NOVARTIS

Clinical Development

ABL001/Asciminib

CABL001A2302 / NCT04948333

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

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
06-Oct-2021	Prior to DB lock	Creation of final version	N/A - First version	NA
07-Mar-2024	Prior to dry-run	Amendment 1	See details below	See details below
16-July-2024	Post week 48 DBL	Addendum 1	See details below	See details below

Amendment 1

The following are the changes in the SAP:

- Updated on List of abbreviations and corrected typos through this document.
- Clarified the analyses for FAS or SAF2 through this document.
- Table 2-1: Updated to clarify the analysis set for each objective.
- Section 2.1: Safety analysis added to the week 48 and week 96 analysis. No formal statistical testing to be done at EOT analysis.
- Table 2-4: New source data and corresponding conditions added for last contact date.
- Section 2.2: Definitions of FAS and FAS2 updated.
- Section 2.2.1: Categories for mutation status at baseline revised.
- Section 2.3.1: Disposition summary related to relationship with COVID-19 removed.
- Section 2.4.1: Dose intensities will be summarized for both SAF and SAF2.
- Section 2.5.3: Updated handling of missing intercurrent events.
- Section 2.5.5: Updated the analysis strategy for missing values not related to intercurrent events.
- Section 2.6.1.3: Revised the definition of treatment failure.

- Section 2.6.2: Updated the analysis for high-risk ACAs
- Section 2.6.2: Revised the definition of Duration of MMR
- Section 2.7.4.2: Updated the cardiovascular risk assessment measures
- Section 5.4.1: Revised the definition of Confirmed loss of MMR
- Section 5.4.4: Added new definition of treatment failure.
- Added new references.

Addendum 1

- Replaced BCR-ABL with BCR::ABL throughout the document
- Section 2.2: Updated the method of identification and confirmation of the MMR status at baseline for all subjects.
- Section 2.5.3: Updated the strategy to handle intercurrent events 4a and 4c.
- Section 3: Added reference to ASCEMBL CSR for sample size calculations
- Section 5.4.1: Updated the method of imputation for “Not Detected” BCR::ABL ratio
- Section 5.6.1: The method of Multiple Imputation was removed.
- Section 6: Reference was updated.

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List of abbreviations

ACA	Additional Chromosomal Abnormalities
ADD	Average Daily Dose
AE	Adverse Event
AP	Accelerated Phase
ATC	Anatomical Therapeutic Classification
BC	Blast Crisis
BCR::ABL	BCR::ABL fusion gene(also called Philadelphia chromosome)
b.i.d.	Bis in Die
BUN	Blood Urea Nitrogen
CCyR	Complete Cytogenetic Response
CHR	Complete Hematological Response
CM	Concomitant Medication
CML-CP	Chronic Myelogenous Leukemia – Chronic Phase
CRF	Case Report Form
CRS	Case Retrieval Strategy
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DMS	Document Management System
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOsT	End of study treatment
EOT	End of treatment in the treatment phase (subject level)
ELN	European Leukemia Network
FAS	Full Analysis Set
FAS2	Full Analysis Set 2
FDA	Food and Drug Administration
IA	Interim Analyses
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IRT	Interactive Response Technology
IS	International Scale
MDASI-CML	MD Anderson Symptom Inventory – Chronic Myelogenous Leukemia
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mg	milligram(s)
mL	milliliter(s)
MMR	Major Molecular Response
MR4	Molecular Response 4 log reduction from baseline
MR4.5	Molecular Response 4.5 log reduction from baseline
CCI	CCI
OS	Overall Survival
PCR	Polymerase Chain Reaction

PFS	Progression Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
QTcF	QT interval corrected by Fridericia's formula
q.d.	Quaque Die / Once a day
RAP	Reporting & Analysis Process
SAE	Serious Adverse Event
SAF	Safety Set
SAF2	Safety Set 2
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
TFLs	Tables, Figures, Listings
TFR	Treatment Free Remission
TKIs	Tyrosine Kinase Inhibitors
TTF	Time to Treatment Failure
WBC	White Blood Cell(s)
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses of primary objective, secondary objectives and selected exploratory objectives for the clinical study reports (CSR) of study CABL001A2302, a phase 3b, multi-center, open-label, treatment optimization study of oral asciminib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors.

