NOVARTIS

Clinical Development

ABL001/Asciminib/ Scemblix®

CABL001J12302 / NCT05456191

A phase IIIb, multi-center, open-label, randomized study of tolerability and efficacy of oral asciminib versus nilotinib in patients with newly diagnosed Philadelphia Chromosome Positive Chronic Myelogenous Leukemia in Chronic Phase

Statistical Analysis Plan (SAP)

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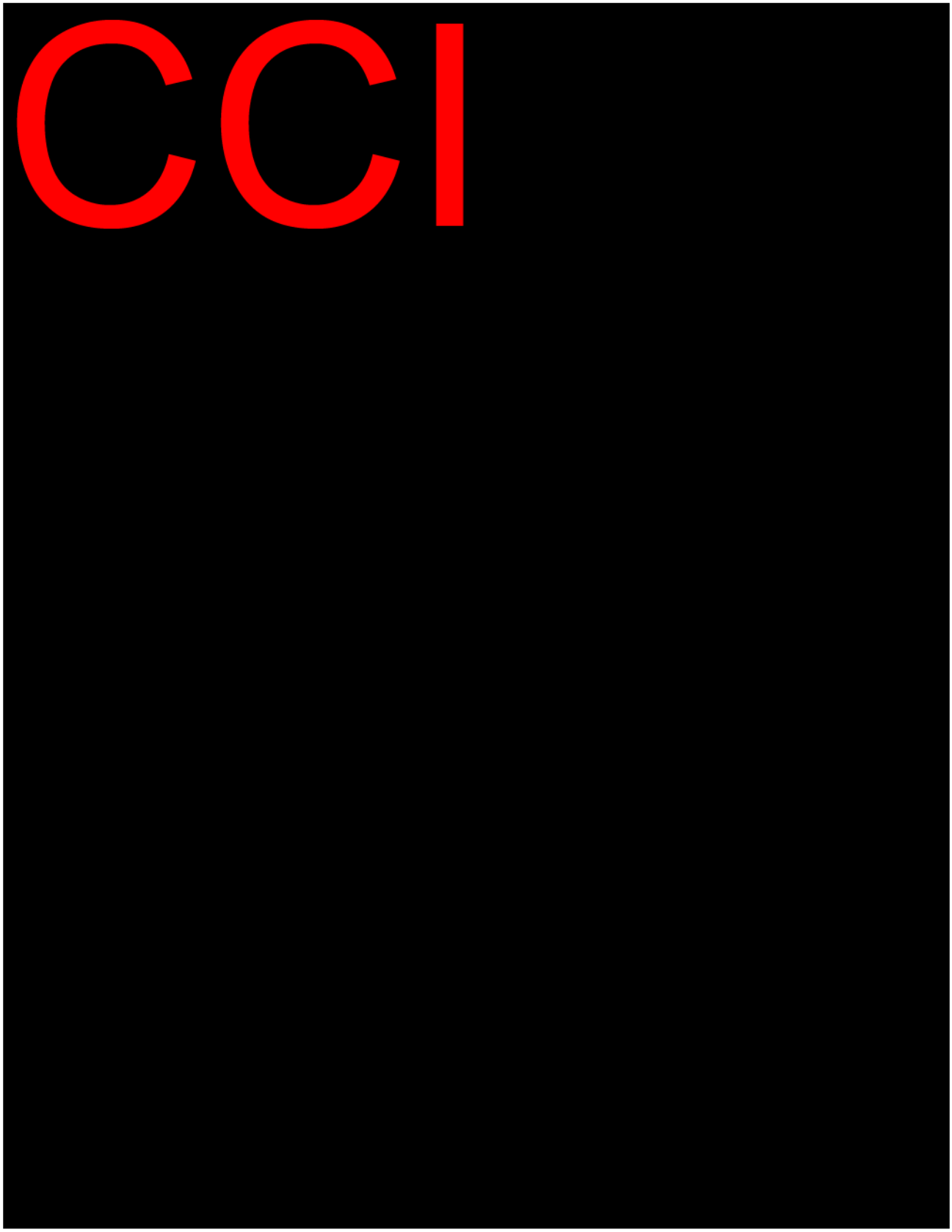
05-Jan-2024	Prior to iDBL	Protocol amendment 1	Amendment 1	Details are described below
03-Oct-2024	Prior to iDBL	Protocol amendment 2	Amendment 2	Details are described below
06-June-2025	Prior to PA DBL	Primary week 48 analysis DCO update	Amendment 3	Details are described below

Amendment 1

The main reason for this SAP Amendment 1 is to add one formal interim analysis to allow for an early assessment of the tolerability of asciminib. The changes and sections impacted (all changes can be found in the tracked version of this document):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Amendment 2

Amendment 3

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List of abbreviations

2G	Second Generation
ADD	Average Daily Dose
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AP	Accelerated Phase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BC	Blast Crisis
BCR::ABL	BCR::ABL fusion gene (also called the Philadelphia chromosome)
BID	Twice A Day
BMI	Body Mass Index
BP	Blood Pressure
CBC	Complete blood count
CCI	Charlson Comorbidity Index
CCyR	Complete Cytogenetic Response
CHR	Complete Hematological Response
CIF	Cumulative Incidence Function
ConMeds	Concomitant Medications
CRF	Case Report Form
CRS	Case Retrieval Strategy
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular disease
DAR	Drug Administration Record
DBL	Data Base Lock
DI	Dose Intensity
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
DMS	Document Management System
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELN	European Leukemia Network
ELTS	EUTOS long-term survival
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
FD	First Dose or First Administration of A Randomized Study Treatment
CCI	[redacted]
HLGTs	High Level Group Terms
HLT	High Level Terms

HRQoL	Health-related Quality of Life
IA	Interim Analyses
ICF	Informed Consent Form
IE	Intercurrent Events
IS	International Scale
LD	Last Dose or Last Administration of A Randomized Study Treatment
LPFT	Last Patient First Treatment
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMR	Major Molecular Response
NCI	National Cancer Institute
NMQ	Novartis MedDRA Queries
OS	Overall Survival
PDI	Planned Dose Intensity
PFS	Progression Free Survival
Ph+CML-CP	Philadelphia Chromosome Positive Chronic Myelogenous Leukemia in Chronic Phase
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcome
PT	Preferred Term
QD	Once A Day
QoL	Quality of Life
RAP	Reporting & Analysis Process
RDI	Relative Dose Intensity
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SMQs	Standardized MedDRA Queries
SOC	System Organ Class
TBL	Total Bilirubin
TFLs	Tables, Figures, Listings
TTD	Time to Discontinuation
TTDAE	Time to Discontinuation of Study Treatment Due to Adverse Event
TTF	Time to Treatment Failure
ULN	Upper Limit of Norm
WBC	White Blood Cell
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary
WoC	Withdrawal of Informed Consent

1 Introduction

This Statistical Analysis Plan (SAP) describes the planned primary analyses for the primary objectives, the secondary objectives, and exploratory objectives as defined in the amended protocol CABL001J12302 Clinical Study Protocol (CSP) version 01. These analyses have been defined prior to the randomization of the first participant in the study and more details are added to clarify the analysis methods in this amendment. In addition, one formal interim analysis was added to the CABL001J12302 CSP version 01, and the analyses data will be provided in a CSR and other reports as needed. This SAP amendment 2 provides more details on endpoints and analysis methods.

The data output shells accompanying this document will be in the Tables, Figures and Listings (TFL) shells document, and the specifications for derived variables and datasets will be in the Programming Datasets Specifications (PDS) document.

The SAP, TFL shells and PDS documents may also serve as a reference for the creation of any output required outside the CSR, e.g. abstracts, posters, presentations and manuscripts. Data used for these analyses will have a status aligned to the database lock guidance.

All changes to the planned analyses described in this document required before or after database lock will be made through an amendment or addendum, respectively.

1.1 Study design

Study CABL001J12302 is a phase IIIb, multi-center, open-label, randomized study of tolerability and efficacy of oral asciminib versus nilotinib in subjects with newly diagnosed Philadelphia Chromosome Positive Chronic Myelogenous Leukemia in Chronic Phase (Ph+CML-CP). The two treatment arms are:

- Investigational treatment arm: oral asciminib 80 mg QD,
- Comparator treatment arm: oral nilotinib 300 mg BID.

Unless otherwise specified, in this document asciminib refers to asciminib starting dose 80 mg QD and nilotinib refers to nilotinib starting dose 300 mg BID. Nilotinib is a second generation (2G) TKI.

It is planned that 550 participants are to be randomized in 1:1 ratio to the two treatment arms. The final number of randomized participants may be smaller or larger than 550 depending on when the targeted number CCI of discontinuations of study treatment due to adverse event (the event of interest) will occur. The participants are stratified at randomization based on the EUTOS long-term survival (ELTS) score (low, intermediate, or high). The IRT system allocates participants equally to the treatment arms within a stratum.

Participants continuously receive the assigned treatment until approximately CCI discontinuations of either study treatment due to adverse event are reached in the study. At the time when this event criteria is met, participants who have completed treatment but have not had a safety follow up performed or their post-treatment patient reported outcomes (PROs) collected, should complete these assessments. For participants in survival follow-up at the time

the event criteria is met, survival follow-up should be collected until the end of study. End of study (EOS) is defined as when approximately CCI discontinuations of either study treatment due to adverse event have been reached and when end of treatment and the last PRO assessments are completed for all participants.

The formal interim analysis will be performed when approximately CCI discontinuations of either study treatment due to adverse event occur, and the primary analysis will be performed when approximately CCI discontinuations of either study treatment due to adverse event occur.

1.2 Study objectives, endpoints and estimands

Table 1-1 contains the study primary objectives and the associated endpoints that will be formally tested using the pre-specified testing strategy (see Section 2.5 of the current document). The primary estimands are described in Section 1.2.1. Table 1-1 also contains secondary and exploratory objectives and endpoints for which descriptive statistics will be provided.

Table 1-1 Objectives and Related Endpoints

Objective(s)	Endpoint(s)
Primary Objective(s) • The primary objective of the study is to assess the tolerability of asciminib versus nilotinib, in participants with newly diagnosed CML-CP, with respect to the time to discontinuation of study treatment due to adverse event (TTDAE).	**Endpoint(s) for primary objective(s)** • Time to discontinuation of study treatment due to adverse event (TTDAE). 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 adverse event (AE)
Secondary Objective(s) • **Secondary objective on efficacy** ○ To compare the efficacy of asciminib versus nilotinib at and by all scheduled data collection time points	**Endpoint(s) for secondary objective(s)** • MMR **at** all scheduled data collection time points. • MMR **by** all scheduled data collection time points. • MR4.0 and MR4.5 **at** and **by** all scheduled data collection time points. • Complete Hematological Response (CHR) **at** and **by** all scheduled data collection time points. • *BCR::ABL1* ≤1% at and by all data collection time points. • Duration of MMR, MR4.0, MR4.5. • Time to first* MMR, first MR4.0, first MR4.5. • Time to treatment failure. • Event Free Survival. • Progression free survival. • Overall survival. • *by competing risk analysis
• Time to Treatment Discontinuation (TTD) for selected reasons of discontinuation	• TTD due to selected reasons (i.e. Discontinuation due to lack of

Objective(s)	Endpoint(s)
	efficacy/treatment failure/disease progression/suboptimal response/death)
• **Secondary objectives on PRO** ○ To assess the effect of asciminib versus nilotinib 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.
• **Secondary objectives for safety** ○ To characterize the safety and tolerability profile of asciminib versus nilotinib during the course of study.	• Type, frequency and severity of adverse events, dose modification due to adverse event, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG changes, and other safety data (vital signs, physical examination).

Exploratory Objective(s)	Endpoint(s) for exploratory objective(s)
CCI	

1.2.1 Primary estimand(s)

The primary estimands are defined in CSP Section 3.1.

The primary clinical question of interest is: What is the safety/tolerability of asciminib (80 mg QD) compared to nilotinib (300 mg BID) in newly diagnosed Ph+ CML-CP subjects with respect to the time to discontinuation of study treatment due to AE (TTDAE) during treatment period, where study treatment discontinuation due to other reasons is considered a competing risk event, *regardless of* dose interruptions/reductions; *regardless of* dosing errors, and any concomitant medication.

The primary estimand is described by the following attributes:

Population: Newly diagnosed adult Ph+ CML-CP subjects, as defined by inclusion/ exclusion criteria; that have asciminib or nilotinib as their first starting dose.

Endpoint: Time to discontinuation of study treatment due to AE, where discontinuation of study treatment due to other reasons is considered as a competing risk event.

