 95% CIs at specified scheduled visits will be presented for each treatment arm (overall and within the stratum defined by pre-randomization selection of TKI). The cumulative incidence curve will be plotted.

In the analysis of FFS, discontinuation from study treatment due to other reasons that are not due to lack/loss of efficacy (e.g.: discontinuations due to: subject/guardian or physician decision, loss to follow-up, pregnancy, study termination, AEs) will be considered as competing risks. In the analysis of EFS, discontinuation from study treatment for other reasons which are not due to AE and not due to lack/loss of efficacy (e.g.: discontinuations due to: subject/guardian or physician decision, loss to follow-up, pregnancy, study termination) will be considered as competing risks.

Analyses for Time to Event End-points (TTF, PFS, OS)

For each endpoint the time to event distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% CIs (Brookmeyer and Crowley 1982) of the medians, along with the proportion of participants who have not experienced the respective events at select scheduled visits (e.g.: 1, 2 and 5 years) and the associated 95% CIs, will be presented for each treatment arm (overall and within the stratum defined by pre-randomization selection of TKI). The hazard ratio between the two treatments arms (overall and within the stratum defined by pre-randomization selection of TKI) will be calculated, along with its 95% CI, using a stratified Cox model. The descriptive p-value obtained using a stratified log-rank test will be also presented. The stratification will be based on both randomization stratification factors (ELTS and pre-randomization selection of TKI) for the overall comparison between

arms; and by the stratification factor of ELTS for the comparison between arms, within the stratum defined by pre-randomization selection of TKI.

12.8.2 Safety endpoints

Analysis Set and Grouping

For all safety analyses, the safety set will be used.

All listings and tables will be presented by treatment arm.

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

1. Pre-treatment period: from day of participant's first informed consent to the day before first administration of study treatment.
2. On-treatment period: from day of first administration of study treatment to 30 days after last actual administration of the same study treatment (asciminib or Investigator selected TKI (imatinib, nilotinib, dasatinib, bosutinib)), including start and stop date.
3. Post-treatment period: starting at day 31 after last administration of any study treatment (asciminib or Investigator selected TKI (imatinib, nilotinib, dasatinib, bosutinib)).

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

AEs

All information obtained on AEs will be displayed by treatment arm and participant.

Summary tables for AEs (AEs) will include only AEs that started or worsened during the on-treatment period. The number (and percentage) of participants with treatment emergent AEs will be summarized by primary system organ class, preferred term and maximum severity (based on CTCAE grades). A participant with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class. Separate summaries will be provided for study medication related AEs, deaths, serious AEs, AEs leading to treatment discontinuation, and AEs leading to dose adjustment. The number (and percentage) of participants with AEs will be summarized by treatment arm, primary system organ class, preferred term and maximum severity.

The incidence of AEs 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 AEs and non-serious AEs will be tabulated.

In addition, selected summaries of AEs will be produced for the overall safety period.

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

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

Clinical laboratory evaluations/abnormalities

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for AEs (CTCAE) v5. 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 v5, results will be categorized as low/normal/high based on laboratory normal ranges.

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

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v5 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v5:

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

For laboratory tests where grades are not defined by CTCAE v5:

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

Vital signs

All vital signs abnormalities will be summarized by treatment arm and listed, notable values will be flagged.

ECG (12-lead)

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

Categorical analysis of QT/QTc interval data based on the number of participants 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 participants will be produced by treatment group.

12.8.3 Tolerability

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

12.8.4 Pharmacokinetics

The PK objective is to characterize the PK of asciminib in newly diagnosed CML-CP patients.

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

Using Safety set, concentration data will be listed. Concentration values below the limit of quantification (BLQ) will be set to zero by the Bioanalyst and displayed in listings as zero with a flag. BLQ values will be handled as zero in any calculations of summary statistics, but handled as missing for the calculation of the geometric means and CVs.

PK parameters will be determined by non-compartmental method(s) using the PK profile of asciminib in participants with full PK sampling on Week 2/Day 14. PK parameters listed in Table 12-1 will be derived and reported, when feasible.

