NOVARTIS

Clinical Development

ABL001/ASCIMINIB

CABL001AUS04 / NCT04666259

An open label, multi-center Phase IIIb study of asciminib (ABL001) monotherapy in previously treated patients with chronic myeloid leukemia in chronic phase (CML-CP) with and without T315I mutation (AIM4CML)

Statistical Analysis Plan (SAP)

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			Removed week 60 assessment and updated time interval for week 72 in table for molecular assessment Added statement for mapping EOT assessment Added week 72 for hematologic response assessment [redacted]	
			Updated the criteria for generating TFLs for subgroup analysis	Section 2.2.1
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			Updated the secondary objectives to align with protocol	Section 2.8
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			Updated time windows for week 48 and 72 for molecular response	Section 2.1.1
			[redacted]	[redacted]

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List of abbreviations

ABL	Abelson proto-oncogene
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATP	Adenosine triphosphate
AUC	Area under the curve
AV	block Atrioventricular block
b.i.d.	bis in die/twice a day
BC	Blast crisis
BCR	Breakpoint Cluster Region gene
BCR-ABL	BCR-ABL fusion gene (also called the Philadelphia chromosome)
BID	bis in diem/twice a day
BMI	Body Mass Index
CBC	Complete Blood Count
CDP	Clinical Development Plan
CDS	Core Data Sheet
CHR	Complete Hematological Response
CI	Confidence Interval
CK	Creatinine Kinase
[redacted]	[redacted]
CML	Chronic Myelogenous Leukemia
CML-AP	Chronic Myelogenous Leukemia-Accelerated Phase
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
CO2	carbon dioxide
[redacted]	[redacted]
CP	Chronic phase
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation

CYP3A4	Cytochrome P450 3A4
DBP	Diastolic Blood Pressure
DDI	Drug-drug interaction
DLCO	Carbon monoxide diffusing capacity
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DQF	Data Query Form
DS&E	Drug Safety and Epidemiology
DSMB	Data Safety Monitoring Board
DSUR	Development safety update report
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
ELN	European Leukemia Network
EOT	End of Treatment
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First In Human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GDPR	General Data Protection Regulation
GFR	Glomerular Filtration Rate
GGT	Gamma-glutamyl transferase
H	Hour
hADME	Human ADME study (Absorption, Distribution, Metabolism and Excretion)
HBsAg	Hepatitis B surface antigen
HDL	High density lipoprotein
i.v.	Intravenous
IB	Investigator’s Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International normalized ratio
IWRS	Interactive Web Response System
IRB	Institutional Review Board

IRT	Interactive Response Technology that includes Interactive Voice Response System and
Km	Michaelis-Menten constant
K-M	Kaplan-Meyer
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LFT	Liver function test
LLN	Lower limit of normal
LLOQ	lower limit of quantification
LSC	Leukemia stem cell
MCyR	Major Cytogenetic Response
mCyR	Minor Cytogenetic Response
[redacted]	[redacted]
MedDRA	Medical dictionary for regulatory activities
Mg	milligram(s)
mL	milliliter(s)
MMR	Major Molecular Response
MRI	Magnetic resonance imaging
NCDS	Novartis Clinical Data Standards
[redacted]	[redacted]
NOVDD	Novartis Data Dictionary
[redacted]	[redacted]
OS	Overall survival
p.o.	oral(ly)
[redacted]	[redacted]
PCR	Polymerase Chain Reaction
PCyR	Partial Cytogenetic Response
PD	Pharmacodynamic(s)
Ph+	Philadelphia chromosome positive
PHI	Protected Health Information
[redacted]	[redacted]
PLT	Platelets
PPD	Premature Participant Discontinuation
PPS	Per-protocol set
[redacted]	[redacted]
PSD	Premature Subject Discontinuation
PSUR	Periodic safety update report
PT	prothrombin time
QD	Quaque die/once a day
QMS	Quality Management System
QT	Q to T interval (ECG)
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RAP	The Report and Analysis Plan
RBC	red blood cell(s)

RDC	Remote Data Capture
RDE	Recommended dose for expansion
REB	Research Ethics Board
RNA	Ribonucleic acid
RoW	Rest of World
RP2D	Recommended phase two dose
RQ-PCR	Real time quantitative polymerase chain reaction
s.c.	Subcutaneous
SAE	Serious Adverse Event
SAP	The Statistical Analysis Plan (SAP) is a regulatory document which provides evidence of preplanned analyses
SBP	Systolic Blood Pressure
SC	Steering committee
sCR	serum creatinine
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBIL	Total bilirubin
TD	Study medication Discontinuation
TdP	Torsades de Pointes
TKI	Tyrosine Kinase Inhibitor
TTF	Time to treatment failure
UGT	Uridin diPhospho-glucuronosyltransferase
ULN	Upper limit of normal
ULQ	upper limit of quantification
US	United States
USPI	US prescribing information
UTI	Urinary Tract Infection
WBC	White blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses of primary objective, secondary objectives [redacted] for the clinical study reports (CSR) of study CABL001AUS04, a phase 3b, multi-center, open-label, study of oral asciminib monotherapy in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with at least 2 ATP-site tyrosine kinase inhibitors (TKI) (i.e. imatinib, nilotinib, bosutinib, dasatinib or ponatinib) in case of absence of T315I mutation or previously treated with at least 1 ATP-site tyrosine kinase inhibitors (i.e. imatinib, nilotinib, bosutinib, dasatinib or ponatinib) in case of presence of T315I mutation.

The main purpose of this document is to describe the statistical methodology that will be used for this clinical study.

The analysis described here will be conducted by Novartis using statistical software SAS® Version 9.4 or higher, according to the Statistical methods and data analysis Section 12of the study protocol.

Unless otherwise specified, the statistical methodologies including the analysis sets, analysis models, algorithms and conventions are following the Oncology study protocol CABL001AUS04 version 03.

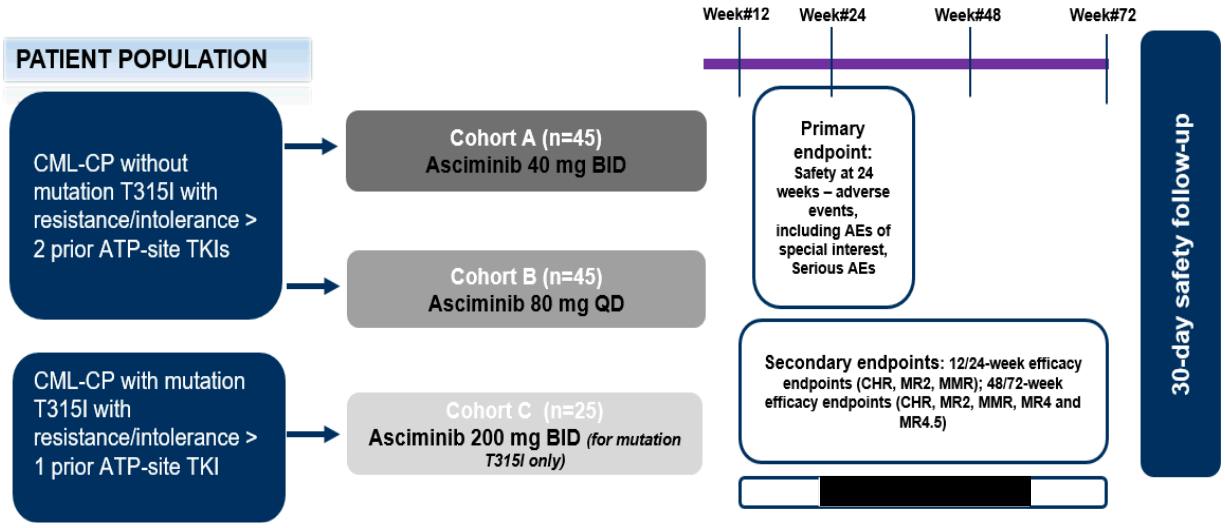
1.1 Study design

This study will be a multicenter Phase IIIb open-label, three-cohort study of asciminib in patients with CML-CP without T315I mutation who have had at least 2 prior TKIs and CML- CP harboring the T315I mutation with at least 1 prior TKI (Figure 1-1). Approximately 115 patients will be enrolled in the study. 90 patients without T315I mutation will be randomly selected in Cohort A & B (45 patients per Cohort). Remaining 25 patients with T315I mutation will be enrolled in Cohort C.