Intercurrent events (IE):

- Change of study treatment per protocol (dose reduction/interruption): *treatment policy strategy*
- Dosing errors (e.g., missed dose): *treatment policy strategy*
- Deviation in any intake of concomitant medications: *treatment policy strategy*
- Intake of prohibited medications: *treatment policy strategy*
- Handling of remaining intercurrent events (IE): no other IE foreseen.

Treatment: The actual study treatment received (asciminib 80 mg QD, or nilotinib 300 mg BID); with or without dose modifications (reductions/interruptions), regardless of dosing errors, deviation in any intake of concomitant medications.

The summary measure: the cause-specific hazard for the event of interest (discontinuation of study treatment due to AE), between the actual treatments received (i.e. for asciminib versus nilotinib) will be analyzed. Competing risk analysis of TTDAE will be performed. The 'discontinuation of study treatment due to AE' will be considered as the event of interest, while discontinuation of study treatment due to end of study will be considered as administrative censoring and discontinuation of study treatment due to other reasons that are not due to AEs or end of study will be considered as competing risk events. Stratification will be by ELTS risk score at diagnosis.

2 Statistical methods

2.1 Data analysis general information

The planned interim analysis and primary analysis will be performed by Novartis. SAS version 9.4 or later will be used to perform the data analyses and to generate tables, figures and listings.

TTDAE will be analyzed by the competing risk analysis stratified based on the randomization stratification factor – ELTS score (low versus intermediate versus high), considering the competing risk event of time-to-discontinuation of study treatment due to other reasons not due to AE or end of study. The p-value will be adjusted for the endpoint TTDAE.

Study data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements. Qualitative (or categorical) data (e.g. gender, race, etc.) will be summarized by means of contingency tables by treatment arm; a missing category will be included as applicable. Percentages will be calculated by using the number of participants in the relevant population or subgroup as the denominator. Quantitative (or continuous) data (e.g. age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation (SD), median, minimum, and maximum as well as 25th and 75th percentiles) by treatment arm. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

The interim analysis data cut-off date is defined as when approximately CCI discontinuations due to AE have occurred. The primary analysis data cut-off date is defined as when approximately CCI discontinuations due to AE have occurred.

To streamline the analysis process and for publication purposes, the clinical trial team decided to implement a single data cut-off to include the week 48 follow-up data in the primary analysis. This data cut-off will occur when approximately CCI discontinuations due to adverse events (AEs), including deaths due to AEs, have taken place, or after all randomized subjects have been on study treatment for at least 48 weeks or discontinued earlier from study treatment prior to week 48 (i.e., LPFT + 48 weeks), whichever occurs later. If the number of events of interest exceeds CCI at the primary analysis data cut-off, a sensitivity analysis may be conducted for the pre-planned CCI events of interest if the observed number of events are large enough.

All statistical analyses will be performed by using all data collected in the database up to the corresponding 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 analyses. Any data collected beyond the cut-off date will not be included in the analyses and will not be used for any derivations.

All events with start date before or on the data cut-off date and end date after the data cut-off date will be reported as ongoing. The same rule will be applied to events starting before or on the data cut-off date but without a documented end date. This approach applies, in particular, to adverse event and concomitant medication reporting. For these events, the end date will not be imputed.

2.1.1 General definitions

2.1.1.1 Study treatment and investigational drug

The study treatment is either asciminib (80 mg QD) or nilotinib (300 mg BID). The investigational drug refers to the Novartis investigational drug, asciminib.

Treatment arms

The treatment arms are defined in Section 1.1 of the current SAP. No crossover of study treatment across arms will be allowed.

Date of first administration of study treatment

The date of first administration of a study treatment or first dose (FD) is defined as the first date when non-zero dose of study treatment is administered to a participant per the Dose Administration Record (DAR) ('Study treatment_ASCIMINIB', 'Study treatment_NILOTINIB') eCRF page, which is a participant level concept. The date of FD will also be referred as the start of study treatment.

Date of last administration of study treatment

The date of last administration of a study treatment or last dose (LD) is defined as the last date when a non-zero dose of study treatment is administered to a participant per the DAR eCRF page. The date of LD is also a participant level concept.

Date of end of study treatment (EOT)

For each participant, the EOT date is the date that the study treatment is ended for him/her. On this date. The date of EOT is the date the participant takes the last dose of study treatment as recorded in the DAR page. The participant should complete his/her EOT assessments following EOT. It is possible that there is a gap between the date of EOT and the date of EOT assessment visit. The date of EOT is a participant level concept.

Date of end of study (EOS)

The date of EOS is when the necessary number of events for primary analysis have been reached and when end of treatment and the last PRO assessments are completed for all participants. Participants who discontinue the study treatment prematurely due to any reason will be followed up for survival until EOS. The unique date of EOS is a study level concept.

Study day

For each participant, the date of randomization is defined as Study Day 1. The day before randomization is defined as Day -1. The study day describes the day of an event or an assessment relative to the reference start date.

The study day is defined as:

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

The reference start date for each participant:

- For safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, etc.) the reference start date is the first dose of the study treatment.
- For all other, non-safety assessments (e.g. molecular response, survival time, disease progression, ECOG performance status, patient reported outcomes (PROs), etc.) the reference start date is the date of the randomization.

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

Time unit

A year is defined as 365.25 days.

A month 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 is defined as 7 days. If duration is reported in weeks, duration in days is divided by 7.

Baseline for the treatment period

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as baseline value or baseline assessment. This also applies to the evaluation of PRO endpoints.

For safety evaluations and baseline data including disease characteristics, the last available assessment, including unscheduled assessments on or before FD is taken as baseline assessment. When the exact time of an assessment is known, the last one before dosing is used.

For pre-dose electrocardiogram (ECG), the last available assessment before the treatment start time is used for baseline. When multiple replicates are available, the average will be used as baseline.

For *BCR::ABL1* mutation related assessments, <= Day 1 (the first day of study treatment administration) assessment is taken as baseline.

In the rare case where multiple laboratory measurements meet the baseline definition, and no further flag or label can identify the chronological order, and if values are from both the central and the local laboratories, the value from the central assessment will be considered as baseline. Otherwise, if the measurements come from a single laboratory, the average will be used as baseline.

If no measurements meet the above definition, the baseline value will be considered missing. Missing baseline values will not be imputed.

2.1.1.2 Last contact date

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

Table 2-1 Last contact date data sources

Source data	Conditions
Date of randomization	No condition
Last contact date/last date participant was known to be alive from Survival follow-up page	Participant status is reported to be alive, lost follow-up or unknown
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term
Start/End dates from drug administration / concomitant medication record	Non-missing dose. Doses of 0 are allowed
End of treatment date from End of treatment (EOT) page	No condition

Any specific efficacy (molecular or cytogenetic) assessment date if available	Evaluation is marked as 'done' or non-missing
Laboratory/PK collection dates	Sample collection marked as 'done'
ePRO completion dates	No condition
Vital signs / ECG 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 data cut-off date. The cut-off date will not be used for last contact date, unless the participant has been seen or contacted on that date. No date post the cut-off date will be used. Completely imputed dates (e.g. the analysis data cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date.

The last contact date will be used for censoring of participants in the analysis of overall survival (OS).

2.1.1.3 On-treatment assessment/event and observation periods

The following three mutually exclusive segments of each participant's overall observation period are defined for adverse event (AE) reporting:

- Pre-treatment period: from the day of the participant's informed consent to the day before his/her FD, i.e. Day -1.
- On-treatment period: from the date of the participant's FD to 30 days after the date of LD (including start and stop date). The 30-days post LD is also referred to as the safety follow-up.
- Post-treatment period: starting at day 31 after the participant's date of LD. The post-treatment period is also referred to as the survival follow-up.

Note that if dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

Efficacy summaries on the FAS, apart from overall survival (OS), progression free survival (PFS) and event free survival (EFS) (as defined in Section 5.3.3), will include data from baseline up to either the last assessment on or before the EOT assessment visit, or on or before treatment failure, whichever is the earliest.

The efficacy assessments, if any, collected post-treatment failure, or post-EOT visit will not be included in any efficacy analysis, except for OS, PFS and, EFS analyses. However, they will be listed and flagged as appropriate.

2.1.1.4 Windows for multiple assessments

Data such as molecular response and hematological response collected over time (including unscheduled visits) will be summarized by scheduled time points. As participants do not always adhere to the visit schedule, visits will be remapped according to visit windows defined as in

Table 2-2 and Table 2-3 to enable at-visit or by-visit analyses. Only these protocol defined visits for molecular responses and hematological responses will have the visit window defined. Each assessment (including the EOT assessment), either scheduled or unscheduled, will have a mapped visit assigned, as long as study day is available, according to the defined visit window up to the date with data included.

If more than one molecular /hematological assessment is assigned to the same time window, the assessment performed closest to the target date will be used for at-visit or by-visit analyses. If multiple assessments within a visit window are equidistant from the target date, then the assessment associated with the lowest value will be used. If there are multiple assessments with the same lowest value, then the earliest assessment will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Table 2-2 Time windows for molecular response

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1#
Week 4	29	Day 2 to day 56
Week 12	85	Day 57 to day 126
Week 24	169	Day 127 to day 210
Week 36	253	Day 211 to day 294
Week 48	337	Day 295 to day 378
Week k (k=60, 72, 84, 96, …, EOT)	7*k + 1	Day (7*k-41) to day (7*k+42)

Day 1 = Date of randomization
EOT assessments are mapped to the time points as needed.

Table 2-3 Time windows complete hematological response

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1#
Week 2	15	Day 2 to Day 21
Week 4	29	Day 22 to Day 56
Week 12	85	Day 57 to Day 126
Week 24	169	Day 127 to Day 210
Week 36	253	Day 211 to Day 294
Week 48	337	Day 295 to Day 378
Week k (k=60,72,84,96, …, EOT)	7 * k + 1	Day (7*k-41) to Day (7*k+42)

Day 1 = Date of randomization
EOT assessments are mapped to the time points as needed.

For PRO data, time windows are defined in Table 2-4 and Table 2-5. Since some ePRO are completed by participants outside the protocol defined site visits, these assessments will appear as unscheduled/diary in the database. All ePRO data are mapped to time intervals in Table 2-3 and Time 2-4 as appropriate. If more than one assessment is available in the same time window, the assessment closest to the planned date will be considered. If two assessments are obtained

with the same time difference compared to the scheduled visit day or the target assessment day, the assessment obtained prior to visit day or target day will be considered. If multiple assessments are obtained on the same day, only the first one will be used in analysis. When no assessment is mapped to a timepoint, a missing assessment is assumed.

Table 2-4 Time windows for PRO: EORTC QLQ-C30, EORTC QLQ-CML24

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1#
Week 4	29	Day 2 to day 42
Week 8	57	Day 43 to day 70
Week 12	85	Day 71 to day 126
Week 24	169	Day 127 to day 252
Week 48	337	Day 253 to day 504
Week 96	673	Day 505 to day 714
Week j (EOT)	7*j+1	Day (upper limit of pervious time interval+1) to day (7*j+14)
Week k (k=EOT+4, EOT+8, EOT+12)	7*k+1	Day (7*k-13) to day (7*k+14)

Day 1 = Date of randomization
EOT and every 4 weeks until 12 weeks after EOT assessments are mapped to the time points as needed.

Table 2-5 CCI

The following is the general rule for the target day of assessment and time interval: for Week k visit, target day of assessment is defined as 7*k+1. For the time interval:

- Lower limit = (upper limit of prior applicable visit) + 1
- Upper limit = (target day of current visit) + integer part of [(target day next applicable visit-target day of current visit) / 2]-1.

2.2 Analysis sets

The analysis sets are defined in Section 9.1 of the CSP.

The **Full analysis set** (FAS) comprises all participants to whom study treatment has been assigned by randomization.

According to the intent to treat principle, participants in the FAS will be analyzed according to the treatment and stratum they have been assigned to during the randomization procedure.

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/assigned 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 primary estimands are based on the treatment policy strategy and will analyze participants according to the actual treatment received in the Safety set, and stratum they have been assigned to during the randomization procedure.

Participant classification

Participant may be excluded from the analysis sets defined above based on the protocol deviations entered in the database and/or on specific subject classification rules defined in Table 2-6. The participants who are not eligible to the study will be summarized separately by inclusion and exclusion criteria.

Table 2-6 Subject classification based on protocol deviations and non-protocol deviation criteria

Analysis set	Protocol deviations leading to exclusion	Non-protocol deviations leading to exclusion
FAS	No written informed consent	Not applicable
Safety set	No written informed consent	No dose of study medication

Withdrawal of Informed Consent

Data collected in the database (via clinical database or third party vendor data transfer) after a participant withdraws informed consent from all further participation in the trial will not be included in the analysis. The date on which a participant withdraws consent is recorded in the eCRF. Data records containing confirmed cases of biological samples analyzed after withdrawal of informed consent (WoC) when not allowed per ICF or local regulations will be flagged and excluded from all analyses including listings.