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

Table 12-1 Non compartmental pharmacokinetic parameters in full PK group

AUC_{last}	The area under the plasma concentration-time curve calculated from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
$AUC_{0\text{-}tau}$	The area under the plasma concentration-time curve from time zero to the end of a dosing interval (tau=24h) at steady-state (amount x time x volume-1)
C_{max}	The maximum (peak) observed plasma drug concentration after dose administration (mass x volume-1)
T_{max}	The time to reach maximum (peak) plasma drug concentration after dose administration (time)
CL/F	The total body clearance of drug from the plasma after oral administration (volume x time-1)

12.8.5 Patient reported outcomes

The respective full analyses sets (FAS, FAS_{IMA}, FAS_{2GTKI}) will be used for analyzing PRO data unless specified differently.

The EORTC QLQ-C30 (version 3.0) and the EORTC QLQ-CML24 will be used to assess general health related quality of life and impairment related to the patient's CML (respectively). Change from baseline in Overall Scores and individual domains each PRO instruments will be summarized using descriptive statistics for each treatment arm (overall and by strata defined by pre-randomization selection of TKI). Participants 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.

All PRO measures require participant's direct completion and will be administered utilizing electronic device for data collection at scheduled time points from screening to EOT.

Missing data items in a scale will be handled according to the manual for each instrument. No imputation will be applied if the total or subscale scores are missing at a visit. All measures will assess differences between the treatment arms (overall and by strata defined by pre-randomization selection of TKI).

Additional analyses may be performed if deemed necessary. Such analyses will be defined in the SAP.

Additional details for the analyses, models and missing data handling will be specified in the SAP.

12.9 Analysis of exploratory endpoints

12.9.1 Exploratory Biomarkers

This trial is not designed to address specific biomarkers-related hypotheses, the analysis of the data should be viewed as exploratory and hypotheses generating. There may be circumstances when a decision is made to stop a collection, or not to perform or discontinue the analysis of samples due to either practical or strategic reasons. Under such circumstances, the sample size number may be too small or the quality of the data not sufficient to perform any data analysis and the available data will be only listed.

Additional analyses that may be performed after the completion of the end-of-study CSR will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in a stand-alone analysis plan document.

Data transformations, such as base 2 logarithms, may be used to summarize and adequately analyze the data and will be described in detail in the SAPs.

Data analysis principles

Analysis sets

Unless otherwise mentioned, the Full Analysis Set is used to describe biomarkers; Safety Set is used to assess the relationship between biomarkers and selected safety endpoints, while the PK Set is used to assess the relationship between PK parameters and biomarkers. Since no imputation is usually planned, the number of participants included in a given analysis will reflect the number of participants in the chosen analysis set which have valid biomarker assessments.

Basic tables, figures and listings

Unless otherwise specified, analysis will be performed by treatment arm and overall. Analysis may also be presented by each stratum based on pre-randomization selection of TKI separately.

The exploratory biomarker objectives in this study are

- To characterize [redacted] and their association with molecular response.
- To conduct gene expression analysis in peripheral blood to predict treatment response.
- To explore the impact of the immune landscape of peripheral blood on treatment response.

Continuous biomarkers (e.g.: gene expression) will be summarized using means, medians, SDs, minimums, and maximums, by visit. Both level and change from baseline levels (absolute,

percent and fold changes) will be summarized for biomarker that also have assessments at post-baseline visits.

Categorical biomarkers (e.g.: % cells for immune microenvironment markers, BCR-ABL1 mutation status etc.) will be summarized using frequency counts and percentages.

Associations between biomarker levels/change from baseline levels (e.g.: expression profile) and clinical end-points (e.g. MMR, TTF, OS etc.) will be explored through suitable figures. Associations between continuous biomarkers levels/change from baseline levels and categorical end-points (e.g. MMR) will be explored through box-plots/strip-plots showing the biomarker levels (or change from baseline levels) versus categories of response. Associations between biomarkers levels/change from baseline levels (suitably categorized) and time to event end-points (e.g. TTF, OS etc.) will be explored through KM plots. Details will be provided in the SAPs and may be reported separately.

If sample size is limited then the biomarker data will be listed. For large panels, selected sets of relevant markers will be chosen for the listing.

12.9.2 Pharmacogenomics

The impact of baseline genetic variants of the [redacted] genes on asciminib exposure will be explored. Using PAS, summary statistics for plasma concentration at scheduled time points and/or selected PK parameters (e.g. AUC, Cmax) will be summarized by genetic variant groups. These analyses may be reported separately.

In addition or instead of the [redacted] pharmacogenomics analysis, other genetic analyses on the impact of genes that are thought to be related to the asciminib metabolism and action or disease may be performed.