The study will contain following Cohorts:

- Cohort A (45): where patients will receive asciminib at 40 mg twice daily
- Cohort B (45): where patients will receive asciminib at 80 mg once daily
- Cohort C (25): patients harboring the T315I mutation will be treated on the dose of 200 mg twice daily.

Figure 1-1 Schematic of study design



For patients without T315I mutation, patients will be selected randomly between Cohort A, where patients will be given asciminib at 40 mg twice daily (BID) and Cohort B, where patients will receive asciminib at 80 mg daily (QD) to minimize selection bias. In Cohort C, patients harboring the T315I mutation will be enrolled and treated on the dose of 200 mg twice daily (BID). The higher dose required for that patient population is related to its required concentration to attain optimal blockade of the kinase activity. Patients will continue therapy until disease progression, unacceptable toxicity, or elective treatment discontinuation.

AEs, SAEs, and laboratory evaluation for 24 weeks is the primary endpoint in this study. AEs, SAEs and laboratory evaluation for Cohort A, B and Cohort C, during 48, 72 weeks is the secondary safety endpoint.

The primary analysis will be performed after all patients have been followed for at least 24 weeks or have discontinued study earlier. The end of study medication analysis will be performed after all patients have been followed for at least 72 weeks or have discontinued study earlier. The PFS/OS update analysis will be performed during 24, 48 and 72 weeks of the last patient received the first study dose.

No formal interim efficacy analysis is planned in this study. As the primary time point is by 24 weeks, the primary analysis will be an interim analysis performed when the last patient completes 24 weeks of treatment or discontinues early. As appropriate, annual interim analyses may be planned for publication or any regulatory purpose. Only summary statistics will be provided.

Final Analysis will be performed when the last patient completes 72 weeks of treatment or discontinues early.

1.2 Study objectives and endpoints

Table 1-1 Objective(s) Endpoint(s)

Primary Objective(s)	Endpoint(s) for primary objective(s)
• To evaluate safety profile of monotherapy asciminib in CML- CP in 3L and beyond, for Cohorts A and B	• AEs, SAEs and laboratory evaluation for 24 Weeks.
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate safety profile of monotherapy asciminib in CML- CP in 3L and beyond, for Cohort C	• AEs, SAEs and laboratory evaluation for 24 Weeks.
• To evaluate safety profile of monotherapy asciminib in CML- CP in all Cohorts A, B and C	• AEs, SAEs and laboratory evaluation for Cohort A, Cohort B and Cohort C, during 48, 72 weeks
• To estimate the rate of patients with hematologic and molecular response by specific time points for Cohort A, B and C	• Rate of CHR, MR2, MMR, by 12, 24, 48, 72 weeks of therapy
• To estimate the rate of patients with deep molecular response by specific time points for Cohort A, B and C	• Rate of MR4, MR4.5 by 48, 72 weeks of therapy
• To estimate time to hematologic and molecular response	• Time to CHR, MR2, MMR, MR4, MR4.5
• To evaluate the duration of hematologic and molecular response	• Duration of CHR, MR2, MMR, MR4 and MR4.5
• To Evaluate the progression free survival (PFS)	• PFS during 24, 48 and 72 weeks
• To Evaluate Overall Survival (OS)	• OS during 24, 48 and 72 weeks
[redacted]	

2 Statistical methods

2.1 Data analysis general information

All analysis will be performed by Novartis.

It is planned that the data from all centers that participate in this protocol will be used for analysis. Analysis datasets and statistical outputs will be produced using the most recent SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA) or higher, and stored in Novartis global programming & statistical environment (GPS).

There is no formal planned interim analysis.

Data included in the analyses

The analysis data cut-off dates for the planned analyses are:

- Primary analysis: After random allocation of all patients in their respective Cohort, have been on study medication for 24 weeks or discontinued earlier, i.e., LPFT + 24 weeks.
- Final safety, efficacy [redacted] analyses: 30 days after all patients have been on treatment for at least 72 weeks or discontinued earlier, i.e., LPFT + 72 weeks + 30 days. (Note: After the study medication period, the assigned study medication will be made available, may be outside of this study, to patients who in the opinion of the investigators are still deriving clinical benefit.)

All statistical analyses will be performed using all data collected in the database up to the respective data cut-off date. All data with an assessment date or event start date (e.g., vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.
All events with start date before or on the respective cut-off date and end date after the respective cut-off date will be reported as ongoing. The same rule will be applied to events starting before or on the respective cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.

Categorical data (e.g., gender, race, etc.) will be summarized by frequency and percentages by Cohort along with 95% Confidence interval (as appropriate); a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant Cohort as the denominator. 95% Confidence Interval for the percentages will be evaluated using Clopper-pearson method.

Continuous data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e., mean, standard deviation, median, minimum, Q1, Q3, and maximum) by Cohort [redacted] For time to event and duration, , median, 25th percentile & 75th percentile,

estimated rate by specific timepoints will be reported along with their respective 95% Confidence interval(s).

2.1.1 General definitions

Investigational drug and study medication

Investigational drug will refer to the ABL001 only. Whereas ***study medication*** will refer to ABL001 [asciminib (40 mg BID, 80 mg QD or 200 mg BID)]. Novartis is supplying asciminib to the investigational site as 20 mg and 40 mg tablets.

Treatment Cohorts

Patients without T315I mutation status are selected randomly between Cohort A (without T315I) and Cohort B (without T315I). Patients harboring the T315I mutation are allocated to Cohort C.

Without T315I mutation		**With T315I mutation**
Cohort A	Cohort B	Cohort C
40 mg BID	80 mg QD	200 mg BID

Date of first administration of study medication

The date of first administration of study medication is derived as the first date when a non-zero dose of study medication was administered as per the Dosage Administration Record (DAR) electronic case report form (eCRF). The date of first administration of study medication will also be referred as ***start of study medication***.

The date of first administration of study medication is the same as the date of first administration of investigational drug.

Date of last administration of study medication

The date of last administration of study medication is defined as the last date when a non-zero dose of study medication was administered as per the DAR eCRF.

The date of last administration of study medication is the same as the date of last administration of investigational drug.

Study day

The study day describes the day of the event or assessment date, relative to the reference start date.

- The date of the event (visit date, onset date of an event, assessment date, etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date, etc.) − reference start date if event precedes the reference start date.

The reference start date for safety assessments (e.g., adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, [redacted] etc.) is the start of study medication.

The reference start date for all other, non-safety assessments (e.g., molecular response, survival time, disease progression, ECOG performance status, [redacted] etc.) is the date of random allocation of patient to their respective Cohort.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

For "time since event" data (e.g., medical history), the duration (in days) will be calculated as treatment start date-diagnosis date.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 (=365.25/12) days. If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

A week length is defined as 7 days. If duration is reported in weeks, duration in days will be evaluated by dividing duration in weeks by 7. All the time related study endpoints will be reported in Weeks, until stated or specified.