2.2.1 Subgroup of interest

Subgroup analyses will use the same method as for the respective overall analysis sets. The objective for these analyses is to identify any potential patterns, trends, or issues that may be limited to a subgroup of participants. Unless otherwise specified, summary tables and figures will be generated only for subgroups with at least 15 participants.

The primary endpoint TTDAE will be summarized by the following subgroups to examine the homogeneity of treatment effect, provided that the respective primary analysis based on the Safety set is statistically significant:

- Stratification factor: ELTS score (low versus intermediate versus high) based on the randomization data from IRT
- Sex: female or male
- Race: Asian, White or Others
- Age groups

  Age group 1
  - 18 years ≤ age < 65 years
  - 65 years ≤ age < 75 years
  - age ≥ 75 years

  Age group 2
  - age < 65 years
  - age>=65 years
- Geographical regions: Germany, Europe excluding Germany, or Others

No formal statistical test of hypotheses will be performed for the subgroups, only point estimate of the treatment effect and 95% CI will be provided.

Other subgroups may be analyzed as appropriate.

2.3 Participant disposition, demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment arm for the FAS, unless otherwise specified. Summaries will be reported by treatment arm and for all participants, and listings will be reported by treatment arm.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum and maximum will be presented. For selected parameters, 25^{th} and 75^{th} percentiles will also be presented. No inferential statistics will be provided.

2.3.1 Participant disposition

Enrollment by country and center will be summarized for all screened participants and also by treatment arm using the FAS. The number and percentage (number (%)) of randomized participants included in the respective analyses sets will be presented overall and by treatment arm. The number (%) of screened and not-randomized participants and the reasons for screening failure will also be displayed. The number (%) of participants in the FAS who are still on

treatment, who discontinued the study treatment phases and the reason of discontinuation will be presented overall and by treatment arm.

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

- Number (%) of participants who were randomized (based on data from IRT system).
- Number (%) of participants who were randomized but not treated (based on DAR eCRF page).
- Primary reason for not being treated (based on "End of Treatment Phase Disposition" eCRF page).
- Number (%) of participants who were treated (based on DAR eCRF pages of each study treatment completed with non-zero dose administered).
- Number (%) of participants who are still on-treatment (based on "End of Treatment Phase Disposition" page not completed).
- Number (%) of participants who discontinued the study treatment phase (based on the "End of Treatment Phase Disposition" page).
- Primary reason for study treatment phase discontinuation (based on the "End of Treatment Phase Disposition" page).
- Number (%) of participants who have entered the survival follow-up (based on the "Post treatment follow-up Disposition" page).

Protocol deviations

The number (%) of participants in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the Study Specification Document) and by treatment arm. All protocol deviations will be listed. In addition, the number (%) of participants in the FAS with any pandemic related protocol deviation (pandemic specific protocol deviations, as well as non-specific pandemic-protocol deviations with a pandemic-relationship) will be tabulated by deviation category (as specified in the Study Specification Document) overall and by treatment arm.

Analysis sets

The number (%) of participants in each analysis set will be summarized by treatment arm and strata.

2.3.2 Demographics and other baseline characteristics

All demographic and baseline characteristics data will be summarized and listed by treatment arm. This includes categorical data such as age groups (Section 2.2.1), sex, race, ethnicity, ECOG performance status, geographical regions; and continuous data such as age, weight, height, body mass index (BMI), which is calculated as weight[kg] / (height[m]^2).

Reporting for DSUR and PSUR

Two summary tables using the Safety set will be produced for DSUR and PSUR reporting:

1. Per each treatment arm and the two treatment arms combined: the number (%) of participants in the different age groups, and in each combination of sex-by-age group.
2. Per each treatment arm and the two treatment arms combined: the number (%) of participants in the different race groups.

Baseline stratification factors

Randomization will be stratified based on the participant's ELTS score (low versus intermediate versus high). The ELTS is categorized as (Pfirrmann, Markus, et al.),

An ELTS score value ≤ 1.5680 defines the low-risk group;

An ELTS score value > 1.5680 but ≤ 2.2185 defines the intermediate-risk group;

An ELTS score value > 2.2185 defines the high-risk group.

The number (%) of participants in each stratum (ELTS score) based on data obtained from the IRT system will be summarized overall and by treatment arm for the FAS. Discordances between the stratum recorded in IRT at the time of randomization and the stratum recorded in the clinical database, through the data collected on eCRF will be cross-tabulated and listed.

Diagnosis and extent of cancer

All diagnosis and extent of cancer data will be summarized by treatment arm. Time (weeks) since initial diagnosis to the time of randomization, time of first dose of study treatment, time of first hydroxyurea/anagrelide will be summarized. Also proportion of participants with extramedullary involvement: any extramedullary involvement (Yes/No) and location of extramedullary involvement (e.g. Spleen, Liver) will be presented.

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on eCRF will be summarized by treatment arm. The summary will be presented by primary system organ class (SOC), preferred term (PT) and treatment arm. Medical history and current medical conditions will be coded using the Medical Dictionary for Drug 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.

The cardiovascular risk factors (e.g. heavy smoking, low physical activity, unhealthy diet, etc.), and family medical history of each participant (e.g. for ischemic heart disease, cardiac arrhythmia, sudden death, high cholesterol, diabetes mellitus, heart defects (congenital heart disease), heart failure, etc.) are collected prior to randomization. A listing will be presented.

Others

Selected data collected at baseline, including informed consent for additional research on study data and biological samples will be listed.

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

2.4.1 Study treatment / compliance

The study treatments are described in the CSP Section 6.1. The Safety set will be used for the analyses related to study treatment compliance during the *treatment period*. The treatment period is defined as the period between the date of FD and the date of LD, inclusively.

Duration of exposure, actual cumulative dose, average daily dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of participants in each interval. The number (%) of participants who have dose reductions or interruptions, and the reasons will be summarized.

Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

To summarize exposure data for treatment, this will be based on participants in the Safety set with the date of LD and the date of FD.

2.4.1.1 Duration of exposure to study treatment

Duration of exposure to study treatment (in days) for participant i is defined as

$$date\ of\ LD_i - date\ of\ FD_i + 1.$$

Summary of duration of exposure to study treatment include descriptive statistics by treatment arm. These summary statistics will be reported by the following time intervals:

- $<$ 24 weeks
- $\geq$ 24 weeks
- $\geq$ 48 weeks
- $\geq$ 96 weeks

and every 48 weeks thereafter until the EOS. The duration of exposure is only based on the date of FD and date of LD, and the days with zero daily dose will not be excluded from duration of exposure.

The **duration of exposure in participant-years** for a treatment arm is the total of the duration of exposure in years from all the participants in that treatment arm, i.e.

$$\sum_{i=1}^{n_k}(date\ of\ LD_i - date\ of\ FD_i + 1)/365.25$$

where k=1 or 2 representing either the asciminib or nilotinib, respectively; n_k is the number of participants in the treatment k.

The duration of exposure in participant-years will be summarized for the two treatment arms using descriptive statistics.

2.4.1.2 Cumulative dose

The **actual cumulative dose** refers to the total actual dose administered over the duration for which a participant is on the study treatment as documented in the DAR eCRF. It is the sum of the non-zero total daily doses recorded over the dosing period. For participants who do not take any drug, the actual cumulative dose is by definition equal to zero.

Additionally, the **planned cumulative dose** for a participant is defined as the total planned dose per the protocol up to the date of LD for this participant. The calculations for the planned cumulative dose are:

- Asciminib: 80 mg/day * duration of exposure (day),
- Nilotinib: 300 mg/administration * 2 * duration of exposure (day)

where duration of exposure is defined in Section 2.4.1.1.

The actual cumulative dose will be summarized using descriptive statistics for each of the treatment arm. The planned cumulative dose is only used to define relative dose intensity (see below).

2.4.1.3 Average daily dose

Average daily dose (mg/day) (ADD) for a participant is defined as:

ADD=actual cumulative dose (mg) / number of days on treatment,

where **number of days on treatment** is,

(date of LD-date of FD+1) – number of days with dose interruptions.

The average daily dose will be summarized by descriptive statistics for each of the study treatment arm separately.

2.4.1.4 Dose intensity and relative dose intensity

Dose intensity (mg/day) (DI) for a participant is defined as:

DI=actual cumulative dose (mg) / duration of exposure (day).

For participants who do not take any drug, the dose intensity is zero.

Relative dose intensity (RDI) is defined as follows:

RDI=dose intensity / planned dose intensity,

where **planned dose intensity** (mg/day) (PDI) is

PDI=planned cumulative dose (mg) / duration of exposure (day).

The dose intensity and the relative dose intensity will be summarized using summary statistics separately for each of the study treatment arm.

2.4.1.5 Dose changes, interruptions or permanent discontinuations

Dose changes

A dose change occurs when total daily dose is different from the most recently planned dose. For participants in asciminib arm, the planned initial dose is 80 mg/day (80 mg QD) and dose escalation beyond 80 mg QD for asciminib is not permitted. For participants in the nilotinib arm, the planned initial dose is 600 mg/day (300 mg BID) and dose escalation beyond 300 mg BID for nilotinib is not permitted.

The field "Dose changed" from the DAR eCRF page will be used to determine whether a dose change occurs for a participant. If a dose change occurs, the following are used to determine whether it is a dose reduction or a dose increase:

Reduction: A dose change where the actual total daily dose is lower than the most recently planned dose. However, any dose change to correct a dosing error will not be considered a dose reduction. Since only dose change is collected in the eCRF, the number of reductions will be derived programmatically based on the direction of the change.

Increase: Not applicable.

The number (%) of participants with dose changes and the reasons for the changes will be summarized by study treatment arm. Since a participant can have multiple dose changes, the frequency of reasons for changes can be higher than the number of participants experiencing them. Additionally, participant level listings will be produced.

Dose interruptions and duration of interruptions

The field "Dose interrupted" in the DAR eCRF page will be used to determine whether a dose interruption occurs for a participant. When multiple entries for interruptions are entered on consecutive days with different reasons, they will be counted as separate interruptions. However, if the reason is the same in the multiple entries on consecutive days, then it will be counted as one interruption.

Duration of dose interruption (days) due to any reason will be summarized descriptively. For each participant, the duration of dose interruption will be calculated by adding all individual episodes of dose interruption for that participant.

The number (%) of participants who experience dose interruptions, the reasons for the interruptions, and descriptive statistics for duration of dose interruption will be summarized for each treatment arm. Since a participant can have multiple dose interruptions, the frequency of reasons may be higher than the number of participants experiencing them. Additionally, participant level listings will be produced.

Permanent discontinuation

The field "Drug permanently discontinued" from the DAR eCRF page will be used to determine whether permanent discontinuation occurs for a participant.

The number (%) of participants who discontinue and reasons for discontinuation will be summarized by the study treatment arm. Additionally, participant level listings will be produced.

2.4.2 Prior, concomitant and post therapies

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

Prior anti-cancer therapy

The number (%) of participants who received any prior anti-neoplastic medications will be summarized by treatment arm for the lowest ATC class and preferred term. A listing will also be produced.

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

The above analyses will be performed using the FAS with the following information:

- Number (%) of participants that received prior treatment for CML (Hydroxyurea and/or anagrelide)
- Time on prior treatment for CML (in weeks).

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be summarized overall and by treatment arm for the lowest ATC class and preferred term by means of frequency counts and percentages using FAS.

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

Concomitant therapies

Concomitant therapies are defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a participant coinciding with the study treatment period. Concomitant therapies include medications (other than the study treatments) and medical procedures starting on or after the start date of study treatment, or starting prior to the start date of study treatment and continuing after the start date of study treatment.

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

The summaries for the on-treatment period using the Safety set will include:

- Therapies starting on or after the start of study treatment but no later than the end of on-treatment period and
- Therapies starting prior to start of study treatment and continuing after the start of study treatment.

Any concomitant therapies starting and ending prior to the start of study treatment or starting beyond end of the on-treatment will be flagged in the listing.

The prohibited concomitant medications will be summarized by the lowest ATC class and preferred term up to the end of on-treatment periods. Prohibited medications will be

- concomitant medications with ATC2='Antineoplastic agents' collected on the 'Concomitant Medication' eCRF page where the preferred term is not Hydroxycarbamide;
- And Hydroxycarbamide with starting date or ending date after first dose of study treatment + 15 days.