12.9.3 Exploratory Efficacy

Subgroup analyses will be performed to evaluate the influence of factors such as ELTS scores, pre-randomization selection of TKI, gender, race and age on the primary and key secondary efficacy endpoints (i.e. MMR at Week 48 and MMR at Week 96 respectively).

In addition, a multivariate logistic regression analysis will incorporate the key baseline variables into the model to further evaluate the impact of these variables on these endpoints and to provide a treatment effect estimates which are adjusted for these variables. Adjusted odds ratios for the treatment effects with associated 95% CIs will be presented. Mantel- Haenszel estimates of the common odds ratios and the corresponding 95% CIs will also be provided.

12.9.4 Exploratory Patient Reported Outcomes

Data from PROs measures collected in the study as exploratory study endpoints using the [redacted] will also be assessed. [redacted] will be presented descriptively by treatment group with summary statistics and graphical presentations. Responses to the [redacted] questions will be characterized descriptively with summary statistics by visit and by treatment group.

[redacted]

Additional analyses may be performed if deemed necessary. Such analyses will be defined in the SAP.

12.9.5 Exploratory Heath Care Resource Utilization

The respective full analyses sets (FAS, FAS_{IMA}, FAS_{2GTKI}) will be used for analyzing resource utilization, unless specified differently.

Data relating to resource utilization from the FAS will be used for the purpose of economic evaluation, which will be carried out and reported as a separate activity outside the CSR. The measures of HCRU include: hospitalization (H), emergency room (ER) visit, general practitioner (GP) visits, specialist (Sp) visit and urgent care (UC) visit. HCRU will be assessed as follows: frequency and duration of hospitalization from baseline up to EOT; frequency of ER visits from baseline up to EOT; frequency of additional outpatient office visits general practitioner, specialist, and urgent care visits from baseline up to EOT. Hospitalization visits will also record the number of days on ward and the type of ward (hospital unit) and the discharge status. At each HCRU collected, the reason for the visit, i.e. related to CML, AE related to CML therapy or other reason, will be collected, in order to quantify the impact of treatment on healthcare resources. HCRU data by treatment arm will be summarized in the primary analysis CSR and the end of study treatment CSR, with descriptive statistics (n, mean, median, SD, min, max) for quantitative variables, and count and percentage for qualitative variables.

12.10 Interim analyses

No formal interim analysis is planned in the study. Safety outputs will be prepared for the data monitoring committee (DMC) as outlined in section Section 10.2.3.

12.11 Sample size calculation

Historical estimates for efficacy of the TKIs in the control arm were available from published literature on the pivotal trials of nilotinib, dasatinib and bosutinib respectively, in newly diagnosed patients with CML-CP.

Table 12-2 Historic MMR rates from pivotal TKI trials in newly diagnosed patients with CML-CP

		MMR rate at/by* 48 weeks (n)		MMR rate by 96 weeks (n)	
Study Acronym	Investigational Drug	Imatinib Arm (400mg QD)	Investigational Drug Arm	Imatinib Arm (400mg QD)	Investigational Drug Arm
BFORE	Bosutinib 400 mg QD	0.37 (n=241)	0.47 (n=246)	0.58 (n=241)	0.67 (n=246)

Study Acronym	Investigational Drug	MMR rate at/by* 48 weeks (n)		MMR rate by 96 weeks (n)	
		Imatinib Arm (400mg QD)	Investigational Drug Arm	Imatinib Arm (400mg QD)	Investigational Drug Arm
BELA	Bosutinib 500 mg QD	0.27 (n=252)	0.41 (n=250)	0.49 (n=252)	0.59 (n=250)
DASISION	Dasatinib 100 mg QD	0.28* (n=260)	0.46* (n=259)	0.47 (n=260)	0.65 (n=259)
ENESTND	Nilotinib 300 mg BID	0.22 (n=281)	0.44 (n=283)	0.44 (n=281)	0.71 (n=283)

BFORE: Cortes et al 2018
BELA: Cortes et al 2012
DASISION: Kantarjian et al 2010A
ENESTND: Saglio et al 2010

Random effects meta-analyses are performed using the historical published data and is implemented in R 3.4.3 using the package 'Meta' Balduzzi et al 2019 .

A random effects meta-analysis of MMR at/by Week 48 from the published data gives us estimated proportions (95% CI) of participants that are in MMR at Week 48 for imatinib of 0.28 (0.23, 0.34), and for 2G TKIs of 0.44 (0.41, 0.48).