Baseline

For safety & efficacy evaluations, the last available assessment on or before the date of start of study medication of asciminib (40 mg BID, 80 mg QD & 200 mg BID) is taken as ‘‘baseline” assessment.

For pre-dose electrocardiogram (ECG), the last available assessment before the treatment start date/time is used for baseline.

For ECGs, where study requires multiple replicates per time point, the average of these measurements would be calculated for baseline (if not already available in the database).

In rare cases where multiple laboratory measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline.

If patients have no value as defined above, the baseline result will be missing.

On-treatment assessment/event and observation periods

For adverse event, reporting the overall observation period will be divided into two mutually exclusive segments:

- ***Pre-treatment period***: from day of patient’s informed consent to the day before first administration of study medication
- ***On-treatment period***: from date of first administration of study medication to 30 days after date of last actual administration of any study medication (including start and stop date).

Note: Patients will be treated for up to LPFT + 72 weeks. This will be the last actual administration of study medication for each patient if the patient has not discontinued study medication earlier. After this period, the assigned study medication will be made available, may be outside of this study, to patients who in the opinion of the investigators are still deriving clinical benefit.

Visit window

Windows for multiple assessments

In order, to summarize molecular response, Hematologic Response, [redacted] collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If two assessments within a time window are equidistant from the target date, then the average of the two assessments will be used. If multiple assessments on the same date, then the average will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Table 2-1 Time windows for molecular response (BCR-ABL1 quantification by RQ-PCR)

Assessment	Target day of assessment	Time Interval
Baseline	≤ 1	≤ Day 1#
Week 4	29	Day 2 to day 57
Week 12	85	Day 58 to day 127
Week 24	169	Day 128 to day 211
Week 36	253	Day 212 to day 295
Week 48	337	Day 296 to day 421
Week 72	505	Day 422 to day 589

Day 1 = Date of random allocation of patients

EOT assessments are mapped to the time points as needed.

Table 2-2 Time windows for Hematologic response assessment

Assessment	Target day of assessment	Time Interval
Week 12	85	Day 2 to day 127
Week 24	169	Day 128 to day 211
Week 36	253	Day 212 to day 295
Week 48	337	Day 296 to day 421
Week 72	505	Day 422 to day 589

Day 1 = Date of random allocation of patients

EOT assessments are mapped to the time points as needed.

[redacted]

[redacted]

[redacted]

Last contact date

The last contact date will be derived for patients not known to have died at the respective analysis data cut-off date using the last complete date among the following:

Table 2-5 Last contact date data sources

Source data	Conditions
Date of random allocation	No condition
Last contact date/last date patient was known to be alive from Survival Follow-up page	Patient status is reported to be alive, lost to follow-up or unknown
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term
Start/End dates from drug administration record	Non-missing dose. Doses of 0 are allowed
End of treatment date from end of treatment page	No condition
Any specific efficacy (molecular or cytogenetic) assessment date if available	Evaluation is marked as 'done'
Laboratory/[redacted] collection dates	Sample collection marked as 'done'
Vital signs date	At least one non-missing parameter value
Performance status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the respective data cut-off date. The cut-off date will not be used for last contact date unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g., the analysis data cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date.

The last contact date will be used for censoring of patients in the analysis of overall survival.

2.2 Analysis sets

Full Analysis Set (FAS)

The Full Analysis Set (FAS) comprises all patients to whom study medication has been assigned. According to the intent to treat principle, patients will be analyzed according to the study medication and Cohort they have been assigned.

All the secondary efficacy endpoints will be analyzed using FAS.

Safety Set (SS)

The **Safety Set (SS)** includes all patients who received at least one dose of study medication. Patients will be analyzed according to the study medication (regimen) they actually received.

The primary and all safety endpoints analysis will be performed on **Safety Set**.

[redacted]

Patient Classification

Patients may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific patient classification.

During the study, major and minor protocol deviations will be identified and collected on an ongoing basis as they occur. Refer to special data handling in data management documents. The decision whether patients will be included or excluded in the appropriate analysis sets will be determined based on the severity levels of the PDs.

2.2.1 Subgroup analyses

Subgroup analyses will be performed based on the patient's baseline status:

- Age: (< 65 years; ≥ 65 years)
- Patients with resistance: (BCR-ABL ratio at baseline >10%)
- Previous treatment with Ponatinib (Yes or No)
- By number of prior TKI therapies: 2, 3, ≥4

Summary tables and figures will be generated only for subgroups with at least 5% of the total sample size of full analyses set (for efficacy endpoint) or safety set (for safety endpoint).

All primary and secondary endpoints will be analyzed and summarized within each subgroup.
Additionally, as the study is ongoing during COVID-19 pandemic, to address the impact of COVID-19 (if any) AEs, SAEs, Abnormal lab findings and notable vital signs will be summarized and reported if COVID-19 infected patient count exceeds 5% of the total sample size of safety set.

As appropriate, given the significance of the impact of COVID-19 on the enrolled patients, a sensitivity analysis may be performed on the safety and efficacy data evaluating the impact of COVID-19 on the study, if COVID-19 infected patient count exceeds 5% of the total sample size.

2.3 Patient disposition, demographics, and other baseline characteristics

2.3.1 Demographics and baseline characteristics

FAS will be used for all baseline and demographic summaries and listings unless otherwise specified. Patient demographics and baseline characteristics collected will include the following: date of birth, gender (and childbearing potential for female), race and ethnicity, height, weight, all relevant medical history including cardiovascular disease history, CML disease history, including mutation status, and prior and concomitant medication including prior TKI therapy and antineoplastic medication.

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

Summaries will be reported for all patients. No inferential statistics will be provided.

All demographic and baseline disease characteristics data will be summarized by Cohort. Categorical data (e.g., age groups: < 65, and ≥ 65 years, sex, race, ethnicity, ECOG performance status) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g., age, weight, height, body mass index) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum), where BMI (kg/m^2) will be calculated as weight[kg] / (height[m]^2) using weight at screening.

The number (%) of patients in each Cohort A, B & C ("With T315I Mutation" or "Without T315I Mutation") based on data obtained from the IRT system will be summarized based on their respective assigned cohort for all the patients in their respective analysis sets.

2.3.2 Diagnosis and extent of cancer - CML

All diagnosis and extent of CML data will be summarized by Cohort. One summary table will include time (years) since initial diagnosis (descriptive statistics with N, mean, median, standard deviation, minimum and maximum) and historical mutation (frequency counts and percentages). Another table will include extramedullary involvement (frequency counts and percentages).

2.3.3 Medical history

Significant findings that were present prior to the signing of informed consent will be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent will be recorded on the AE page of the patient's eCRF and will be summarized & listed overall and by Cohort.

Medical history and ongoing conditions, including toxicity grade entered on eCRF will be summarized and listed by Cohort. The summary will be presented by primary system organ class (SOC), preferred term (PT) and Cohort. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

In addition, separate summary tables & listings will be produced for medical history possibly contributing to pulmonary diseases, and cardiovascular events.

2.3.4 Patient disposition

All randomly allocated patients by center will be summarized for all enrolled patients by Cohort using the FAS The number (%) of enrolled patients included in the FAS will be presented overall and by Cohort. The number (%) of screened, enrolled and not - enrolled patients and the reasons for screening failure will also be displayed. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented overall and by Cohort.