The content of this SAP addendum 1 is based on the protocol CABL001A2302 version 01 and Case Report Form (CRF) version 6.0. All decisions regarding 48-week primary analysis, 96-week analysis, end of study treatment analysis, and postings for ClinTrial.gov and EudraCT, as defined in this SAP document, have been made prior to the first database lock of the study data for the primary analysis.

1.1 Study design

The study is an international, multi-center, non-comparative, phase IIIb, treatment optimization study of asciminib (randomized 1:1 to either 40 mg b.i.d. or 80 mg q.d.) in adult subjects previously treated with 2 or more TKIs. 156 subjects will be randomized to either asciminib 40 mg b.i.d. or 80 mg q.d. An additional 30 subjects (randomized to either asciminib 40 mg b.i.d. or 80 mg q.d.) intolerant only to last TKI and in MMR at baseline will also be included.

Randomization is only used to have a balance in the allocation of treatment into either asciminib 40 mg b.i.d. or 80 mg q.d. The trial will not be powered to compare both treatments.

In subjects not achieving MMR at 48 weeks or losing the response after the week 48 assessment up to week 108, asciminib dose may be escalated to 200 mg q.d. if in the investigator's opinion

the subject may benefit from the escalation. In addition, there must not be any grade 3 or 4 toxicity while on therapy, or persistent grade 2 toxicity, possibly related to asciminib and unresponsive to optimal management.

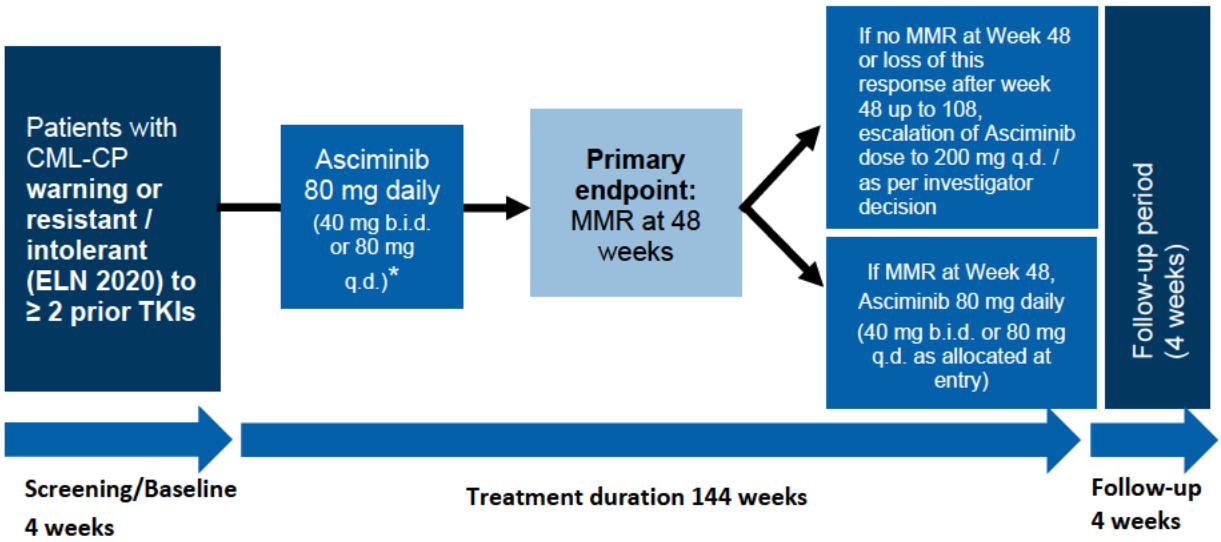
BCR::ABL1 and CCI [redacted] results are required before increasing asciminib dose, therefore the dose escalation can occur at next scheduled visit upon results review of the prior visit. In subjects losing response after the week 48 assessment, the last possible time point to initiate the 200 mg dose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

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

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

The primary endpoint of the study is MMR at 48 weeks.