The assumption on the MMR rate at Week 48 for asciminib is based on extrapolation of data from the FIH CABL001X2101 study and the data from the pivotal CABL001A2301 study in third line patients, to the first line setting.

The proportions of participants that will achieve the primary endpoint of being in **MMR at Week 48** are thus assumed to be:

- 0.525 for asciminib
- 0.28 for imatinib
- 0.45 for any 2G TKI

A random effects meta-analysis of MMR by Week 96 from the published data gives us estimated proportions (95% CI) of participants that are in MMR by Week 96 for imatinib of 0.49 (0.44, 0.55), and for 2G TKIs of 0.66 (0.61, 0.71). A random effects meta-analysis of the difference in rate of MMR by Week 96 and MMR at/by Week 48, from the published data gives us estimated proportions (95% CI) for imatinib of 0.21 (0.17, 0.25), and for 2G TKIs of 0.21(0.17, 0.26). Based on internal data for ENESTnd the difference between MMR by Week 96 and MMR at week 48 is approximately 6% for imatinib and approximately 9% for nilotinib.

The proportions of participants that will achieve the secondary endpoint of **MMR at Week 96** are thus assumed to be:

- 0.635 for asciminib
- 0.43 for imatinib
- 0.56 for any 2G TKI

The study design plans for a 50% versus 50% enrollment of imatinib versus the 2G TKIs into the control arm.

Therefore the proportion of participants that will achieve the primary endpoint of MMR at Week 48 is assumed to be 0.365 for the Investigator selected TKI arm. This proportion is calculated as a weighted average of the 50% of participants on imatinib with the assumed proportion being in MMR at Week 48 of 0.28, and 50% participants on a 2G TKI with the assumed proportion being in MMR at Week 48 of 0.45.

Similarly the proportion of participants that will achieve the primary endpoint of MMR at Week 96 is assumed to be 0.495 for the Investigator selected TKI arm. This proportion is calculated as a weighted average of the 50% of participants on imatinib with the assumed proportion being in MMR at Week 96 of 0.43, and 50% participants on a 2G TKI with the assumed proportion being in MMR at Week 96 of 0.56.

Adjustment for dropouts is not made since any participant that discontinues study treatment prior to Week 48 will be considered a non-responder for the end-point of MMR at Week 48; and any participant that discontinues study treatment prior to Week 96 will be considered a non-responder for the end-point of MMR at Week 96.

The power for rejecting at least one of the two multiple primary hypotheses, tested according to the graphical gatekeeping strategy described in Section 12.7 is computed via simulations in R version 3.6.1 using the package "gMCP" Rohmeyer and Klinglmueller F 2020. The underlying distribution of test statistics in power simulations is assumed to be multivariate normal with the correlation matrix that is a block diagonal matrix (with correlation between the test statistics for H1 and H2=√0.5 and correlation between the test statistic for H3 and H4=√0.5). The non-centrality parameters are the standardized test statistics computed under the alternative assumptions.

Based on a 1-sided 2.5% level of significance, **with 402 participants** and 1:1 randomization ratio between arms (i.e. 201 participants in the asciminib arm and 201 participants in the Investigator selected TKI arm) we have **94.6% power to reject at least one of the null hypotheses from the primary family (F_1={H_1, H_2})**. At this sample size, the **local power** to reject the null hypothesis for **H1 is 88.5%** and **local power** to reject the null hypothesis for **H2 is 92.7%**.

This sample size is based on 10000 simulations and from the non-centrality parameters computed from the assumptions that:

- Asciminib leads to an increase over Investigator selected TKI, in the proportion of participants that are in MMR rate at Week 48, from 0.365 to 0.525, which corresponds to an odds ratio of 1.92 (for asciminib versus Investigator selected TKI).
- Asciminib leads to an increase over imatinib, in the proportion of participants that are in MMR at Week 48, from 0.28 to 0.525 which corresponds to an odds ratio of 2.84 (for asciminib versus imatinib).
- Asciminib leads to an increase over Investigator selected TKI, in the proportion of participants that are in MMR rate at Week 96, from 0.495 to 0.635, which corresponds to an odds ratio of 1.77 (for asciminib versus Investigator selected TKI).
- Asciminib leads to an increase over imatinib, in the proportion of participants that are in MMR at Week 96, from 0.43 to 0.635 which corresponds to an odds ratio of 2.31 (for asciminib versus imatinib).