2.5 Analysis supporting primary objective(s)

The primary objective (see Table 1-1, CSP Table 3-1) of the study is to assess the tolerability of asciminib versus nilotinib, in participants with newly diagnosed CML-CP, with respect to the time to discontinuation of study treatment due to adverse event (TTDAE). The primary endpoint (event of interest) is discontinuation of study treatment due to AE. The primary analysis will be conducted for the Safety set when approximately CCI events occur.

2.5.1 Primary endpoint(s)

The primary endpoint for the primary objective of the study is defined as time to discontinuation of study treatment due to adverse event (TTDAE). TTDAE is defined as the time from the date of first dose of study treatment (date of FD) to the date of discontinuation of study treatment due to adverse event (AE) (including death due to AE) (date of non-zero LD).

For participants ongoing without study treatment discontinuation on or prior to the analysis cut-off date, the TTDAE for this participant will be censored at the analysis cut-off date. Discontinuation due to other reasons not due to AE are considered as a competing risk event.

For those participants who discontinue from the study treatment, the reason for discontinuation will be taken from the EOT disposition page, whereas the date of discontinuation is the date of LD from the DAR records.

2.5.2 Statistical hypothesis, model, and method of analysis

The analyses of TTDAE will be performed using the Safety set. The comparison is between all the participants receiving asciminib as their actual treatment and all the participants receiving nilotinib as their actual treatment. See Section 2.2 for the definition of actual treatment received under Safety set.

The hypotheses corresponding to the primary objective for TTDAE is as follows:

- $\mathbf{H_0}$: 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 nilotinib.

- $\mathbf{H_a}$: 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 nilotinib.

Competing risk analysis of TTDAE will be performed. The 'discontinuation of study treatment due to AE' (including death due to AE) will be considered as the event of interest, while discontinuation of study treatment due to end of study will be considered as administrative censoring and discontinuation of study treatment due to other reasons that are not due to AEs (including death due to AE) or end of study will be considered as competing risk events.

The formal comparison of TTDAE for asciminib vs nilotinib will be implemented via the cause-specific hazard model. The cause-specific hazard model will be stratified based on the stratification factor ELTS score from IRT.

The overall type I error rate will be controlled at 2.5% level. The p-value will be presented. The estimated hazard ratio will also be presented together with the 95% Wald confidence interval.

The cumulative incidence curve will be plotted without stratification factor. The estimated cumulative incidence rates and the corresponding 95% CIs at specified scheduled visits will be presented for each treatment arm (asciminib and nilotinib). The cumulative incidence rate at a specific visit provides an estimate of the probability of experiencing discontinuation of study treatment due to AE at/before this specific visit and also before the non-AE related discontinuation of study treatment.

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2.5.3 Handling of intercurrent events

The intercurrent events (IE) for the primary objective is defined in Section 1.2.1. Below defines how they are handled and provides details:

- Change of study treatment per protocol (dose reduction/interruption): *treatment policy strategy* is applied. The actual value or censored time of TTDAE will be used, regardless of whether there is change of study treatment or not.
- Dosing errors (e.g., missed dose): *treatment policy strategy* is applied. The actual value or censored time of TTDAE will be used, regardless of whether dosing errors occur or not.
- Deviation in any intake of concomitant medications: *treatment policy strategy* is applied. The actual value or censored time of TTDAE will be used, regardless of whether there is any intake of concomitant medication or not.
- Intake of prohibited medications: *treatment strategy* is applied. The actual value or censored time of TTDAE will be used, regardless of whether or not there is any intake of prohibited medication.
- Handling of remaining intercurrent events: no other IE foreseen.

2.5.4 Handling of missing values not related to intercurrent event

For participants ongoing without study treatment discontinuation on or prior to the analysis cut-off date, their TTDAE time will be censored at the analysis cut-off date.

2.5.5 Sensitivity analyses

In the primary analysis, death due to other reasons is considered as a competing risk, similar to other reasons of discontinuation of study treatment (except death due to AE, which are considered as events of interest). To explore the robustness of the analysis, sensitivity analysis considering death as an intercurrent event with composite strategy, will be performed. Death due to any reason is considered as an event of interest defining the primary endpoint.

Another sensitivity analysis is to repeat the primary analysis described in Section 2.5.2 using the stratification factors ELTS based on the data collected on the eCRF.

2.5.6 Supplementary analyses

The cause-specific hazard ratio for the competing risk event (discontinuation from study treatment due to other reasons that are not due to AEs) along with the 95% CI will also be estimated from the cause-specific Cox regression model. In addition, the analysis via the sub-distribution hazard regression approach (Fine and Gray) will also be implemented. These supplementary analyses will be provided for information purposes only.

Besides stratified by ELTS score, the cause-specific hazard model for TTDAE will also be performed stratified by other subgroups of interest defined in Section 2.2.1.

2.6 Analysis supporting secondary objectives

The secondary objectives of the study include multiple objectives for efficacy, PRO and safety (see Table 1-1), including:

- Efficacy: To compare the efficacy of asciminib versus nilotinib at and by all scheduled data collection time points, which include MMR, MR4.0, MR4.5, CHR, *BCR::ABL1* $\leq$ 1%, duration of MMR, MR4.0, MR4.5, time to the first MMR, first MR4.0, first MR4.5, TTF, EFS, PFS, OS, TTD due to selected reasons.
- PRO: To assess the effect of asciminib versus nilotinib on patient-reported disease-related symptoms, functioning, and health-related quality of life (HRQoL), on EORTC QLQ-C30 and EORTC QLQ-CML24.
- Safety: To characterize the safety and tolerability profile of asciminib versus nilotinib during the course of study (Type, frequency and severity of adverse events, dose modification due to adverse event, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG changes, and other safety data (vital signs, physical examination)).

No confirmatory statistical testing for these objectives will be performed, and the nominal p-values may be presented for descriptive purposes only.

2.6.1 Secondary endpoint(s)

2.6.1.1 Secondary endpoints for efficacy

The secondary efficacy endpoints are,

- MMR rates at and by all scheduled data collection time points.
- MR4.0 and MR4.5 rates at and by all scheduled data collection time points.
- Complete Hematological response (CHR) rates at and by all scheduled data collection time points.
- *BCR::ABL1* ≤1% rates at and by all data collection time points.
- Duration of MMR, MR4.0, MR4.5.
- Time to first MMR, first MR4.0, first MR4.5.
- Time to treatment failure (TTF).
- Event Free Survival (EFS).
- Progression free survival (PFS).
- Overall survival (OS).
- TTD due to selected reasons (i.e. Discontinuation due to lack of efficacy/treatment failure/disease progression/suboptimal response/death).

MMR rates at all scheduled data collection time points

At all the protocol-planned visits, these rates are defined as the proportion of participants with MMR at the respective time points.

MMR rates by all scheduled data collection time points

At all the protocol-planned visits, these rates are cumulative MMR rates by the time points and are defined as the proportion of participants who achieve MMR at or before specified visits. If a participant achieves an MMR but then loses it at or before a specific visit, he/she will still be classified as achieving MMR by that specific time point. Baseline values are excluded from this analysis, e.g., for 'by Week 4', the responders from post-baseline (Day 2) until Week 4 (Day 56) are considered, and for 'by Week 12', the responders from post-baseline (Day 2) until Week 12 (Day 126) are considered.

MR4.0/MR4.5/CHR rates at all scheduled data collection time points

At all the protocol-planned visits, these rates are defined as the proportion of participants with MR4.0/MR4.5/CHR respectively at the respective time points.

MR4.0/MR4.5/CHR rates by all scheduled data collection time points

At all the protocol-planned visits, these rates are cumulative MR4.0/MR4.5/CHR respectively rates by time points and are defined as the proportion of participants who achieve MR4.0/MR4.5/CHR respectively at or before specified visits. If a participant achieves an

MR4.0/MR4.5/CHR respectively but then loses it at or before a specific visit, he/she will still be classified as achieving MR4.0/MR4.5/CHR respectively by that specific time point. Baseline values are excluded from this analysis, e.g., for 'by Week 2', the responders from post-baseline (Day 2) until Week 2 (Day 21) are considered; for 'by Week 4', the responders from post-baseline (Day 2) until Week 4 (Day 56) are considered, and for 'by Week 12', the responders from post-baseline (Day 2) until Week 12 (Day 126) are considered.

***BCR::ABL1* ≤1% at all data collection time points**

At all visits, these rates are defined as the proportion of participants who achieve *BCR::ABL1* ≤1% at the respective time points.

***BCR::ABL1* ≤1% by all data collection time points**

Such rates are cumulative *BCR::ABL1* ≤1% rates by the time points, and are defined as the proportion of participants who achieve *BCR::ABL1* ≤1% at or before specified visits. If a participant achieves *BCR::ABL1* ≤1% but then loses it at or before a specific visit, he/she will still be classified as achieving *BCR::ABL1* ≤1% by that specific time point. Baseline values are excluded from this analysis.

Duration of MMR/ MR4.0/MR4.5

Duration of a specified molecular endpoint (MMR/MR4.0/MR4.5) is defined as the time between the date of the first documented achievement of the specified molecular endpoint (MMR/ MR4.0/ MR4.5) and the end date or censoring date of the endpoint, which is calculated as:

(end date or censoring date of MMR/MR4.0/MR4.5 respectively – date of first MMR/MR4.0/MR4.5 respectively +1)/7.

The end date is the earliest date of confirmed loss of the specified molecular endpoint, treatment failure of ELN criteria (Hochhaus et al 2020), progression to accelerated phase (AP) / blast crisis (BC), or CML-related death. Duration of MMR/MR4.0/MR4.5 analyses will be performed for the subset of participants from the FAS who achieved MMR/MR4.0/MR4.5 at any time post-baseline respectively.

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, the loss date/end date of MMR will be defined as the first loss of MMR date), i.e. loss of MMR (i.e. 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 by analysis of another sample taken after an interval of not less than 4 weeks and not more than 6 weeks unless associated with loss of CHR or loss of *BCR::ABL1* ≤ *1%* or progression to AP/BC or CML related death.

For analysis purpose, loss of MMR must be confirmed by the analysis of the next evaluable sample taken after an interval of not less than 4 weeks unless associated with loss of CHR or loss of BCR::ABL1≤1% or progression to AP/BC or CML related death.

Definitions of MMR, MR4.0, MR4.5, loss of MMR, MR4.0, MR4.5 and CHR can be found in Appendix Section 5.3.3.

Time to first MMR/ MR4.0/ MR4.5

Time to first specified molecular endpoint (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 endpoint, which is calculated as:

(date of first documented MMR/MR4.0/MR4.5 respectively – randomization+1)/7.

In the time-to-event analysis, time will be censored at the last molecular assessment (RQ-PCR) date on treatment 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 CSP Section 9.4.1.2, Section 2.6.2.1). Discontinuation from study treatment due to any reason without prior achievement of MMR/MR4.0/MR4.5 will be considered as competing risk events. For participants who progressed to AP/BC, lost CHR or had CML related death, they will be discontinued and considered as competing risk events.

Other time-to-event endpoints

Other time-to-event endpoints include Time to Treatment Failure (TTF), Event Free Survival (EFS), Progression-free Survival (PFS) and Overall Survival (OS).

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 based on ELN criteria (Hochhaus et al 2020),
- Confirmed loss of MMR (the loss date/end date of MMR will be defined as the first loss of MMR date) at any time while on study treatment,
- Progression to AP/BC while on treatment,
- Death from any cause while on treatment,
- Discontinuation of study treatment due to any reason (e.g. discontinuation of study treatment due to AE, investigator/participant decision, lack of efficacy, 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).

Since there are several criteria for treatment failure and if a subject meets two or more criterions, the earliest criterion met will be summarized. If several criteria are met on the same date, the first one met, in the order defined below, will be summarized:

1) Death due to any cause while on treatment
2) Progression to AP/BC

3) BCR::ABL1 ratio (IS) > 10% at 3 months if confirmed within the next 1-3 months after initiation of treatment

4) BCR::ABL1 ratio (IS) > 10% at 6 months after initiation of treatment

5) BCR::ABL1 ratio (IS) > 1% at or after 12 months after initiation of treatment

6) Confirmed loss of MMR at any time while on study treatment

7) Discontinuation from study treatment due to any reason other than AE

8) Discontinuation from study treatment due to AE

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 based on ELN criteria (Hochhaus et al 2020),
- Confirmed loss of MMR (in 2 consecutive tests, the loss date/end date of MMR will be defined as the first loss of MMR date) 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).

Discontinuation from study treatment due to other reasons not due to AE will be considered as competing risk events. For participants that have not experienced an event or a competing risk event prior to or at the analysis cut-off date, the time will be censored at the latest date of (date of last on-treatment assessment or last post-treatment follow-up).