Figure 1-1 Study design



*Treatment assignment to 40 mg b.i.d. or 80 mg q.d. (1:1) will be done through Interactive Response Technology (IRT).

Three analyses are planned for this study, including the 48-week primary analysis, the 96-week analysis, and the End-of-Study-Treatment (EOsT) analysis. The timing when those analyses are conducted is summarized in Section 2.1.

No formal interim efficacy analysis is planned in this study.

1.2 Study objectives, endpoints and estimands

Table 1-1 Objectives and related endpoints

The “Objectives and related endpoints” table is described in the CSP. It is reproduced below to clarify which analyses are performed for the subjects not in MMR at baseline (cohort a in table below), and which analyses are for the additional subjects in MMR at baseline (cohort b in table below).

Objectives	Endpoint(s)
Primary:	
• To estimate the molecular response rate at week 48 of all subjects (40 mg b.i.d. asciminib and 80 mg q.d.) with CML-CP following two or more prior TKI treatments and with no evidence of MMR at baseline. (cohort a)	• Major Molecular Response (MMR) rate at week 48.
Secondary:	
• To evaluate the safety and tolerability of asciminib in subjects with CML-CP following two or more prior TKI treatments. (cohort a, cohort b)	• Type, frequency and severity of adverse events, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG and other safety data (vital signs, physical examination).
• To assess the rate of molecular responses (MMR) in subjects without MMR at baseline, at alternative time points at weeks 12, 24, 36, 72, 96 and 144. (cohort a)	• MMR rate at weeks 12, 24, 36, 72, 96 and 144.
• To assess the rate of molecular responses (MMR) at week 48 for subjects with MMR at baseline (cohort b)	• MMR rate at week 48 for subjects with MMR at baseline.
• To assess the time to MMR (cohort a)	• Time from the date of randomization to the date of first documented MMR
• To assess the rate of early responses of BCR::ABL1 ≤10% and ≤1% at weeks 12, 24, 36 and 48. (cohort a)	• Rate of BCR::ABL1 ≤ 10% and ≤1% at weeks 12, 24, 36 and 48
• To assess the rate of deep molecular responses (MR4 and MR4.5) at weeks 12, 24, 36, 48, 72, 96 and 144. (cohort a)	• Rate of MR4 and MR4.5 at weeks 12, 24, 36, 48, 72, 96 and 144.
• To assess cytogenetic response (% Ph+ metaphases) at weeks 48 and EOT. (cohort a)	• Rate of complete cytogenetic response (CCyR) at weeks 48 and EOT.
• To characterize the impact of additional cytogenetic abnormalities on efficacy. (cohort a)	• Additional chromosomal abnormalities and occurrence of high-risk ACAs
• To assess cumulative molecular responses by all-time points. (cohort a)	• Rate of BCR::ABL1 ≤ 10%, BCR::ABL1 ≤1%, MMR, MR4 and MR4.5 by all-time points.
• To assess duration of MMR. (cohort a, cohort b)	• Duration of MMR: the time from the date of first documented MMR to the earliest date of loss of MMR, progression to AP or BC, or CML-related death.
• To assess sustained deep molecular responses as prerequisite for TFR. (cohort a, cohort b)	• Duration of MR4 without loss of MMR.

• To assess rate of progression (PFS). (cohort a)	• Time from the date of randomization to the earliest occurrence of documented disease progression to AP/BC or the date of death from any cause.
• To assess overall survival (OS). (cohort a)	• Time from randomization to death.
• To assess time to treatment failure (TTF). (cohort a)	• Time from randomization to treatment failure define as BCR::ABL1 > 1%.
• To evaluate subject reported outcomes and quality of life by using QoL scale. (cohort a, cohort b)	• Change in symptom burden and interference from baseline over time according to the MDASI-CML PRO instrument.
Exploratory:	
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

1.2.1 Primary estimand(s)

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

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

The primary estimand is described by the following attributes:

1. Population: CML Subjects with resistance or intolerance to 2 or more prior TKIs per the 2020 ELN recommendations. Further details about the population are provided in Protocol Section 5.