The following summaries will be provided (with % based on the total number of FAS patients):

- Number (%) of patients who were enrolled (based on data from IRT system)
- Number (%) of patients who were enrolled but not treated (based on DAR eCRF page not completed for any study medication component)
- Primary reason for not being treated (based on "End of Screening Phase" and "Withdrawal of Informed Consent(s)" eCRF pages)
- Number (%) of patients who were treated (based on DAR eCRF pages of each study medication completed with non-zero dose administered)
- Number (%) of patients who completed the study medication (based on the "Completion of Treatment disposition phase" Disposition eCRF page)
- Number (%) of patients who discontinued the study medication (based on the "End of Treatment Disposition" page)
- Primary reason for study medication phase discontinuation (based on the "End of Treatment Disposition" page)
- Number (%) of patients who have entered the safety follow-up (based on the "Completed/Discontinuation of Post-Treatment follow-up" Disposition eCRF page)
- Number (%) of patients who completed the safety follow-up (based on the "Completion of Post-Treatment follow-up" Disposition eCRF page)
- Number (%) of patients who discontinued the safety follow-up (based on the "Discontinuation of post-Treatment follow-up" Disposition eCRF page)
- Primary reason for safety follow-up discontinuation (based on the "Discontinuation of post-Treatment follow-up" Disposition eCRF page)

Safety follow-up will not be reported in the disposition summary for primary analyses timepoint (24 weeks).

2.3.5 Protocol deviations

The number (%) of patients in all the analysis sets with CSR reportable protocol deviations will be tabulated by deviation category (as specified in the Study Specification Document) overall and by Cohort. All CSR reportable protocol deviations will be listed.

2.4 Treatments (study medication, rescue medication, concomitant therapies, compliance)

2.4.1 Duration of exposure to study medication

The safety set (SS) will be used for all summaries of study medication.

The duration of exposure will be summarized for each study cohort A, B and C. 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 for each study cohort by descriptive statistics.

- The number of participants will be summarized for SS by study cohort.
- The number (%) of patients who have dose reductions or interruptions, and the reasons, will be summarized by cohort.
- Patient level listings of all doses administered on medication along with dose change reasons will be produced.
- Duration of exposure to study medication is considered by taking into account the duration of exposure of non-zero doses to the investigational drug or control.
- Time on treatment(weeks) = [(date of last administration of study medication) – (date of first administration of study medication) – (days with zero dose) + 1] / 7.
- Duration of exposure to study treatment (weeks) = [(date of last administration of study medication) – (date of first administration of study medication) + 1] / 7.
- The date of last administration of study medication is defined in Section 2.1.1.
- Summary of duration of exposure of study medication will include categorical summaries based on intervals (<24 weeks, ≥24 weeks and < 48 weeks, ≥48 weeks and < 72 weeks, >=72 weeks) and continuous summaries (i.e., mean, standard deviation etc.).

Cumulative dose

Cumulative dose of a study medication is defined as the total dose given during the study medication exposure.

The **planned cumulative dose** for a study medication refers to the total planned dose as per the protocol up to the last date of study medication administration. The calculations for the three separate doses of study medication are:

- Cohort A (ABL001): 40 mg/administration × 2 (administration/day) × duration of exposure (days)
- Cohort B (ABL001): 80 mg/administration × 1 (administration/day) × duration of exposure (days)
- Cohort C (ABL001): 200 mg/administration × 2 (administration/day) × duration of exposure (days)

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the patient is on the study medication as documented in the DAR eCRF. It is the sum of the non-zero total daily doses recorded over the dosing period. For patients who did not take any drug the actual cumulative dose is by definition equal to zero. The actual cumulative dose will be summarized for each of the Cohort.

Dose intensity and relative dose intensity

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows: DI (mg/day) = Actual cumulative dose (mg) / Duration of exposure to study treatment(days).

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as:

PDI (mg/day) = Planned cumulative dose (mg) / Duration of exposure to study treatment(days).

Relative dose intensity (RDI (%)) is defined as follows:

RDI (%) = [DI (mg/day) / PDI (mg/day)]*100.

DI and RDI (%) will be summarized separately for all the three study Cohorts.

Dose changes, interruptions or permanent discontinuations

The number of patients, who have dose reductions, dose interruptions or permanent discontinuations, and the reasons, will be summarized separately for all the three study cohorts.

'Dose Reduced', 'Dose Interrupted' and 'Dose Permanently Discontinued' fields from the DAR eCRF pages will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

The corresponding fields, 'Reason for Dose Reduction', 'Reason for Dose Interruption and 'Reason for Permanent Discontinuation' will be used to summarize the reasons.

A dose change occurs when total daily dose is different from the most recently planned dose. For patients in Cohort A, there is only one planned dose, i.e., 40 mg b.i.d. For patients in Cohort B, there is only one planned dose, i.e., 80 mg/day QD. For patients in Cohort C, the initial planned dose is 200 mg b.i.d i.e., 400 mg/day.

For summarizing interruptions and reasons, multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in the mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Reduction: A dose reduction is where the actual total daily dose is lower than the most recently planned dose. Therefore, any dose reduction to correct a dosing error will not be considered a dose reduction. Only dose reduction is collected in the eCRF and will be summarized for the patient's data available.

2.4.2 Prior, concomitant and post therapies/medication

Prior antineoplastic therapy/medications

The number and percentage of patients who received any prior anti-neoplastic therapy /medications will be summarized by cohort and also for the lowest anatomical therapeutic classification (ATC) class and preferred term. Summaries will include total number of regimens.

Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD). Details regarding WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the SS.

Post treatment anti-neoplastic therapy/medication

The number and percentage of patients who received any anti-neoplastic medication and/or therapy since discontinuation of study medication will be summarized by cohort for setting (e.g., adjuvant, metastatic, etc.) and for the lowest anatomical therapeutic classification (ATC) class and preferred term. Summaries will include total number of regimens, reason for initiation of new therapy, indication, route of administration and reason for discontinuation of therapy.

Anti-neoplastic medications will be coded using the WHO-DD. Details regarding WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the SS.

Prior and Concomitant therapies/Medications

Prior and Concomitant therapies/medications are defined as all interventions (therapeutic treatments and procedures) other than the study medication administered to a patient coinciding with the study medication period. Prior therapies include medications (other than study drugs) and medical procedures started and ended prior to the start date of study medication. Concomitant therapies include medications (other than study drugs) and medical procedures starting on or after the start date of study medication but no later than 30 days after last dose of study medication or starting prior to the start date of study medication and continuing after the start date of study medication.

Prior and Concomitant therapies/medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO ATC classification system and summarized by the lowest ATC class and PT using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and PT. These summaries will include:

- Prior therapies/medications started and ended prior to the start date of study medication.
- Concomitant therapies/medications:

1. Therapies/medications starting on or after the start of study medication but no later than 30 days after last dose of study medication and
2. Therapies/medications starting prior to start of study medication and continuing after the start of study medication.

All prior & concomitant therapies/medications will be listed. Any concomitant therapies/medications starting and ending prior to the start of study medication or starting more than 30 days after the last date of study medication will be flagged in the listing. The safety set will be used for all concomitant therapies/medications' tables and listings.

2.5 Analysis of the primary objective

The primary objective is to evaluate safety profile of monotherapy asciminib in CML-CP in 3L and beyond for Cohorts A, and B. For all primary safety analyses, the Safety Set (SS) will be used, unless stated otherwise.

The variables for the primary analysis are incidence and severity of AEs and SAEs, changes in laboratory values and vital signs, incidence of notable ECG abnormalities.

2.5.1 Primary endpoint

The primary endpoint is to evaluate the safety profile of monotherapy asciminib (ABL001) with AEs, SAEs and laboratory studies' assessment during 24 weeks of therapy in CML-CP patients, for Cohorts A and B i.e., without T315I mutation status. All safety analyses will be based on the safety set (SS).

AE summaries will include all AEs occurring during on-treatment period. All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g., AE relationship to study drug, AE outcome, etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables. Abnormal lab findings, vital signs and notable ECG abnormalities will also be summarized by cohort as explained in Safety analysis section 2.6.

2.5.2 Statistical hypothesis, model, and method of analysis

No formal hypothesis testing is planned for this study.