Progression Free Survival (PFS)

Progression free survival (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 latest date of (date of last on-treatment assessment (PCR, cytogenetic, hematologic or extramedullary) or last post-treatment follow-up).

Overall Survival (OS)

Overall survival (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 analysis cut-off date.

These endpoints are defined for each participant as the duration between the dates of randomization and the earliest occurrence of a relevant event. The relevant events along with the associated endpoints are given in the Table 2-7. An "x" in the columns under Endpoints indicates that the corresponding event (row-wise) is one of the relevant events for that endpoint.

Table 2-7 Definitions of relevant events used to define time-to-event efficacy endpoints

Event	Definition in Appendix	Endpoints			
		TTF	EFS	PFS	OS
1 Treatment failure as defined per ELN 2020 criteria	Section 5.3.3	x	x		
2a Progression to AP/BC while on treatment	Section 5.3.3	x	x	x	
2b Progression to AP/BC during survival follow-up	Section 5.3.3		x	x	
3 Confirmed loss of MMR (in 2 consecutive tests) at any time while on study treatment	Section 5.3.3	x	x		
4 Discontinuation from study treatment due to any reason other than AE	NA	x			
5 Discontinuation of study treatment due to AE	NA	x	x		
6a Death due to any cause while on treatment	NA	x	x	x	x
6b Death due to any cause during survival follow-up	NA		x	x	x

Participants who do not experience any of the relevant event or competing risk event on or before the analysis cut-off date or the closing of study are considered censored for the corresponding endpoint.

Time (in months) of each time-to-event efficacy endpoint is calculated as:

(date of earliest occurrence among the relevant events or censoring – date of randomization +1)/30.4375.

Time to Treatment Discontinuation (TTD) for selected reasons of discontinuation

Time to discontinuation (TTD) of study treatment due to selected reasons (i.e. lack of efficacy/ treatment failure/ disease progression/ suboptimal response/ death) is defined as the time from the date of randomization to the date of discontinuation of study treatment due to any of the selected reasons.

For analysis purpose, the reasons of 'Unsatisfactory therapeutic effect', 'Progressive Disease' and 'Death' are considered from the Disposition eCRF page.

For participants ongoing without study treatment discontinuation on or prior to the analysis cut-off date, the TTD due to selected reasons for this participant will be censored at the analysis cut-off date. TTD due to other reasons not due to the selected reasons are considered as a competing risk event.

For those participants who discontinue from the study treatment, the reason for discontinuation will be taken from the EOT disposition page, whereas the date of discontinuation is the date of LD from the DAR records.

2.6.1.2 Secondary endpoints for PRO

The secondary endpoints for PRO include change from baseline in overall scores and individual scales of the EORTC QLQ-C30 (version 3.0) and EORTC QLQ-CML24.

The EORTC QLQ-C30 and the EORTC QLQ-CML24 will be used to assess work productivity and activity impairment related to the participants' CML.

The **QLQ-C30** consists of

(i) 5 functioning scales: physical, role, emotional, cognitive and social;

(ii) 3 symptoms' scales: fatigue, nausea/vomiting and pain;

(iii) 6 single-item scales: dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact;

(iv) the global health status quality of life (QoL) scale.

Each of the multi-item scales includes a different set of items – no item occurs in more than one scale. A high score for functional and QoL items/scales from the QLQ-C30 represents better function and QoL. A high score in symptoms items from QLQ-C30 represents worse symptoms.

A data error with the EORTC QLQ-C30 Question 30 was detected in July 2023. The question 30 "How would you rate your overall quality of life during the past week?" reflected "0" in some of the responses. The numeric scale range was incorrectly implemented in the Y-Prime database. This question displayed a 0-7 number scale when the copyrighted questionnaire indicated it should have been 1-7.

The CABL001J12302 study team have decided to correct the Q30 question screen, so that newly enrolled participants would use the corrected version of the question. Participants already enrolled in the study who have already answered QLQ-C30 will continue to answer the old version with the 0-7 scale to keep consistency in the scale within participants. Due to the delay in EC approval and full enrollment has been achieved on June 11th, 2024, the correction on Q30 question is not implemented, which means the Q30 question has displayed 0-7 number scale for all enrolled subjects for both baseline and post-baseline assessments.

Q29 and Q30 contribute to the sub-score "Global Health Status / QoL". They should both have a range from 1 to 7. According to the EORTC QLQ-C30 scoring manual for version 3.0, the responses from these two questions are averaged first and then transformed to a 100% scale.

Since the incorrectly set up Q30 now has a different range, i.e., from 0 to 7, the EORTC has recommended transforming the two responses independently prior to taking the average. The formula used for the transformation is

$$S = \left\{\frac{RS - minimum}{range}\right\} \times 100$$

where RS is the raw score which can be any value selected from 1 to 7 for Q29, and any value selected from 0 to 7 for Q30. The minimum in the equation now takes value 1 for Q29 and 0 for Q30, and the range is 7-1=6 and 7-0=7 for Q29 and Q30, respectively. After applying the scale transformation to both Q29 and Q30 outcomes, the global health sub-score is the average of these two transformed values.

Hence, despite the QLQ-C30 not being a validated instrument any longer with the skewed scale for Q30, the incorrect Q30 data already collected will be utilized to calculate the global health sub-score.

The **QLQ-CML24** consists of

(i) 22 multi-scale items: impact on daily life, symptom burden, impact on worry/mood, satisfaction with care;

(ii) 2 single items: body image problems, and satisfaction with social life.

A higher score on most of the item scales in QLQ-CML24 reflects a larger impairment in the corresponding domain, with the exception of the satisfaction with care, and satisfaction with social life, where a higher score reflects a higher level of satisfaction.

2.6.1.3 Secondary endpoints for safety

To characterize the safety and tolerability profile of asciminib versus nilotinib during the course of study on type, frequency and severity of adverse events, dose modification due to 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). These safety endpoints for which descriptive statistics and listings are provided are discussed in Section 2.7 of the current document.

2.6.2 Statistical hypothesis, model, and method of analysis

2.6.2.1 Analyses for secondary efficacy endpoints

Analyses for response endpoints

The FAS will be used for the response endpoints (MMR/MR4.0/MR5.0/CHR/*BCR::ABL1*) at and by scheduled data collection time points. 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 95% CI based on the Clopper-Pearson method will be presented by treatment arm.

Comparisons of proportions of responders using one-sided stratified Cochran-Mantel-Haenszel test for the endpoints at and by scheduled visits will be conducted for asciminib vs. nilotinib stratified by ELTS score from IRT.

The stratified Cochran-Mantel-Haenszel estimates of the common risk difference will be provided, together with the corresponding two-sided 95% CI for asciminib vs. nilotinib stratified by ELTS score from IRT.

Analyses for time-to-event endpoints related to responses

Duration of MMR/MR4.0/MR4.5

The FAS will be used for duration of MMR/MR4.0/MR4.5 respectively. These time-to-event endpoints will be analyzed by Kaplan-Meier (KM) method and presented by KM plots for the subset of participants from the FAS who achieved MMR/MR4.0/MR4.5 at any time post-baseline respectively. The estimated median duration along with the 95% CI (Brookmeyer and Crowley, 1982), along with the proportion of participants who are still MMR/MR4.0/MR4.5 responders at specified scheduled visits and the associated 95% CI, will be presented for each treatment arm.

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

The FAS will be used 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 of study treatment due to any reason (intolerance, failure, AE, death, etc.) without prior achievement of the endpoint (MMR/MR4.0/MR4.5) will be considered as competing risk. Note that participants who progressed to AP/BC, lost CHR or have CML-related death will be discontinued from study treatment and considered as competing risk events.

The estimated cumulative incidence rates and 95% CI at specified scheduled visits will be presented for each treatment arm. The cumulative incidence curve will be plotted. For the competing risk analysis, time to first achievement of the endpoint (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 Event Free Survival (EFS)

Competing risk analysis of EFS will be performed. The estimated cumulative incidence rates and 95% CIs at specified schedule visits will be presented for each treatment arm. The cumulative incidence curve will be plotted.

In the analysis of EFS, discontinuation from study treatment for other reasons which are not due to AE will be considered as competing risks.

Analyses for time-to-event endpoints (TTF, PFS, OS)

For other time-to-event endpoints (TTF, PFS, OS), 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 selected time points and the associated 95% CIs, will be presented for each treatment arm. The hazard ratio between the two treatments arms will be calculated, along with its 95% CI, using a stratified (treatment arm) Cox model. The descriptive p-value obtained using a stratified (treatment arm) log-rank test will be also presented.

Analyses for TTD due to selected reasons

A competing risk analysis will be performed for 'TTD due to selected reasons', considering 'discontinuation of study treatment due to selected reasons (i.e., Discontinuation due to lack of efficacy/treatment failure/disease progression/suboptimal response/death)' as the event of interest, while discontinuation from study treatment due to other reasons than the selected reasons as competing risk events. The estimated cumulative incidence rates and 95% CIs at specified scheduled visits will be presented for each treatment arm (asciminib and nilotinib). The cumulative incidence curve will be plotted. The comparison of TTD due to selected reasons for asciminib versus nilotinib will be implemented via the cause-specific hazard model for the event of interest. The descriptive p-value and the hazard ratio between the two treatment arms will be calculated, along with its 95% CI.

2.6.2.2 Analyses for secondary PRO endpoints

The FAS will be used for analyzing PRO data for EORTC QLQ-C30 and EORTC QLQ-CML24 unless specified differently.

Line Plot or heatmap to indicate change from baseline in overall scores and individual domains in each PRO instrument will be provided with a summary table. Line plot will be used for continuous data and heatmap will be used for categorical data. 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. Baseline is as defined in Section 2.1.1.1.

All PRO assessments require participants' direct completion and will be administered utilizing electronic device for data collection at scheduled time points from baseline to end of PRO assessments.

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. More information on PRO analysis time windows can be found in Section 2.1.1.4.

Compliance to the schedule of administration of the PRO questionnaire will be summarized by treatment arm, for baseline and scheduled post-baseline assessment time points. The following categories, as programmed based on the questionnaires, will be used to describe whether the questionnaire is completed at a specific time point:

1. yes, fully or partially completed
2. no, all missing

2.6.2.3 Analyses for secondary safety endpoints

The analyses for secondary safety endpoints are discussed in Section 2.7.

2.6.3 Handling of intercurrent events

Not applicable.

2.6.4 Handling of missing values not related to intercurrent event

2.6.4.1 For endpoints related to responses

In general, participants will be considered as a non-responder at a specific time point or visit in the following situations:

- Discontinuing the treatment prior to a specific time point due to any reason
- Meeting failure criteria
- Lack or missing a documented response
- Lack or missing of an available assessment for determining the response at the specified visit.

If evaluations are performed at unscheduled visits closer to the specified visit (before or after), these will be taken care of by the time windows defined by Table 2-2.

Molecular response (*BCR::ABL1* ≤1% /MMR/MR4.0/MR4.5) at specific time points

For MMR at time points, participants with missing PCR evaluation at Week 48 visit will be imputed as MMR responders if they have non-missing PCR evaluations at both Week 36 and Week 60 visits, and both meet the MMR criteria (*BCR::ABL1* levels (IS) ≤ 0.1%), assuming that MMR is maintained between Week 36 and Week 60. If PCR evaluations are performed at unscheduled visits closer to the Week 48 visit (before or after), these will be taken into account for the imputation.

The handling of missing MMR at Week 96 values are similar to that for MMR at Week 48, only that Week 84 and Week 108 PCR assessments are used instead of Week 36 and Week 60, respectively.

For other molecular response (*BCR::ABL1<=1%*/MR4.0/MR4.5) at specific time points, the category "missing" will be assigned to

- Ongoing cases, i.e. participants without assessment at the specific time point who have not discontinued study treatment and have not been treated sufficiently long for a specific time point
- Discontinued due to lack of efficacy, progressive disease/death prior to a specific time point
- Discontinued due to other reasons prior to a specific time point

Molecular response (*BCR::ABL1* ≤1% /MMR/MR4.0/MR4.5) by specific time points

The category "missing" will be assigned to participants for whom an evaluable response assessment was never provided.

Time to MMR/MR4.0/MR4.5

For participants in the FAS who have not experienced any MMR/MR4.0/MR4.5 event or a competing risk event respectively, the time will be censored as follows in the competing risk analysis:

- If a participant does not achieve the specified response event or a competing risk event 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.
- In case no on-treatment response assessment was performed, the participant will be censored at day 1.

Discontinuation of study treatment due to any reason (intolerance, AE, failure, progression, death, etc.) without prior achievement of the endpoint (*BCR::ABL1* ≤1% /MMR/MR4.0/MR4.5) will be considered as a competing risk event.