2. Endpoint: MMR achieved at week 48 while on study treatment without meeting any treatment failure criteria prior to week 48. A subject will be counted as having achieved MMR at week 48 if he/she meets the MMR criterion (BCR::ABL1 level $\leq$ 0.1%) at week 48 while on study treatment unless the subject met any treatment failure criteria prior to week 48.

3. Treatment of interest: the investigational treatment asciminib taken for at least 48 weeks, with or without dose modification, dose interruption or any intake of concomitant medications, or intake of prohibited medications.

4. List of intercurrent events:

a) Treatment discontinuation (i.e. having performed an EOT visit) prior to week 48 due to any reason

b) Dose modification, dose interruption, or any intake of concomitant medications.

c) Intake of prohibited medications.

5. The summary measure: MMR rate and its 95% confidence interval at week 48.

Handling of intercurrent events is discussed in Section 2.5.3.

1.2.2 Secondary estimand(s)

Not applicable.

2 Statistical methods

2.1 Data analysis general information

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

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

- 48-week primary analysis: Formal testing of the primary endpoint will be performed. Analyses of other efficacy endpoints at and by week 48 and safety analyses will also be performed.
- 96-week analysis: Analyses of efficacy endpoints at and by week 96 and safety analyses will be performed.
- End of study treatment analysis is similar to the 96-week analysis without formal statistical testing. All efficacy and safety analyses will be included.

Except where categorically stated, all analyses, including the primary analysis will be conducted on **all** participant data (excluding the additional subjects who were intolerant to the last TKI and were in MMR at baseline). The purpose of having two randomized groups is not for comparison, but to provide data on different dosing regimens. Randomization is only used to have a balance in the allocation of treatment into either asciminib 40 mg b.i.d. or 80 mg q.d.

Data included in the analyses

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

- 48-week Primary analysis: After all randomized subjects have been on study treatment for 48 weeks or discontinued earlier, i.e., LPFT + 48 weeks.

- 96-week analysis: After all randomized subjects have been on study treatment for 96 weeks or discontinued earlier, i.e., LPFT + 96 weeks.
- End of study treatment analysis: 30 days after the EOsT. (Note: After the study treatment period, every effort will be made to continue provision of the study treatment to subjects who in the opinion of the investigators are still deriving clinical benefit through alternative options if asciminib is not commercially available).

All statistical analyses will be performed using all data collected in the database up to the respective data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the respective cut-off date and end date after the respective cut-off date will be reported as ongoing. The same rule will be applied to events starting before or on the respective cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

General analysis conventions

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

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of subjects in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum).

2.1.1 General definitions

Investigational drug and study treatment

Investigational drug, will refer to asciminib. No additional treatment beyond investigational drug is included in this trial.

Treatment groups

- Asciminib 40 mg b.i.d. (Subjects randomized to asciminib 40 mg b.i.d. at the beginning of the study)
- Asciminib 80 mg q.d. (Subjects randomized to asciminib 80 mg q.d. at the beginning of the study)

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

Date of end of study treatment (EOsT)

The EOsT date is the date that the study treatment is ended for the entire study. On this date, subjects are treated for at maximum 144 weeks, unless subjects have discontinued study treatment earlier.

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a non-zero dose of study treatment was administered as per the Study Treatment electronic case report form (eCRF). The date of first administration of study treatment will also be referred as start of study treatment.

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

Start Date of dose escalation

The start date of dose escalation is derived as the first date when a subject had dose escalated to 200 mg q.d. of study treatment as per the Subject Status Dose Escalation case report form (eCRF).

Date of last administration of study treatment

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

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

Study day

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

The 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 safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, etc.) is the start of study treatment.

The reference start date for all other, non-safety assessments (e.g. molecular response, disease progression, ECOG performance status, patient reported outcomes (PRO), etc.) is the date of randomization.

The reference start date for dose escalation (200 mg q.d.) is the date when a subject starts first escalated dose.

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

A week length is defined as 7 days. If duration is reported in weeks, duration in days will be 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. In the context of baseline definition, the efficacy evaluations also include PRO and performance status.