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

2.5.3 Handling of missing values

Missing data for measures of safety will not be imputed.

2.6 Safety analyses

All safety analyses will be based on the safety set (SS). All listings and tables will be presented by Cohort.

2.6.1 Adverse events (AEs)

All the adverse events reported after administration of study drug to 30 days after the last date of drug to the patient are known as treatment emergent adverse events (TEAEs).

The summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs). In addition, a separate summary for death including on-treatment deaths will be provided. All AE will be listed and those collected during the on-treatment period (TEAE) will be flagged.

TEAEs will be summarized by number and percentage of patients having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. TEAE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In TEAE summaries, the primary system organ class will be presented alphabetically, and the preferred terms will be sorted within primary SOC in descending frequency. The sorting order for the preferred term will be based on their frequency in the ABL001 arm Cohort A.

The following treatment emergent adverse event summaries will be produced by Cohort:

- Overview of TEAEs and deaths

- TEAEs by SOC and PT
- Summary by relationship
- Seriousness
- Leading to treatment discontinuation
- Leading to dose interruption/adjustment
- Requiring additional therapy and leading to fatal outcome

  For posting to ClinTrial.gov and EudraCT, a summary table of on-treatment deaths and serious AEs and another summary table of non-serious AEs by treatment, both including occurrences (an occurrence is defined as >1 day between start and prior end date of record of same preferred term) and sorted by SOC and PT, will be presented as well.

All the adverse events will be graphically displayed by Cohorts using bar chart.

2.6.2 Adverse events of special interest / grouping of AEs

Data analysis of AESIs

An adverse event of special interest (AESI) are defined as adverse events (serious or non-serious) which are of scientific and medical concern specific to compound ABL001 as mentioned in Table 5-5. For which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. The latest approved version of CRS prior to the respective database lock will be used.

For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during the on-treatment period will be summarized.

Summaries of these AESIs will be provided by cohort. If sufficient number of events occurred, analysis of time to first occurrence will be applied.

A listing of all grouping levels down to the MedDRA PTs used to define each AESI will be generated.

2.6.3 Deaths

Separate summaries for on-treatment / TEAE and all deaths will be produced by system organ class and preferred term, by cohort.

All deaths will be listed, where on treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened patients.

2.6.4 Laboratory data

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. Details of CTCAE grading and imputation rules are presented in Appendix 5.3.

For laboratory tests where grades are not defined by CTCAE v5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

On analyzing laboratory, data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the laboratory parameter collected no later than 30 days after the last study medication administration date.

The following summaries will be produced separately for hematology and biochemistry laboratory data (by laboratory parameter and cohort):

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only for the worst grade observed post-baseline in the on-treatment period.
- Shift tables to compare baseline CTCAE grades to the worst on-treatment grade for laboratory tests where grades are not defined by CTCAE v5.0
- Shift tables using the low/normal/high/ (low and high) (or project specific) classification to compare baseline to the worst on-treatment value.
- Newly or worsening laboratory abnormalities will be summarized, separately.

The following listings will be produced separately for hematology and biochemistry for the laboratory data:

- Listings of all laboratory data, with corresponding CTCAE grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period with corresponding CTCAE v5 grades will be flagged.
- Listing of all CTCAE grade 3 or 4 laboratory toxicities
- Box plot(s) for all laboratory parameters over time will be plotted and displayed by Cohort.

2.6.5 Other safety data

2.6.5.1 ECG and cardiac imaging data

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

Absolute values/change from baseline will be summarized over time. As appropriate, the number and percent of patients will be tabulated by category. In addition, a listing of patients with at least one notable ECG value will be produced.

Data handling

The average of the triplicate ECG parameters at each time point will be used in the analyses.

Data analysis

The number and percentage of patients with notable ECG values will be presented by Cohort. Notable values are defined below:

- QT, QTcF
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm

- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

A listing of only the patients with notable ECG values will be produced. In the listing the assessments collected during the on-treatment period will be flagged.

2.6.5.2 Vital signs

Data on vital signs will be tabulated and summarized descriptively as follows:

- Number and percentage of patients who shift from non-notable at baseline to notable post- baseline. Also, bar chart with 95% CI will be presented for the notable changes.

The number and percentage of patients with notable vital sign values (high/low) in systolic blood pressure, diastolic blood pressure, pulse rate, weight and temperature will be presented by Cohort.

A listing of notable vital sign values will be produced. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.6.5.3 Cardiovascular and Pulmonary risk factor assessment

Prior to random allocation of patients to cohort and at the end of treatment, cardiovascular risk factors collected will be listed by cohort.

Prior to random allocation of patients to cohort and at Week 20, pulmonary function tests including assessment of the lung volumes FEV1, FVC, FEV1/FVC, TLC, VC and DLCO will be performed, if clinically indicated. A listing will be presented by cohort.

[redacted]

2.7 Analysis of the key secondary objective

Not applicable

2.8 Analysis of the secondary objective(s)

The secondary objective(s) of the study are:

- To estimate the rate of hematologic and molecular responses at specific time points for
- Cohort A, B and C
- Rate of CHR, MR2, MMR, MR4, MR4.5 in 12, 24, 48, 72 weeks of therapy
- To estimate time to hematologic and molecular response
- Time to CHR, MR2, MR4, MR4.5 in 12, 24, 48, 72 weeks of therapy

- To evaluate the duration of hematologic and molecular response
- Duration of MR1, MR2, MMR, MR4 and MR4.5
- To evaluate Progression Free Survival (PFS)
- To evaluate Overall Survival (OS)

2.8.1 Secondary safety endpoints

The secondary safety endpoints are:

- AEs, SAEs and laboratory evaluation for Cohort A, Cohort B and Cohort C, by 48, 72 weeks

All secondary safety analysis will be performed similar to the above primary safety analysis using Safety set (SS) by 48, 72 weeks. Additionally, a separate safety summary up to 24 weeks will be provided for Cohort C.

2.8.2 Secondary efficacy endpoints

The secondary efficacy endpoints are:

- Rate of CHR, MR2, MMR, by 12, 24, 48, 72 weeks of therapy
- Rate of MR4, MR4.5 by 24, 48, 72 weeks of therapy
- Time to CHR**,** MR2, MMR, MR4, MR4.5
- Duration of CHR, MR2, MMR, MR4 and MR4.5
- PFS during 24, 48 and 72 weeks
- OS during 24, 48 and 72 weeks

For all secondary efficacy analyses, the Full Analysis Set (FAS) will be used, unless stated otherwise.

For secondary efficacy analysis, proportion of patients achieving the response levels will be presented together with an exact 95% Clopper-Pearson confidence interval. For time to event and duration, PFS & OS, median, 25th percentile & 75th percentile will be reported along with their respective 95% Confidence Interval.

Rate of CHR, MR2, MMR, by 12, 24, 48, 72 weeks of therapy and Rate of MR4 & MR4.5 by 24, 48, 72 weeks of therapy

- The rate of **Complete Hematologic Response (CHR)** by 12, 24, 48 and 72 weeks. **CHR** is defined as all of the following present for ≥ 4 weeks:
  - WBC count < 10 x 10^9/L
  - Platelet count < 450 x 10^9/L
  - Basophils < 5%
  - No blasts and promyelocytes in peripheral blood
  - Myelocytes + metamyelocytes < 5% in peripheral blood
  - No evidence of extramedullary disease, including spleen and liver

- The rate of **molecular response (MR2)** by 12, 24, 48 and 72 weeks after the start of first study medication. **MR2** is defined as ≥ 2 log reduction of BCR-ABL transcript from standardized baseline or ≤ 1% BCR-ABL/ABL % by international scale, measured by real-time quantitative PCR (RQ-PCR).