2.6.4.2 For time-to-event efficacy endpoints

Censoring is defined for each time-to-event endpoint in Section 2.6.1.1. All censoring are considered as right, independent censoring.

2.6.4.3 For PRO endpoints

Missing data items in a scale will be handled according to the manual for each PRO 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.

2.6.4.4 For TTD due to selected reasons

For participants ongoing without study treatment discontinuation on or prior to the analysis cut-off date, their TTD due to selected reasons time will be censored at the analysis cut-off date.

2.6.5 Sensitivity analyses

Not applicable.

2.6.6 Supplementary analyses

Not applicable.

2.7 Safety analyses

The study has primary objective of TTDAE which will be formally tested. Its analysis is discussed in Section 2.5 of the current document. This section describes the analyses of all other safety objectives as given in Table 1-1.

All safety analyses will be based on the Safety set. All listings and tables will be presented by treatment arm (asciminib and nilotinib). With the exception of the primary endpoint of TTDAE which will be formally tested as described in Section 2.5, no other safety endpoint will be formally tested.

All AEs are assigned to one of the three mutually exclusive segments defined in Section 2.1.1.3. In other words, each AE is considered to have occurred either during the pre-treatment period, or the on-treatment period, or the post-treatment period. If dates are incomplete in a way that clear assignment to pre-, on-, or post-treatment period cannot be made, then the respective AE data will be assigned to the on-treatment period.

Safety summaries (tables/figures) on the Safety set will include only data from the on-treatment period. One exception is the baseline data, which will also be summarized where appropriate (e.g. change from baseline summaries). In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period. In addition, a separate summary for death including on-treatment and post-treatment deaths will be provided.

All safety data (including those from the pre-treatment, post-treatment) will be listed and flagged as appropriate.

2.7.1 Adverse events (AEs)

AE summaries will include all AEs occurring during the on-treatment period (i.e. that starting date is within the on-treatment period). All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs (e.g. toxicity grade, AE relationship to study treatment, AE outcome, action taken, etc.). All AEs with start date outside the on-treatment period (i.e. with start dates during the pre-treatment or post-treatment period) will be flagged in the listings.

The number (%) of subjects with AE starting during the on-treatment period will be summarized in the following ways:

- by treatment, primary system organ class (SOC) and preferred term (PT)
- by treatment, primary system organ class, preferred term and maximum severity (Common Terminology Criteria for Adverse Events (CTCAE) grade).

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

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be summarized. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same PT will be summarized under the maximum CTCAE grade recorded for the event. AEs will be assessed according to the CTCAE version 5.0. AE with missing CTCAE grade will be included in the ‘All grades’ column of the summary tables.

In AE summaries, the primary SOC will be presented alphabetically and the PTs will be sorted within primary SOC in descending frequency. The sorting order for the PT will be based on their frequency in the asciminib arm. The summaries will show ‘All grades’ (including AEs with missing grade) and ‘Grade ≥3’.

The following AE summaries will be produced by treatment arm for the Safety set: overview of adverse events and deaths, AEs by SOC and PT, summarized by relationship, seriousness,

leading to treatment discontinuation, leading to dose interruption, leading to dose adjustment, requiring additional therapy, and leading to fatal outcome.

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

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

In order to account for differences in exposure between the treatment arms, incidence rates of AEs and SAEs will be presented by adjusting for duration of treatment period in participant - years (Section 5.4.3 for exposure-adjusted incidence rate).

2.7.1.1 Adverse events of special interest / grouping of AEs

An adverse event of special interest (AESI) is a grouping of adverse events that are of scientific and medical concern specific to compound asciminib. These grouping are defined using MedDRA terms, standardized MedDRA queries (SMQs), high level group terms (HLGTs), high level terms (HLT) and preferred terms (PTs). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or and existing SMQ, narrow or broad. These searches will be defined in the electronic Case Retrieval Strategy (eCRS) in the Document Management System (DMS) and a listing of search terms will be provided in the CSR. The latest approved version of CRS prior to the respective data base lock will be used.

For each specified AESI, number (%) of participants with at least one event of the AESI occurring during the on-treatment period will be summarized together with the individual preferred terms in that grouping. In addition, number (%) of participants with at least one AESI by maximum CTC grade, treatment-related AESIs, serious AESIs as well as action taken and outcome of the respective AESI will be summarized.

Summaries of these AESIs will be provided by treatment arm (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, death, etc.). The cumulative incidence over time and the corresponding figures (figures are only produced when >15% subjects with an event in at least one treatment arm) will be provided considering death and discontinuation due to any reason as competing risk events.

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

2.7.2 Deaths

Separate summaries for on-treatment and all deaths (*including post-treatment deaths* not in the AE eCRF but in the survival eCRF) will be produced on the Safety set by treatment arm, SOC and PT.

All deaths will be listed, where deaths occurring during the pre/post-treatment, will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

2.7.3 Laboratory data

Graphical summary (e.g., line graphs with error bar for standard deviations or boxplot) for each on-treatment lab parameter in hematology and biochemistry will be provided.

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (NCI) CTCAE version 5. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests where grades are not defined by CTCAE v5, results will be categorized as low/normal/high based on laboratory normal ranges. On analyzing laboratory data, all sources (central and local laboratories) will be combined. If data from central lab is available, then central lab data will be used for analysis. In the case that central lab data is not available but local lab data is available, then local lab data will be used for analysis. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date.

The following summaries (based on the Safety set) will be generated separately for hematology, and biochemistry tests (by laboratory parameter and treatment):

For laboratory tests where grades are defined by CTCAE v5:

- Worst post-baseline CTCAE version 5.0 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 version 5.0 grades to compare 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 classification to compare respective baseline to the worst on-treatment value.

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and alkaline phosphatase (ALP). The number (%) of participants with worst post-baseline values as per Novartis DILI Clinical Safety guidelines will be summarized for the criteria defined by single lab parameter. For combination of various parameters, the worst post-baseline values from each single parameter are taken into consideration, i.e. it may not come from the concurrent measurement (i.e. same assessment). For combined and concurrent of various parameters, the post-baseline values from the same assessment are taken into consideration.

The following summaries will be produced,

- ALT or AST > 3x upper limit of norm (ULN)

- ALT or AST > 5x ULN
- ALT or AST > 8x ULN
- ALT or AST > 10x ULN
- ALT or AST > 20x ULN
- TBL > 2x ULN
- TBL > 3x ULN
- ALT or AST >3x ULN & TBL > 2x ULN
- ALT or AST >3x ULN & TBL > 2x ULN & ALP >= 2x ULN
- ALT or AST >3x ULN & TBL> 2x ULN & ALP < 2x ULN
- Elevated ALT or AST & BILI (>2x baseline and >2x ULN)
- Elevated ALT or AST & BILI (>2x baseline and >2x ULN) & ALP>=2x ULN
- Elevated ALT or AST & BILI (>2x baseline and >2x ULN) & ALP<2x ULN

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

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

Data handling

The average of the triplicate ECG parameters at each time point which have been handled by lab, will be used in the analyses.

For unscheduled visits, ECGs that are reported on the same day and within 30 minutes apart from each other will be assumed to be sequential ECGs and thus will be used by lab to compute the mean of the ECG parameters.

Unscheduled ECG measurements will not be used in computing the summary statistics for change from baseline at each post-baseline time point. However, they will be used in the outlier analyses (e.g. QTc > 450 ms, > 480 ms, or > 500 ms at any time point, or an increase from baseline in QTc > 30 ms or > 60 ms). End of treatment ECG measurements for discontinued participants will be considered as an unscheduled measurement in case it occurs outside a scheduled visit.

Data analysis for ECG

The number (%) of participants with notable ECG values will be presented by treatment arm for the Safety set. Notable values are defined below:

QT, QTcF

- New value of > 450 and ≤ 480 ms
- New value of > 480 and ≤ 500 ms
- New value of > 500 ms
- Increase from baseline of > 30 ms and ≤ 60 ms
- Increase from baseline of > 60 ms

HR

- Increase from baseline > 25% and to a value > 100 bpm
- Decrease from baseline > 25% and to a value < 50 bpm

A listing of participants with all ECG assessments will be produced and notable values will be flagged. A separate listing of only the participants with notable ECG values will also be produced. In each listing, the assessments collected outside the on-treatment period will be flagged.

2.7.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (BP) (mmHg).

Data analysis

Notable vital sign values during on-treatment period in participants with non-notable values at baseline (e.g. systolic BP > 90 and < 180 mmHg for analysis of systolic BP) will be summarized using the criteria in the Table 2-8.

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

A listing of all vital sign assessments will be produced by treatment arm and notable values will be flagged. A separate listing of only the participants with notable vital sign values will also be produced. In the listing, the assessment collected outside of on-treatment period will be flagged.

Table 2-8 Notable vital sign values

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%
Weight (kg)	Increase >=10% from baseline	Decrease >= 10% from baseline
Body temperature (°C)	>= 39.1	-

ECOG performance status

ECOG performance status collected on treatment will be summarized. Shift tables will be provided comparing baseline with best and worst values during study for each treatment arm.

Tolerability

Tolerability of each study treatment will be assessed by summarizing the number of participants with dose modification (dose interruptions and dose reductions). Reasons for dose interruptions and dose reductions will be summarized.

2.8 Pharmacokinetic endpoints

Not applicable.

2.9 PD and PK/PD analyses

Not applicable.

2.10 Patient-reported outcomes

The study has secondary objectives for patient-reported outcomes (PROs) on EORTC QLQ-C30 and EORTC QLQ-CML24, which are discussed in Section 2.6.1.2 and Section 2.6.2.2. In addition, there are CCI [redacted]

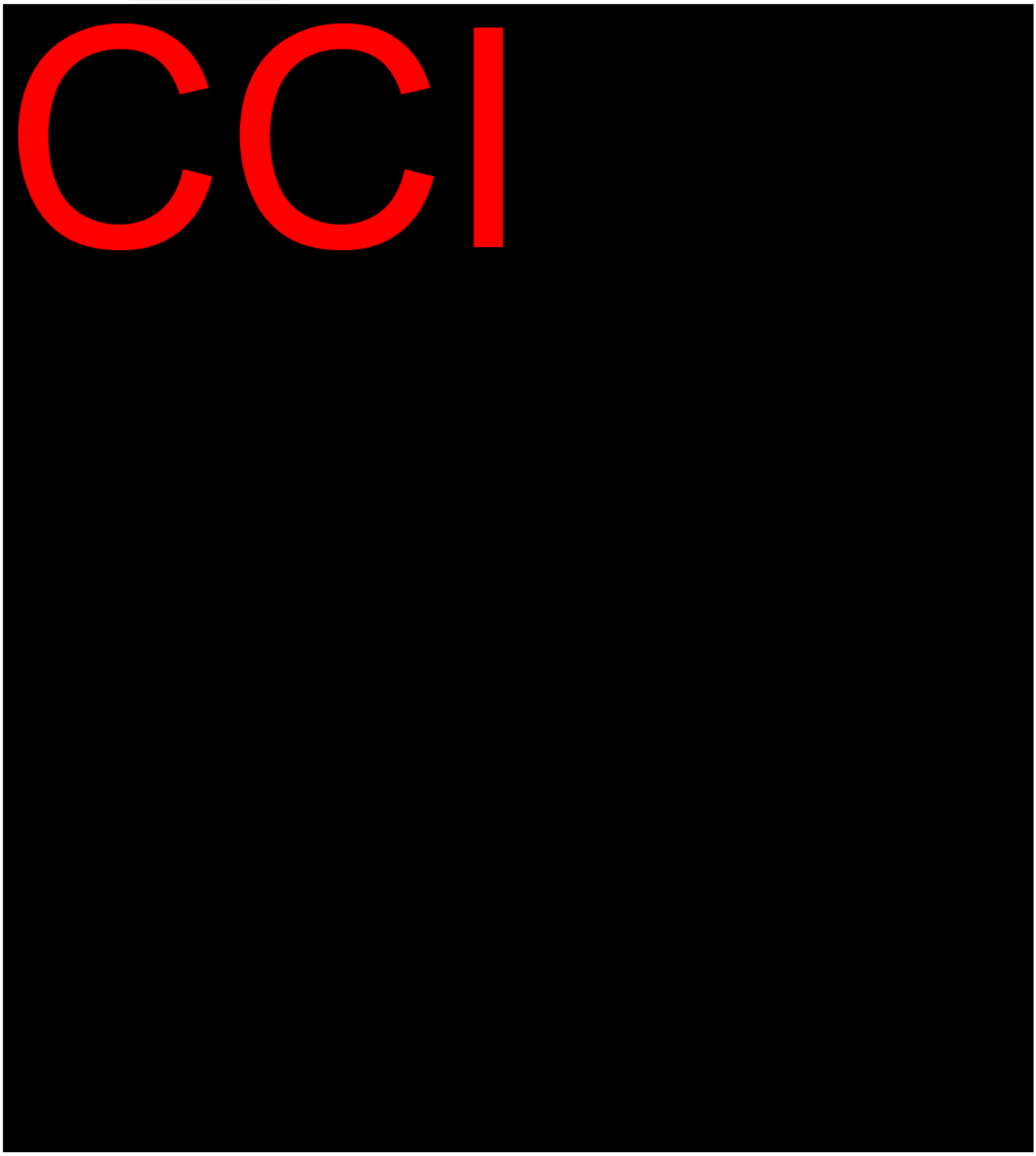
2.11 Biomarkers

Besides the secondary objective for efficacy on *BCR::ABL1* ≤1% at and by all data collection time points as discussed in Section 2.6, the CCI [redacted]

2.12 Other Exploratory analyses

CCI [redacted]

2.12.1 CCI



2.12.2 CCI

CCI

2.12.3 CCI

CCI

2.12.4 CCI

CCI

2.13 Interim analysis

One formal interim analysis is planned when approximately CCI discontinuations due to AE (the event of interest) have occurred. This formal interim analysis will allow for an early assessment of the tolerability of asciminib.