The secondary end-point of Time to discontinuation due to AE will be assessed based on the sample size as defined for the primary endpoints. The graphical gatekeeping procedure described in Section 12.7 ensures preservation of the overall one-sided type I error at 0.025.

Table 12-3 Sensitivity of power to changes in the MMR assumptions (N=402)

MMR at Week 48				MMR at Week 96				Power to reject at least one of H1 or H2	Local power to reject H1	Local power to reject H2	Local power to reject H3	Local power to reject H4
Asc.	Inv. selected TKI	2G TKIs	Ima.	Asc.	Inv. selected TKI	2G TKIs	Ima.					
0.525	0.365	0.450	0.280	0.635	0.495	0.560	0.430	94.56 %	88.46 %	92.73 %	65.70 %	74.43 %
0.525	0.400	0.520	0.280	0.635	0.530	0.630	0.430	92.13 %	69.72 %	91.69 %	41.60 %	67.52 %
0.480	0.365	0.450	0.280	0.590	0.495	0.560	0.430	80.61 %	62.13 %	78.53 %	26.59 %	41.30 %
0.500	0.365	0.450	0.280	0.610	0.495	0.560	0.430	88.26 %	75.96 %	86.11 %	43.76 %	57.20 %

Asc.=asciminib; Inv.=Investigator; 2G TKIs = second generation TKIs (nilotinib/ dasatinib/ bosutinib); Ima.=imatinib

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 ICF, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants.

Any amendments to the protocol will require IRB/IEC 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 representatives, 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.

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 EudraCT or 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).

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 should be submitted to Novartis/Sponsor before publication or presentation.

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.

13.4 Quality Control and Quality Assurance

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

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

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

13.5 Data Protection

Participants will be assigned a unique identifier by Novartis/Sponsor. Any participant records or datasets that are transferred to Novartis/Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis/Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis/Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis/Sponsor has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

13.6 Participant Engagement

The following participant engagement initiatives are included but not limited in this study and will be provided, as available, for distribution to study participants at the timepoints indicated.

If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter
- Trial Feedback Questionnaires (TFQ)
- Plain language trial summary-after CSR publication

14 Protocol adherence

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

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

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

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Concomitant Medications. Prohibited medication and medication to be used with caution

In general, the use of any concomitant medication deemed necessary for the care of the participant is permitted in this study, except as specifically prohibited in Section 6.2.2 for participants.

The following lists are based on the internal [Pharmacokinetic Sciences memorandum on Drug-Drug Interaction] (release date: Apr-2021), which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling (2017), and the University of Washington's Drug Interaction Database (2017). These lists are not comprehensive and are only meant to be used as a guide. Please contact the medical monitor with any question.

Table 16-1 Concomitant medications to be used with caution

Category	Drug Names
Torsade de pointe (TdP) TdP/QT risk: Known	amiodarone, anagrelide, arsenic trioxide, astemizole (off us mkt), azithromycin, bepridil (off us mkt), chloroquine, chlorpromazine, cilostazol, cisapride (off us mkt), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on us mkt), donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, grepafloxacin (off market worldwide), halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (off mkt worldwide), mesoridazine (off mkt worldwide), methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl, pentamidine, pimozide, probucol (off mkt worldwide), procainamide (oral off us mkt), propofol, quinidine, sevoflurane, sotalol, sparfloxacin (off us mkt), sulpiride (not on us mkt), terfenadine (off us mkt), thioridazine, vandetanib
TdP/QT risk: Possible[1]	alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine, asenapine, bedaquiline, bortezomib, buprenorphine, capecitabine, ceritinib, clomipramine, clozapine, crizotinib, cyamemazine (cyamepromazine) (Only on Non US Market), dabrafenib, dasatinib, degarilix, delamanid (off US mkt), desipramine, dexmedetomidine, dolasetron, eribulin, ezogabine, famotidine, felbamate, fingolimod, foscarnet, gemifloxacin, granisetron, hydrocodone extended-release, iloperidone, imipramine (melipramine), isradipine, lapatinib, lenvatinib, leuprolide, lithium, mifepristone, mirabegron, mirtazapine, moexipril/hctz, nicardipine, nilotinib, norfloxacin, nortriptyline, ofloxacin, olanzapine, osimertinib, oxytocin, paliperidone, panabinostat, pasireotide, pazopanib, perflutren lipid microspheres, pipamperone (not on us mkt), promethazine, quetiapine, ranolazine, rilpivirine, risperidone, roxithromycin (on non us mkt), saquinavir, sertindole (on non us mkt), sorafenib, sunitinib, tacrolimus, tamoxifen, telavancin, telithromycin, tetrabenazine (orphan drug in us), tizanidine, tolterodine, toremifene, trimipramine, vardenafil, vemurafenib, venlafaxine, vorinostat, zotepine
TdP/QT risk: Conditional[1]	amantadine, amisulpride, amitriptyline, atazanavir, chloral hydrate, diphenhydramine, doxepin, fluoxetine, furosemide (frusemide), galantamine, hydrochlorothiazide, hydroxyzine, hydroxychloroquine, indapamide, itraconazole, ivabradine (on non us mkt), ketoconazole, loperamide, metoclopramide, metronidazole, nelfinavir, pantoprazole, paroxetine, posaconazole, quinine sulfate, ritonavir, sertraline, solifenacin, telaprevir, torsemide, trazodone, voriconazole, ziprasidone
Strong inducers of CYP3A4/5	carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort (Hypericum perforatum)