For safety evaluations, the last available assessment, including unscheduled assessments before the date of start of study treatment is taken as "baseline" assessment.

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

For ECGs requiring triplicate measures per time point, the average of these measurements will be reported by sites in eCRF baseline.

For mutations, the screening/baseline assessment is taken as "baseline" assessment.

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

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

On-treatment assessment/event and observation periods

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

1. ***pre-treatment period***: from day of subject's informed consent to the day before first administration of study treatment

2. ***on-treatment period:*** from date of first administration of study treatment to 30 days after date of last administration of study treatment (including start and stop date).

3. ***post-treatment period:*** starting at day 31 after last administration of study treatment.

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.

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

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

Efficacy summaries on the FAS and FAS 2 (apart from OS and PFS) include data from baseline up to either the last assessment on or before the End of Treatment (EoT) visit or before or on treatment failure, whichever is the earliest.

The efficacy assessments collected post-treatment failure or post-EoT visit are not included in any efficacy analyses (except for OS and PFS analyses). However, they will be listed and flagged as appropriate.

Windows for multiple assessments

Data such as molecular response, cytogenetic response collected over time (including unscheduled visits) will be summarized by scheduled time point. As subjects do not always adhere to the visit schedule, visits will be remapped according to visit windows defined in Tables 2-1 to Table 2-3 of this document to enable by-visit analysis. Only those protocol-defined visits will have the visit window defined. Each assessment (including the end of treatment 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 assessment is assigned to the same time window, the assessment performed closest to the target date will be used for by-visit statistical analyses. If 2 assessments within a visit window are equidistant from the target date, then the average of the 2 assessments will be used. If multiple assessments are on the same date, then the the average will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Table 2-1 Time windows for molecular response

Assessment	Target day of assessment	Time Interval
Baseline	≤ 1	≤ Day 1[#]
Week 12	85	Day 2 to day 127
Week 24	169	Day 128 to day 211
Week 36	253	Day 212 to day 295
Week 48	337	Day 296 to day 379
Week k (k=60, 72, …)	Kx7 + 1	Day kx7-40 – kx7+43

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

Table 2-2 Time windows for cytogenetic response

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1#
Week 48	337	Day 253 to day 420
EOT*	EOT	EOT

Day 1 = Date of randomization. Should bone marrow assessments have been performed before the main informed consent is signed but within 56 days of Week 1 Day 1, no further bone marrow sampling will be required at screening and local assessment data will be collected.

* Only required for Early Discontinuation due to lack of response / loss of response

For PRO data time windows will be defined for descriptive summary by visit. 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, the assessment obtained prior to visit will be considered.

Table 2-3 Time windows for PRO: MDASI-CML

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1#
Week 4	29	Day 2 to day 57
Week 12	85	Day 58 to day 127
Week 24	169	Day 128 to day 253
Week 48	337	Day 254 to day 421
Week 72	505	Day 422 to day 589
Week 96	673	Day 590 to day 757
Week 120	841	Day 758 to day 925
EOT (Week 144)	1009	Day 926 to day 1009

Day 1 = Date of randomization

The general rule for the target day of assessment and time interval is: For Week k visit, target day of assessment is defined as k*7+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 of next applicable visit” – “target day of current visit”)/2.

Last contact date

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

Table 2-4 Last contact date data sources

Source data	Conditions
Date of randomization	No condition
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term
Start/End dates from drug administration record	Non-missing dose. Doses of 0 are allowed
Study disposition date	The date of the subject's last protocol assessment performed in the study phase
Any specific efficacy (molecular or cytogenetic) assessment date if available	Evaluation is marked as 'done'
Laboratory/PK collection dates	Sample collection marked as 'done'
Vital signs date	At least one non-missing parameter value
Performance status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the respective data cut-off date. The cut-off date will not be used for last contact date, unless the subject was 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 subjects in the analysis of overall survival.