The interim analyses will be performed by an independent statistician. At the time of the formal interim analysis, the independent DMC will determine whether the interim analysis has crossed the pre-specified boundary or not. Regardless of the interim analysis results the study will continue until the primary analysis. Results from the interim analysis will only be communicated to the clinical team or any party involved in the study conduct (apart from the independent statistician and DMC members), if the boundary has been crossed.

The study is expected to be fully enrolled, i.e. approximately 550 participants are expected to be randomized, at the time of the interim analysis, when CCI events have occurred.

An alpha-spending function according to a two-look (Gamma Family) group sequential design with parameter $\gamma =$ CCI (equivalent to CCI significance level) as implemented in EAST (version 6.5) will be used to construct the boundary (Hwang, Shih, and DeCani, 1990). Since the observed number of events at the interim analysis may not be exactly equal to the planned number of events, the boundary will need to be re-calculated using the pre-specified alpha-spending function and based on the actual number of observed events at interim and targeted

total number of events (CCI) to calculate the exact information fraction. The observed p-value at the interim analysis will then be compared against the re-calculated boundary.

Based on the choice of the alpha-spending function described above and if the interim analysis is performed exactly at CCI events, the boundary expressed on the p-value scale at the interim is calculated as p=CCI. The observed (i.e. nominal) p-value has to be less than the p-value scale boundary CCI to conclude a significant result.

The primary analysis will be performed when approximately CCI events have occurred. If exactly CCI events are obtained at the primary analysis, the observed p-value will have to be less than CCI to declare statistical significance. The boundary for the interim analysis and primary analysis are pre-specified based on the alpha-spending function such that the overall significance level across all analyses is maintained at CCI.

In addition, regular safety review will be performed by the DMC, as outlined in CSP Section 10.1.4.1. Such safety analyses do not inflate the type I error for the primary endpoint hypothesis testing and thus no adjustment for multiplicity is required.

3 Sample size calculation

Sample size calculation has been detailed in Section 9.9 of the CSP.

Section 9.9 of the CSP:

The asciminib week 96 study treatment discontinuation rate due to AE (TTDAE) of CCI is assumed, based on conservatively rounding asciminib data CCI from the 3L study (ASCEMBL: CABL001A2301).

The nilotinib estimate for week 96 study treatment discontinuation rate due to AE of CCI, is based on the CSR data on file from the CCI study, which is the most recent study in Germany on use of nilotinib in 1L CML-CP.

Therefore, the cumulative probability to not discontinue from study treatment due to AE at week 96 for asciminib and nilotinib (comparator arm) are estimated as CCI and CCI, respectively.

The dropout rates at week 96 are calculated by subtraction of the study treatment discontinuation rate due to AE from the study treatment discontinuation rate due to all reasons for asciminib and nilotinib, which are estimated as CCI and CCI respectively.

The assumptions of sample size calculation for the primary endpoint, TTDAE, are summarized as:

- One-sided level of significance with $\alpha =$ CCI;
- Power=CCI;
- CCI cumulative probability to not discontinue due to AE at week 96, for asciminib and nilotinib, respectively with the difference of $\delta =$ CCI;
- CCI dropout rates at week 96, for asciminib and nilotinib, respectively;

- Accrual period of approximately 96 weeks at a uniform rate. The treatment duration is 96 weeks;
- 1:1 randomization for asciminib and nilotinib;
- One formal interim analysis using "Gamma Family" alpha spending function with parameter $\gamma =$ CCI (equivalent to $\alpha =$ CCI) for boundary, performed when around CCI discontinuations due to AE will occur.

Based on the assumptions, CCI events in total for two arms will be needed to detect a $\delta =$ CCI by 96 weeks after last participant first treatment (LPFT). A total of 550 participants will need to be randomized to observe the CCI events. The sample size calculation was conducted with software package EAST version 6.5.

Primary endpoint(s)

The sample size calculation is based on the primary endpoint TTDAE. The hypotheses to be tested and details of the testing strategy are described in Section 2.5.2.

The hypotheses for sample size calculation are based on the proportional hazard assumption such that,

$$H_0: HR = 1$$

$$H_\alpha: HR < 1$$

And the study is designed to achieve CCI power at $HR =$ CCI (corresponding to CCI vs. CCI cumulative probability to not discontinue due to AE at week 96, for asciminib and nilotinib, respectively) with a significance level of CCI . It is calculated that a total of CCI events need to be observed. This calculation assumes a one-sided log-rank test at the overall CCI level of significance, participants randomized to the two treatment arms in a 1:1 ratio, and a two-look group sequential design with a Gamma Family ($\gamma =$ CCI , equivalent to CCI significance level) alpha spending function performed when approximately CCI events occur.

Assuming that enrolment will continue for 24 months at a uniform rate, and CCI and CCI dropout rates for asciminib and nilotinib, a total of approximately 550 participants will need to be randomized to observe the targeted CCI events at about 24 months after the randomization date of the last participant, i.e. 48 months after the randomization date of the first participant. The enrolment rate is assumed as 23 participants per month.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

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

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

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

Scenario 2: If the dose end date is completely missing and the EOT page is available, the EOT completion date should be used.

- After imputation, compare the imputed end date with start date of treatment, if the imputed date is < start date of treatment, then **use the treatment start date**.

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

5.1.2 AE date imputation

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

Table 5-1 Imputation of start dates for AE

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  ○ Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

Missing Element	Rule
day	• If available month and year = month and year of study treatment start date then ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. ○ Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates for AE

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 with partial/missing dates will be displayed as such in the data listings.

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

5.1.3 Concomitant medication date imputation

The imputation rules for concomitant medications (ConMeds) are the same as described in Section 5.1.2.

5.1.3.1 Prior therapies date imputation

The imputation rules for prior therapies are the same as described in Section 5.1.2.

5.1.3.2 Post therapies date imputation

The imputation rules for post therapies are the same as described in Section 5.1.2.

5.1.3.3 Other imputations

The imputation rules for other safety assessments (e.g. VS, LB, EG) are the same as described in Section 5.1.2. Missing CML disease diagnosis date will be imputed only for missing day, which is to be replaced as 15th of the (known) month. When the month or the year is/are also missing, the diagnosis date is considered missing.

5.2 AEs coding/grading

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

AEs grading will be done according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.

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 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. 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. The latest available version of the document based on the underlying CTCAE version 5 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE v5, 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.

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

Corrected Calcium (mmol/L) = Calcium (mmol/L) +0.02 (40 – [Albumin (g/L)]

For calculation of laboratory CTCAE grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mmol/L) as for calcium. CTCAE grades for the corrected calcium will be assigned as described above for grading.

5.3.1 Hematology

Immature cells (promyelocytes, myelocytes, metamyelocytes and blasts) will not be displayed in shift tables and will only be listed.

Immature cells are manually counted only if anomalies are detected during the automatic testing. Therefore, when the automatic testing has been performed but no data is transferred for immature cells, then it is assumed that no immature cell exists and their values can be imputed to 0. Note that there should not be any imputation in case the automatic testing has not been

performed or the test of immature cells is present with missing value in the database (this would mean the test was to be performed but could not).

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 certain differential

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

For example, suppose WBC differential percentage for neutrophil is known to be 20%, then the neutrophil count is calculated as (WBC count) * (20/100).

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

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

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

5.3.2 Biochemistry

In order to avoid double reporting of the same information, all available values for BUN and UREA will be reported under the parameter name BUN (mmol/L) in listing using the following conversion rule: UREA (mmol/L) =2.14 BUN (mmol/L) (Lamb E et al., 2012).

5.3.3 Molecular response

Scaling towards an international standard will be performed for all molecular results using laboratory specific conversion factors. In this process, the raw ratio between BCR::ABL1 and the control gene ABL1 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 ICON MMD laboratory will be used in this study. The lab conversion factor for this assay is 1 (Brandford and Hughes, 2006).

The BCR::ABL1 ratio in international scale (IS) % is calculated by multiplying the raw BCR::ABL1 ratio with the lab specific conversion factor and then by 100:

BCR::ABL1 ratio (IS) (in %) = (BCR::ABL1 / ABL1) * conversion factor * 100.

The BCR::ABL ratio in IS % provided by the central laboratory will be used in the analyses.

Molecular response categories

Molecular response based on BCR::ABL1 ratio is categorized as follows:

- 10% < BCR::ABL1 ratio

- 1% < BCR::ABL1 ratio ≤ 10%
- 0.1% < BCR::ABL1 ratio ≤ 1%
- 0.01% < BCR::ABL1 ratio ≤ 0.1%
- 0.0032% < BCR::ABL1 ratio ≤ 0.01%
- BCR::ABL1 ratio ≤ 0.0032%
- No evidence of typical transcript

Subjects with no evidence of typical transcript will be identified with any one of the following conditions satisfied:

1. Has no BCR::ABL1 detected transcript by RQ-PCR at any timepoint (e.g. BCR::ABL1 is "not evaluable" /missing/ 0% for all RQ-PCR results) and with no evidence of typical transcript by NGS at any timepoint;
2. Has an RQ-PCR result <1% IS BCR::ABL1 at screening or baseline; or,
3. Has evidence of atypical transcript by NGS at any timepoint, for e.g. e19a2.

For participants with no evidence of typical transcript at the time of screening, they are categorized in a separate category and will not be counted towards any of the above category.

Major molecular response (MMR)

Major molecular response (MMR) is defined as a value of ≤ 0.1% of BCR::ABL1 ratio on the international scale (IS). This endpoint corresponds to a ≥ 3 log reduction in BCR::ABL transcripts from a standardized baseline value for untreated CML participants, which was established in the IRIS study (STI5710106). MMR will be considered as a binary variable with participants achieving MMR grouped as 'responders' and participants who not achieving MMR or participants with missing PCR evaluations grouped as 'non-responders'. Participants with no evidence of typical transcript will be grouped as 'non-responders'.

Loss of MMR

Unconfirmed loss of MMR is defined as an increase in *BCR::ABL1*/ABL to >0.1% by international scale (IS) in association with a ≥5-fold rise in *BCR::ABL1*/ABL from the lowest value achieved up to that time point on study treatment and replicated by a second analysis of the same sample. Loss of MMR must be confirmed by the analysis of another sample taken after an interval of not less than 4 weeks and not more than 6 weeks unless associated with loss of CHR or loss of BCR::ABL1≤1% or progression to AP/BC or CML related death.

If there is any assessment in between indicating a BCR::ABL1 ratio of ≤0.1% or a ≤5-fold increase in BCR::ABL1 ratio from the lowest value achieved up to that time point on study treatment, then the initial indication of loss of MMR cannot be confirmed. However, an assessment indicating (unconfirmed) loss of MMR will be considered as confirmed loss of MMR if the participant had loss of CHR or loss of BCR::ABL1 ≤1% after the achievement of MMR. CML-related death or progression to AP or BC will be considered as confirmed loss of MMR in any case (if they occurred on treatment) (given that the participant achieved prior MMR).

Thus to summarize:

- Unconfirmed loss of MMR is defined as *BCR::ABL1* level (IS) >0.1% in association with a ≥5-fold rise in *BCR::ABL1*/ABL1 from the lowest value achieved up to that time point 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 the analysis of another sample taken after an interval of not less than 4 weeks and not more than 6 weeks unless associated with loss of CHR or loss of *BCR::ABL1*≤1% or progression to AP/BC or CML related death.