• The rate of **major molecular response (MMR)** by 12, 24, 48 and 72 weeks after the start of first study medication. MMR is defined as ≥ 3 log reduction of BCR-ABL transcript from standardized baseline or ≤ 0.1% BCR-ABL/ABL % by international scale, measured by real-time quantitative PCR (RQ-PCR).

• The rate of **molecular response (MR4)** by 24, 48 and 72 weeks after the start of first study medication. **MR4** is defined as ≥ 4 log reduction of BCR-ABL transcript from standardized baseline or ≤ 0.01% BCR-ABL/ABL % by international scale, measured by real-time quantitative PCR (RQ-PCR).

• The rate of the **molecular response (MR4.5)** by 24, 48 and 72 weeks after the start of first study medication. **MR4.5** is defined as ≥ 4.5 log reduction of BCR-ABL transcript from standardized baseline or ≤ 0.0032% BCR-ABL/ABL % by international scale, measured by real-time quantitative PCR (RQ-PCR).

For rate of MR2, MMR, MR4, MR4.5 by any pre-specified time point patients will be consider as responder if he/she achieve the particular response at least once by the specific timepoint. If patient discontinuing the treatment prior to a specific time point due to any reason and not achieved the particular response before the discontinuation will be considered as non-responder.

For each time point, the proportion of patients achieving the specific response levels will be presented together with an exact 95% Clopper-Pearson confidence interval by cohort. The rates over time will be displayed graphically using the Bar Charts with 95% C.I. as whiskers.

Note: Patient(s) who have reported for molecular response(s) at baseline will not be included in time to event analyses.

Time to CHR, MR2, MR4, MR4.5 in 72 weeks of therapy

Time to achieving a response level is defined as the time from the date of the first dose of study medication to the first documented achievement of a response level.
Time to achieve a specific response level will be analyzed using the Kaplan-Meier Product- Limit method. Patients who are known to be without achieving that response level will be censored at the last molecular & hematologic assessment.
The estimated cumulative incidence rates and 95% confidence intervals at 12, 24, 48 and 72 weeks will be presented. The cumulative incidence curve will be plotted. , if applicable. The analyses will be performed using FAS by cohort.

For patients in the FAS who have not experienced any molecular and/or hematologic response, the time will be censored as follows in the Kaplan-Meier analysis:

- If a patient does not achieve the specified response before the cut-off date for the analysis, censoring time will be the last molecular assessment (PCR) date on treatment prior to the cut-off date or the EoT visit, whichever comes first.
- If a patient discontinues study treatment prior to achieving a response for a reason other than disease progression or death, then the patient will be censored at the last molecular assessment (PCR) date on treatment prior to the cut-off date or the EoT visit, whichever comes first.

- If a patient discontinues study treatment prior to achieving a response due to progression or death, then the censoring time will be set to the longest follow-up time in the treatment group, that is, consider the response is impossible to reach.
  In case no on-treatment response assessment was performed, the patient will be censored at day 1.

Duration of CHR, MR2, MMR, MR4 and MR4.5

Duration of Response (DOR) is the time from the date of the first documented molecular (MR2, MMR, MR4, MR4.5) or Hematologic (CHR) response to the date of first documented loss of that response or death due to any cause or progression to AP/BC, whichever occurs first.

The start date is the date of first documented response and the end date is defined as the date of the first documented loss of that response or death due to any cause or progression to AP/BC. Participants continuing without that event will be censored at the date of their last adequate molecular of hematologic response assessment.

DOR for each response level will be analyzed using the Kaplan-Meier Product-Limit method.

Estimates of DOR at specific timepoint and the 25th, median and 75th percentile of the DOR and their 95% confidence intervals will be provided, if applicable.

2.8.1.1 Other secondary efficacy endpoints

Progression-Free-Survival (PFS) is defined as time from the first dose of study medication to disease progression to AP/BC or death due to any cause, whichever occurs first during 24,48 and 72 weeks.

For patients without progression, the patient will be censored at the last molecular assessment date the patient was known to be alive and without progression (on or before the cut-off date).

PFS will be analyzed using the Kaplan-Meier Product-Limit method. Patients who do not progress will be censored at the last adequate assessment. Estimates of the 25th, median and 75th percentile of the PFS and their 95% confidence intervals will be provided, if applicable.

Overall survival (OS) is defined as the time from the first dose of study medication to death due to any cause during 24, 48 weeks and 72 weeks during study.

If a patient is not known to have died, then OS will be censored at the latest date the patient was known to be alive (on or before the cut-off date). All deaths will be taken into account whatever the death occurred, i.e., even after interruptions, or discontinuation of study medication due to any reason.

OS will be analyzed using the Kaplan-Meier Product-Limit method. Patients who do not progress will be censored at the last adequate assessment. Estimates of the 25th, median and 75th percentile of the OS and their 95% confidence intervals will be provided, if applicable.

2.8.3 Handling of missing values/censoring/discontinuations

MMR rates by specific time points:

Patients without any documented response for which an evaluable response assessment was never provided will be considered as non-responders for the period of time up to that time point.

Molecular response category by specific time points: The category "Missing" will be assigned to patients for whom an evaluable response assessment was never provided.

Time to MMR: For patients in the FAS who have not experienced any MMR, the time will be censored as follows in the Kaplan-Meier analysis:

If a patient does not achieve the specified response before the cut-off date for the analysis, censoring time will be the last molecular assessment (PCR) date on treatment prior to the cut-off date or the EoT visit, whichever comes first.

If a patient discontinues study treatment prior to achieving a response for a reason other than disease progression or death, then the patient will be censored at the last molecular assessment (PCR) date on treatment prior to the cut-off date or the EoT visit, whichever comes first.

If a patient discontinues study treatment prior to achieving a response due to progression or death, then the censoring time will be set to the longest follow-up time in the treatment group, that is, consider the response is impossible to reach.

In case no on-treatment response assessment was performed, the patient will be censored at day 1.

Duration of MMR: For patients who have not experienced any event (loss of MMR, progression to AP/BC, or CML-related death), the duration will be censored at the last molecular assessment (PCR) date on treatment.