2.2 Analysis sets

The subject population for the study includes subjects resistant or intolerant to 2 or more prior TKI treatments without MMR at baseline, and an additional group of subjects who were intolerant to the last TKI and were in MMR at baseline. Note that the YR data domain from IRT will be used to identify the stratification groups for the study population, and the biomarker data (B1 domain) containing BCR::ABL ratio will be used to confirm the MMR status at baseline for all subjects. If there is discrepancy between YR and B1 data, the MMR status at baseline will be assessed based on the B1 data.

The Analysis Sets are stated as follows:

Full Analysis Set

The Full Analysis Set (FAS) comprises all participants to whom study treatment has been assigned by randomization except the additional subjects who were intolerant to the last TKI and were in MMR at baseline.

Full Analysis Set 2

The Full Analysis Set 2 (FAS 2) comprises only the additional subjects who were intolerant to the last TKI and were in MMR at baseline and to whom study treatment has been assigned by randomization.

Safety Set

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

Safety Set 2

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

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

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

Withdrawal of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from further participation in the trial will not be included in the analysis. The date on which a subject withdraws consent is recorded in the eCRF.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already

started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

2.2.1 Subgroup of interest

Subgroup analyses of the primary efficacy endpoint to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics may be conducted on the following subgroups, if there are at least 10 subjects in each category:

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

  Note: Only one reason for discontinuation is allowed for each prior therapy.
- Number of prior TKI therapies: 2, 3 or ≥4
- Cytogenetic response status at baseline: Major (MCyR) - 0 to 35% Ph+ metaphases; Complete (CCyR) - 0% Ph+ metaphases; Partial (PCyR) - >0 to 35% Ph+ metaphases; Minor (mCyR) - >35 to 65% Ph+ metaphases; Minimal - >65 to 95% Ph+ metaphases; or None - >95 to 100% Ph+ metaphases.
- Prior TKI treatment: imatinib, nilotinib, dasatinib, bosutinib, radotinib or ponatinib
- Prior ponatinib: Yes or No
- Mutation status at baseline: Non-mutant or mutant

Other subgroup may be analyzed as appropriate.

2.3 Subject disposition, demographics and other baseline characteristics

2.3.1 Subject disposition

The number (%) of randomized subjects included in the FAS and FAS2 will be presented overall and by treatment group (40mg bid or 80mg qd). The number (%) of screened and not-randomized subjects and the reasons for screening failure will also be displayed. The number (%) of subjects in the corresponding analysis set who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment group (40 mg bid or 80 mg qd).

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

- Number (%) of subjects who were randomized (based on data from IRT system)
- Number (%) of subjects who were randomized but not treated (based on study treatment eCRF page not completed for any study treatment component)

- Primary reason for not being treated (based on "Disposition" eCRF page)
- Number (%) of subjects who were treated (based on study treatment eCRF pages of each study treatment completed with non-zero dose administered)
- Number (%) of subjects who are still on-treatment (based on the "subject status" and "Treatment Disposition" page not completed);
- Number (%) of subjects who discontinued the study treatment phase overall, before Week 48 and Week 96 (based on the "Subject status" and "Disposition" page)
- Primary reason for study treatment phase discontinuation overall, before Week 48 and Week 96 (based on the "Disposition" page).

Separate disposition tables will be presented for subjects with dose escalation.

Protocol deviations

The number (%) of subjects in the FAS and FAS2 with any protocol deviation will be tabulated by deviation category (as specified in the Study Specification Document) overall. All protocol deviations will be listed. In addition, the number (%) of subjects in the FAS and FAS2 with any COVID-19 related protocol deviation (COVID-19 specific protocol deviations as well as non-specific COVID-19 protocol deviations with a COVID-19 relationship) during the treatment period will be tabulated by deviation category (as specified in the Study Specification Document) overall.

Analysis sets

The number (%) of subjects in each analysis set (defined in Section 2.2) will be summarized.