For analysis purpose, loss of MMR must be confirmed by the analysis of the next evaluable sample taken after an interval of not less than 4 weeks unless associated with loss of CHR or loss of BCR::ABL1≤1% or progression to AP/BC or CML related death.

MR4.0 and Loss of MR4.0

MR4.0 is defined as a value ≤ 0.01% of BCR::ABL1 ratio on the IS (this corresponds to a ≥ 4 log reduction in BCR::ABL1 transcripts from a standardized baseline value for untreated CML participants). MR4.0 will be considered as a binary variable with participants achieving MR4.0 grouped as 'responders' and participants who not achieving MR4.0 or participants with missing PCR evaluations grouped as 'non-responders'. Participants with no evidence of typical transcript will be grouped as 'non-responders'.

Loss of MR4.0 is defined as BCR::ABL1 IS > 0.01% confirmed by subsequent sample analysis within 12 weeks showing loss of MR4.0 associated with a ≥ 5-fold rise in BCR::ABL1 from the lowest value achieved on study treatment, unless it is associated with loss of CHR, loss of *BCR::ABL1 ≤ 1%* or progression to AP/BC or CML-related death.

MR4.5 and Loss of MR4.5

MR4.5 is defined as a value of ≤ 0.0032% of BCR::ABL1 ratio on the IS (this corresponds to a ≥ 4.5 log reduction in BCR::ABL1 transcripts from a standardized baseline value for untreated CML participants). MR4.5 will be considered as a binary variable with participants achieving MR4.5 grouped as 'responders' and participants who not achieving MR4.5 or participants with missing PCR evaluations grouped as 'non-responders'. Participants with no evidence of typical transcript will be grouped as 'non-responders'.

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 loss of CHR, loss of *BCR::ABL1 ≤ 1%*, or progression to AP/BC or CML-related death.

Hematologic response

Complete hematologic response (CHR)

CHR is defined when all of the following criteria are present at any assessment which is confirmed by another assessment at least after 4 weeks:

- White blood cells (WBC) count < 10 × 10^9 /L
- Platelet count < 450 × 10^9 /L
- Basophils < 5%
- No blasts and promyelocytes in peripheral blood
- Myelocytes + metamyelocytes < 5% in peripheral blood
- No evidence of extramedullary disease, including spleen and liver.

The assessment is not considered CHR, if there are any values indicative of CML in AP or BC (i.e. by blasts in bone marrow if available). The information used for hematological assessment will be obtained from the laboratory, extramedullary and bone marrow data (if available), all merged by participant and date. To accommodate for missing parameters, specific laboratory results may be carried forward up to 14 days such that assessments performed within a two-week period can be combined into one complete evaluation of hematological response. A value will be carried forward for no more than up to the subsequent valid assessment of the respective laboratory parameter. If even after applying this carry-forward algorithm, any of the above laboratory parameters is not available at a given assessment date, the response assessment will be considered missing, unless any of the available values (including those carried forward) indicates that there is no response in which case the assessment will be 'No response'.

For confirmation of CHR, both the initial CHR as well as the confirming assessment (at least 4 weeks after the initial assessment) must satisfy all the criteria mentioned above and no assessment in between indicates 'No response'. The terms "confirmed CHR" and "CHR" are used as synonymous give that the definition of CHR mentioned above already includes a requirement for confirmation.

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

Loss of CHR

Loss of CHR is defined by meeting any of the following:

- WBC count > 20 × 10^9/L
- Platelet count ≥ 600 × 10^9/L
- Appearance of blasts or promyelocytes in peripheral blood
- Appearance of myelocytes + metamyelocytes ≥ 5% in peripheral blood
- Progressive splenomegaly refractory to therapy (i.e. ≥ 5cm below left intercostal margin)

The last bullet is not applicable as the information is not collected in eCRF page.

In addition, CML related death or progression to AP or BC will be considered as loss of CHR in any case (if they occurred on treatment).

Treatment Failure

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

- *BCR::ABL1* ratio (IS) > 10% at 3 months if confirmed within the next 1–3 months after initiation of treatment

- *BCR::ABL1* ratio (IS) > 10% at 6 months after initiation of treatment
- *BCR::ABL1* ratio (IS) > 1% at or after 12 months after initiation of treatment
- Detection of a *BCR::ABL1* mutation which may be associated with imminent resistance to study treatment (asciminib or nilotinib) or high-risk additional chromosome abnormalities in Ph+ cells at any time after initiation of study treatment.

  The criteria related to the BCR::ABL1 mutation or high-risk additional chromosome abnormalities in Ph+ cells will not be used.

All *BCR::ABL1* assessments from central lab, including scheduled and unscheduled are utilized. Per protocol the allowed visit window for any given visit +5 days from the target assessment day. The events for 'treatment failure' will be,

- If *BCR::ABL1* ratio (IS) > 10% on or after **day 85** (Day 85 for 12 Weeks visit) but on or before **day 168** (Day 169 for 24 Weeks visit - 1 day), and the >10% is confirmed within day 24 to day 90;
- If *BCR::ABL1* ratio (IS) > 10% on or after **day 169** (Day 169 for 24 Weeks visit) but on or before **day 336** (Day 337 for 48 Weeks visit - 1 day);
- If *BCR::ABL1* ratio (IS) > 1% on or after **day 337** (Day 337 for 48 Weeks visit).

If a participant has multiple assessments that satisfy the treatment failure criteria, the earliest date is considered as the date of treatment failure.

CML progression to accelerated phase (AP) or blast crisis (BC)

For the evaluation of CML progression to AP or BC, the following criteria will be used. Accelerated phase (AP) is defined by any of the following:

- ≥ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate
- ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate
- ≥ 20% basophils in the peripheral blood (unless within the first 3 months of study treatment).
- Thrombocytopenia (<100 x 10^9/L) that is unrelated to therapy*

*As thrombocytopenia is a known adverse reaction to CML therapy, platelets <100 x 10^9/L are only considered as CML-AP if the subject had these values within 30 days of treatment discontinuation due to disease progression. Additionally, isolated thrombocytopenia at baseline which is deemed by the investigator as not CML-AP, does not fulfill the criteria of progression to CML-AP.

Blast crisis (BC) is defined by any of the following:

- ≥ 30% blasts in peripheral blood or bone marrow aspirate
- Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e. chloroma).

Any isolated laboratory value of elevation of basophils, assessed by the investigator as not advanced phase within the first 4 weeks of study treatment, will not be considered as progression, unless the patient discontinues study treatment due to progression or unsatisfactory therapeutic effect within the first 8 weeks.

Should a participant be classified as both AP and BC, BC takes precedence as it is a more severe state of the disease.

CML-related deaths

CML-related death is considered as any death during treatment or follow-up (safety or survival)

- if the principal cause of death is marked as "study indication" in the eCRF by the investigator, or
- if the death occurred subsequent to documented progression to AP/BC and the cause of death is reported as "unknown" or not reported by the investigator.

With respect to the second bullet, as "unknown" cause of death will be coded to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term 'Death', this MedDRA coding will be used in the derivation of CML-related death.

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

Cause-specific hazard

The cause-specific hazard model will be implemented using SAS procedure PROC PHREG (with TIES=EXACT option in the MODEL statement) considering the stratification factor. In the PROC PHREG statements, STATUS (0,2) will be specified whereas 0 for censored participants and 2 for the participants who discontinued from study treatment due to the competing risk events. The p-value will be presented to declare the significance. The estimated hazard ratio with the 95% Wald confidence interval will also be presented.

Two-sided p-values for hazard ratios are generated by SAS by default. One-sided p-values can be derived based on the following algorithm:

- If the TTDAE hazard rate for the asciminib treated patients is lower than or equal to that for the nilotinib, then the one-sided p-value for the test is p/2, where p is the two-sided p-value.
- If the TTDAE hazard rate for the asciminib treated patients is higher than for the nilotinib, then the one-sided p-value is 1-p/2.

Find-Gray Subdistribution hazard model

The subdistribution hazard model will be fitted by using PROC PHREG in SAS, with specifying STATUS (0) for censored participants and EVENTCODE=1 for the event of interest. The p-

value will be presented together with hazard ratio and 95% Wald confidence interval. The p-value will be adjusted in the same way as in Cause-specific hazard model.

Cumulative incidence function

The cumulative incidence functions can be plotted by the PLOTS (OVERLAY=STRATUM) = CIF option in the PROC PHREG procedure.

5.4.2 Analysis supporting secondary objective(s)

Proportion estimation

For the secondary efficacy endpoints at/by time points, unstratified proportions of responders in each treatment arm along with their two-sided Clopper-Pearson 95% CI's (SAS procedure PRO FREQ with the EXACT option) will be reported.

Two estimates of the difference in the response rates will be generated. The first is the unstratified difference in the response rates and its Wald's 95% CI (SAS procedure PROC FREQ with RISKDIFF option of TABLES statement, to request the unconditional risk differences). And the second is the Cochran-Mantel-Haenszel estimate of common risk difference and its 95% CI (SAS procedure PROC FREQ with RISKDIFF(COMMON) option of TABLES statement, to request the common(stratified) risk differences).

Kaplan-Meier estimates

An estimate of the time-to-event in each treatment arm will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The standard error and confidence interval of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 2015]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized, and the 95% confidence band will be calculated by using the option CONFTYPE=LOGLOG. Percentiles (25^{th}, 50^{th} (median survival), 75^{th}) for each treatment arm will be obtained along with 95% confidence intervals by the method of [Brookmeyer and Crowley 1982].

The Kaplan-Meier curve can be generated by the procedure PROC LIFETEST with PLOT=SURVIVAL (ATRISK CB) option.

Cox proportional hazards model

In the Cox proportional hazards (PH) model, the hazard ratio will be estimated by using the SAS procedure PROC PHREG (with TIES=EXACT option in the MODEL statement). In a stratified unadjusted Cox model, the MODEL statement will include the treatment arm variable as the only covariate, and the STRATA statement will include stratification variable(s). Hazard ratio with two-sided 95% confidence interval will be based on the Wald test.

5.4.3 Exposure-adjusted incidence rate

To adjust for different durations of exposure across treatment arms, the incidence rate (IR) per 100 patient-years of exposure (exposure-adjusted incidence rates of adverse events) will be calculated.

The IR per 100 patient-years is defined as a Numerator/Denominator, where

- Numerator = 100 * number of participants with the adverse events of interest (not the number of events; one participant may have more than one event).
- Denominator = patient-years = (among all participants in the population, sum of the duration of exposure (in days) until the first onset of the adverse event of interest, if the participant experienced the adverse event, or until the date of last dose if the participant did not experience the adverse event) / 365.25.

5.5 Rule of exclusion criteria of analysis sets

Please refer to Section 2.2 for full analysis set and safety set.

6 Reference

Branford S, Hughes T. (2006). Diagnosis and monitoring of chronic myeloid leukemia by qualitative and quantitative RT-PCR. Methods Mol Med; 125:69-92.

Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time. Biometrics, 38, 29 – 41.

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases, 40(5), 373-383

Clopper CJ and Pearson ES. (1934). "The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial", Biometrika 26: 404-413.

Collett, D. (2015). Modelling survival data in medical research. CRC press.

D'Agostino Sr, R. B., Vasan, R. S., Pencina, M. J., Wolf, P. A., Cobain, M., Massaro, J. M., & Kannel, W. B. (2008). General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation, 117(6), 743-753.

Hochhaus A, Baccarini M, Silver RT, et al. (2020), "European LeukemiaNet 2020, recommendations for treating chronic myeloid leukemia". Leukemia 34: 966-984.

Hwang, I. K., Shih, W. J., & De Cani, J. S. (1990). Group sequential designs using a family of type I error probability spending functions. Stat. in medi; 9(12): 1439-45.

ICH E9(R1) Harmonized Guideline: addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019.

Gordon Lan, K. K., & DeMets, D. L. (1983). Discrete sequential boundaries for clinical trials. Biometrika, 70(3), 659-663.

Lamb E, et al. (2012). Kidney Function Tests in Elsevier Health Sciences (Ed), Tietz Textbook of Clinical Chemistry and Molecular Diagnostics (Chapter 25).

Kaplan, E. L., & Meier, P. (1958). Nonparametric estimation from incomplete observations. Journal of the American statistical association, 53(282), 457-481.

Mantel, N., & Haenszel, W. (1959). Statistical aspects of the analysis of data from retrospective studies of disease. Journal of the national cancer institute, 22(4), 719-748.

Pfirrmann, Markus, et al. "The EUTOS long-term survival (ELTS) score is superior to the Sokal score for predicting survival in chronic myeloid leukemia." Leukemia 34.8 (2020): 2138-2149.