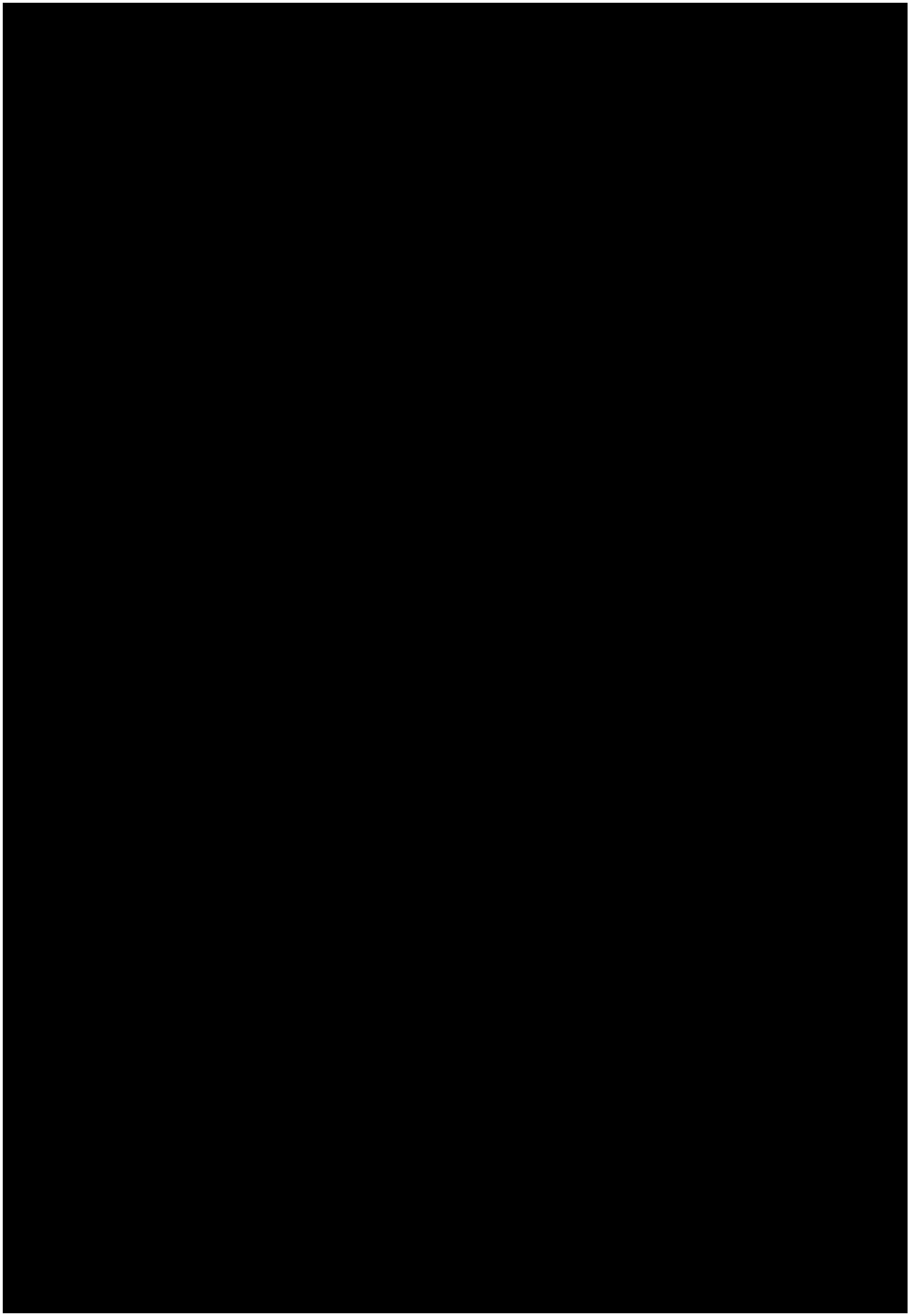
PFS: For patients who have not experienced protocol defined event (disease progression to AP/BC or death from any cause), the patients will be censored at the date of last study assessment (PCR, cytogenetic, hematologic or extramedullary) before the cut-off date.

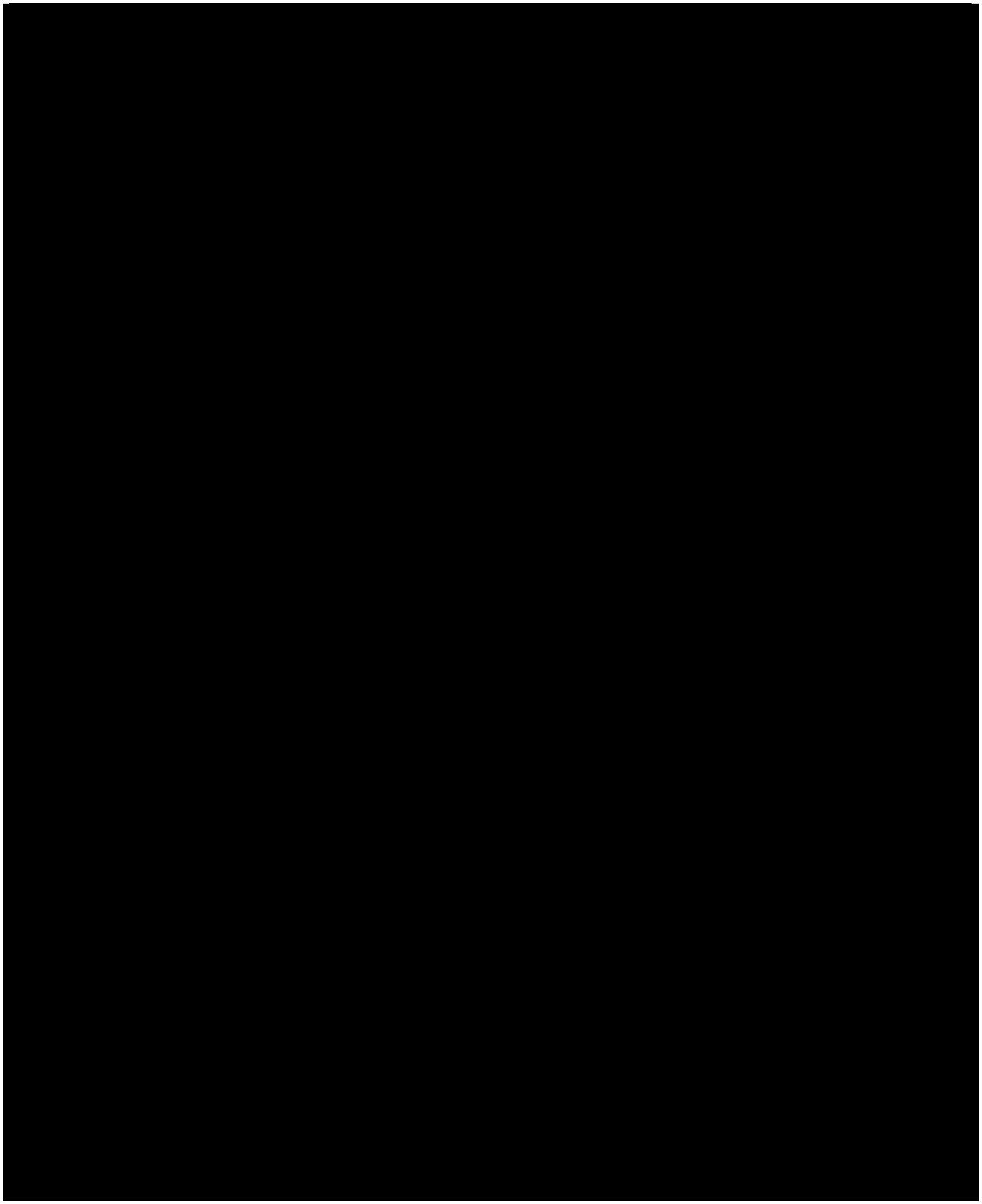
OS: Patients who are alive at the time of the analysis data cutoff date will be censored at the date of last contact (see Section 2.1.1) before the cut-off date.

2.8.4 Statistical hypothesis, model, and method of analysis

There is no formal hypothesis to test in this study.

[redacted]





2.10 Interim analysis

As the primary time point is by 24 weeks, the primary analysis will be an interim analysis. The primary analysis will be performed when the last patient completes 24 weeks of treatment or discontinues early.

As appropriate, annual interim analyses will be planned for publication or any regulatory purpose. No formal interim analysis will be performed. Only summary statistics will be provided.

Final Analysis will be performed when the last patient completes 72 weeks or discontinues early. A final CSR will be written.

3 Sample size calculation

This is an open label, three-cohort study to assess safety and efficacy of study of asciminib (ABL001) monotherapy in patients with chronic myeloid leukemia in chronic phase (CML-CP) previously treated with at least 2 prior TKIs (tyrosine kinase inhibitors) and CML-CP patients harboring the T315I mutation previously treated with at least 1 prior TKIs.

For all CML-CP with the exception of those harboring the T315I mutation, there will be random allocation of patients to eliminate selection bias at the time of cohort allocation. Those patients will be assigned to either Cohort A consisting of asciminib 40 mg BID patients or Cohort B consisting of asciminib 80 mg QD. For CML-CP patients harboring the T315I mutation, they will be assigned to Cohort C with asciminib 200 mg BID, which is the dose required for that patient population. It is worthwhile mentioning that random allocation of patients in cohorts A and B will be pursued for patient selection only. The study is not powered to show differences in Primary and Secondary endpoints between study cohorts.