Category	Drug Names
Narrow Therapeutic index substrates of CYP2C9	phenytoin, warfarin (also sensitive)
Narrow Therapeutic index substrates of CYP3A4/5	alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus, terfanadine,
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, 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

[1]Check: crediblemeds.org/healthcare-providers/drug-list for the most updated list. This list gets updated periodically. Kindly refer to the above links for latest information.

16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-2 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 3 × 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
If ALT or AST abnormal at baseline:	• ALT or AST > 3x baseline or > 300 U/L (whichever occurs first)

Table 16-3 Follow up requirements for liver laboratory triggers - Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	• Maintain treatment • Repeat liver tests within 48-72 hours	Monitor liver tests weekly until resolution to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	• Interrupt treatment • Repeat liver tests within 48-72 hours • Hospitalize if clinically appropriate • Establish causality	Monitor liver tests weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, TBL, Alb, PT/INR, ALP and GGT)

Criteria	Actions required	Follow-up monitoring
	• Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)
Any AE potentially indicative of a liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF	Based on Investigator's discretion investigation(s) for contributing factors for the liver event can include: 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.

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-4 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 participant hospitalization /specialized treatment
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor participant regularly (frequency at Investigator's discretion) until either: Event resolution: sCr within 10% of baseline, or Event stabilization: sCr level with ±10% variability over last 6 months	

[+] Corresponds to KDIGO criteria for Acute Kidney Injury

16.4 Appendix 4: Eligibility based on serologic markers for hepatitis B and C

Table 16-5 Eligibility based on serologic marker for hepatitis B and C

Test	Result				
HBsAg	+	-	-	-	-
HBcAb	Any	+	-	+	-
HBsAb	Any	-	+	+	-
HCV Ab	Any	Any	-	-	-
Eligibility	Not Eligible	Indeterminate	Eligible	Eligible	Eligible

If indeterminate results are obtained, viral DNA (hepatitis B) or RNA (hepatitis C) should be measured to confirm negative viral status.

HBsAg positive: Indicates active infection and risk for reactivation with fulminant hepatitis. These subjects are not eligible for the trial.

HBcAb positive: As a standalone marker it can indicate four possibilities: Resolved infection (Immune due to natural infection), false-positive anti-HBc (susceptible for infection), low level chronic infection and resolving acute infection

HBV-DNA should be performed if only HBcAb is positive at screening and if positive then the subjects are not eligible for the trial. Even if HBV-DNA is negative suggesting resolved infection, there is still a risk for HBV reactivation. In these cases, HBV-DNA should be monitored on a monthly basis to detect HBV reactivation.

Both HBcAb and HBsAg are positive Indicates active infection and risk for reactivation with fulminant hepatitis. These subjects are not eligible for the trial. Hence HBV-DNA testing is not necessary.

HBsAb positive: As a standalone marker, it indicates successful vaccination or previous infection that has been successfully resolved if the only positive finding. These subjects are eligible for the trial.

HBsAg negative, HBcAb positive, HBsAb positive: Resolved or latent infection. These

subjects are eligible for this trial, however, they are at risk for viral reactivation

HCV Ab positive: Indicates active infection and risk for reactivation. These subjects are not eligible for the trial.

All markers negative: No prior exposure or vaccination to hepatitis B and no prior exposure to Hepatitis C. Subjects are eligible for the trial.