Primary objective of the study is to assess safety profile of this combination drug during 24 weeks for all cohort patients.

A sample size of 40 evaluable patients for Cohort A is estimated based on a two- sided 95% confidence interval for an incidence rate of an AE using the large sample normal approximation that will extend 0.12 from the observed incidence rate of an AE (precision or margin of error of 12%) for an expected incidence rate of 18%. Considering drop-out rate of 10%, approximately 45 patients will be enrolled for safety assessment for the Cohort A of this study.

Retaining the same assumptions, approximately 45 patients will also be enrolled for Cohort B. Additionally for Cohort C, approximately 25 patients will be enrolled.

Thus, approximately total 115 (45+45+25=115) patients will be enrolled for Cohort A (n1=45) and Cohort B (n2=45) and for Cohort C (n3=25) of the study.

4 Change to protocol specified analyses

No change to the protocol specified analysis has been made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rules should be used for the imputation of the dose end date for a given study medication component.

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

- Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.
- Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:
  Use Dec31yyyy
- Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:
  Use EOT date
- Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date:
  Use last day of the Month (mm)
- All other cases should be considered as a data issue and the statistician should contact the data manager of the study.
- After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:
- Use the treatment start date

Patients with missing start dates are to be considered missing for all study medication component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE, ConMeds and safety assessment date imputation

The imputations specified in this section are only used for analyses of time to and duration of AEs and concomitant medications.

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates
day, month	• If available year = year of study medication study medication start date then o If stop date contains a full date and stop date is earlier than study medication study medication start date then set start date = 01JanYYYY o Else set start date = study medication study medication start date. • If available year > year of study medication study medication start date then 01JanYYYY • If available year < year of study medication study medication start date then 01JulYYYY
Day	• If available month and year = month and year of study medication study medication start date then o If stop date contains a full date and stop date is earlier than study medication study medication start date then set start date= 01MONYYYY. o Else set start date = study medication study medication start date. • If available month and year > month and year of study medication study medication start date then 01MONYYYY • If available month and year < month year of study medication study medication start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
Day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as ‘ongoing’ rather than the end date provided.

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer

Completely missing dates will not be imputed. Partial dates of diagnosis will be compared to the treatment start date.

- If DIAG year < study treatment start date year and DIAG month is missing, the imputed DIAG date is set to the mid-year point (01JULYYYY).
- Else if DIAG month is not missing, the imputed DIAG date is set to the mid-month point(15MONYYYY).
- If DIAG year = study treatment start date year and (DIAG month is missing OR DIAG month is equal to study treatment start month), the imputed DIAG date is set to one day before study treatment start date.

5.2 AEs coding/grading

Adverse events are coded using the latest available version of Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters (embedded below). The latest available version of the document based on the underlying CTCAE version v5.0 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE v5.0, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and

high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

EASE LAB - CTC grades in Novartis Or

Imputation Rules

CTCAE grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of white blood cells (WBC).

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

The following rules will be applied to derive the WBC differential percentages when only differential counts are available for a xxx differential

xxx %value = (xxx count × 100) / WBC count

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1 and calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTCAE grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTCAE grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

5.3.1 Derivation of PCR results and loss of response(s)

Scaling towards an international standard will be performed for all molecular results using laboratory specific conversion factors. In this process, the raw ratio between BCR-ABL and the control gene ABL is calculated and multiplied by the lab -specific conversion factor ([Branford and Hughes 2006]). Therefore, using the international unit, the BCR-ABL ratio will be presented in %. The MRDx assay using PAXgene ^{TM} Blood RNA tubes from MMD laboratory will be used in this study. The lab conversion factor for this assay is 1.1.

The BCR-ABL ratio in IS % is calculated by multiplying the raw BCR-ABL ratio with the lab-specific conversion factor and then by 100:

BCR-ABL ratio (in %) = (BCR-ABL / ABL) * conversion factor * 100

For consistency with elsewhere reported molecular response rates, the result may be expressed also as log-reduction. This is defined as the following:

BCR-ABL Log-Reduction = $-\log_{10}$ (BCR-ABL ratio in %)

For example, $-\log_{10}(0.001) = 3$ log reduction for a ratio of0.1%.

The following binary variables will be used when molecular response is reported.

Table 5-3 Response categories for molecular response

MR (Molecular Response)		BCR-ABL ratio (%)	Log-reduction category
MMR	Yes	≤ 0.1%	≥ 3-log reduction
	No	> 0.1%	< 3-log reduction
MR2	Yes	≤ 1%	≥ 2 log reduction
	No	> 1%	< 2 log reduction
MR4	Yes	≤ 0.01%	≥ 4 log reduction
	No	> 0.01%	< 4 log reduction
MR4.5	Yes	≤ 0.0032%	≥ 4.5-log reduction
	No	> 0.0032%	< 4.5-log reduction

Loss of Responses

Loss of MR2 is defined as increase of BCR-ABL/ABL to > 1% by international scale (IS). BCR-ABL less than 1% according to the IS can be regarded as an equivalent to CCyR. Loss of MR2 must be confirmed by subsequent sample analysis within 4 to 6 weeks.

Loss of MMR is defined as increase of BCR-ABL/ABL to > 0.1% by international scale (IS) in association with a ≥ 5-fold rise in BCR-ABL from the lowest value achieved on study treatment and replicated by a second analysis of the same sample. Loss of MMR must be confirmed by subsequent sample analysis within 4 to 6 weeks showing loss of MMR associated with a ≥ 5-fold rise in BCR-ABL from the lowest value achieved on study treatment, unless it is associated with confirmed loss of CHR to AP/BC or CML-related death.

5.4 Listing of AESIs

All the adverse event of special interest (AESI) that are of scientific and medical concern specific to compound ABL001, collected from previous trials are mentioned below with Preferred Term (PT) and system Organ Class (SOC) in Table 5-5.

Table 5-4 List of AESIs reported for ABL001(Asciminib)

Preferred Tem	**System Organ Class**
Pancreatic toxicity	Gastrointestinal disorders
Hemorrhage	Vascular disorders
Edema and fluid retention	General disorders and administration site conditions
Hepatotoxicity (including laboratory terms)	Hepatobiliary disorders
Myelosuppression (Leucopenia)	Blood and lymphatic system disorders
Hypersensitivity	Immune system disorders
Hepatotoxicity (clinical events)	Hepatobiliary disorders
GI toxicity	Gastrointestinal disorders
Pancreatic toxicity (clinical events)	Gastrointestinal disorders
Myelosuppression (Thrombocytopenia)	Blood and lymphatic system disorders
Hepatotoxicity (including laboratory terms)	Hepatobiliary disorders
QTc prolongation	Cardiac disorders
Ischemic heart and CNS conditions	Vascular disorders
Hepatotoxicity (including laboratory terms)	Hepatobiliary disorders
Hepatotoxicity (including laboratory terms)	Hepatobiliary disorders
Cardiac failure (clinical events)	Cardiac disorders
Phototoxicity	Skin and subcutaneous tissue disorders
Myelosuppression (cytopenias affecting more than one lineage)	Blood and lymphatic system disorders
Myelosuppression (Erythropenia)	Blood and lymphatic system disorders
Ischemic heart and CNS conditions	Vascular disorders
Reproductive toxicity	Reproductive system and breast disorders
Hepatitis B virus reactivation	Infections and infestations
Hepatotoxicity (clinical events)	Hepatobiliary disorders

6 Reference

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