2.3.2 Demographics and other baseline characteristics

For the subjects resistant or intolerant to 2 or more prior TKI treatments without MMR at inclusion to the trial, the FAS will be used for all demographics and baseline summaries and listings (except disease characteristics). For the additional subjects who were intolerant to the last TKI and were in MMR at baseline, the FAS 2 will be used for demographics and baseline summaries and listings (except disease characteristics). All the demographics and baseline characteristics will be summaried and listed for FAS and FAS 2.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed. Categorical data (e.g. age groups: 18 - <65, 65 - <75, and ≥ 75 years and 18 - <65, ≥ 65 years, sex, race, ethnicity, ECOG performance status) will be summarized by frequency counts and percentages; the number and percentage of subjects with missing data will be provided. Continuous data (e.g. age, weight, height, body mass index) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum), where BMI (kg/m^2) will be calculated as weight[kg] / (height[m]^2) using weight at screening.

Diagnosis and extent of cancer

All diagnosis and extent of cancer data will be summarized. The summary table will include time (years) since initial diagnosis (descriptive statistics with N, mean, median, standard deviation, minimum and maximum) and historical mutation: present (unknown, mutant, non-mutant), historical CML-associated mutation status (E225K, E255V, E355G, T315I, etc.) (frequency counts and percentages). This table will also include extramedullary involvement: any extramedullary involvement (Yes/No) and location of extramedullary involvement (Spleen, Liver) (frequency counts and percentages).

Medical history

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

In addition, separate listings will be produced for medical history possibly contributing to liver dysfunction, and medical history of protocol solicited cardiovascular events.

The cardiovascular risk factors, smoking, low physical activity, unhealthy diet, and others, are collected at screening and the EoT visit. A listing will be presented.

Family medical history of each subject for ischemic heart disease, cardiac arrhythmia, sudden death, high cholesterol, diabetes mellitus, heart defects (congenital heart disease), and heart failure is also collected at screening. A listing will be presented.

Other

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 Safety set (SAF, SAF 2) will be used for the analyses below unless otherwise specified.

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 subjects in each interval. The number (%) of subjects 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 subjects in the corresponding Safety set with the date of last administration of study treatment and the date of first administration of study treatment.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to the investigational drug:

Duration of exposure to study treatment (weeks) = ((date of last administration of study treatment) – (date of first administration of study treatment) + 1) / 7.

The **duration of exposure in subject-years** is the total of the duration of exposure in years from all the subjects in the treatment.

The date of last administration of study treatment is defined in Section 2.1.1.

Summary of duration of exposure to study treatment will include categorical summaries based on intervals (less than 24 weeks, at least 24 weeks, at least 48 weeks, at least 96 weeks) and continuous summaries (i.e. mean, standard deviation etc.).

Cumulative dose

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

The **planned cumulative dose** for a study treatment refers to the total planned dose as per the protocol up to the last date of study treatment administration. The calculation for the study treatments is:

- ABL001: 80 mg/day × duration of exposure prior to dose escalation (day) + 200 mg/day × duration of exposure since dose escalation (day) (if applicable),
  where the starting day of dose escalation is identified as the first record in the Subject status_Dose escalation eCRF page and Study Treatment eCRF with dose increased to 200 mg once daily and reason “Lack of efficacy” at or after 48 weeks on treatment.

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

Dose intensity and relative dose intensity

Average Daily Dose (ADD) is defined as:

ADD (mg/day) = Actual cumulative dose (mg) / Time on treatment (day).

Time on treatment (weeks) = ((date of last administration of study treatment) – (date of first administration of study treatment) + 1 – number of days with dose interruption*) / 7

*This includes the half days before and after the period with 0 dose if the treatment was interrupted after the morning dose and/or resumed in the evening (1 day record with QD dose administered before or after a record with 0 dose).

Dose intensity (DI) for subjects with non-zero duration of exposure is defined as follows:

DI (mg/day) = Actual cumulative dose (mg) / Duration of exposure to study treatment (day).

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

Planned dose intensity (PDI) is defined as:

PDI (mg/day) = Planned cumulative dose (mg) / Duration of exposure (day).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg/day) / PDI (mg/day).

ADD, DI and RDI will be summarized separately for the two dose regimens.

Dose changes, interruptions or permanent discontinuations

The number of subjects who have dose increase, dose reductions, dose interruptions or permanent discontinuations, and the reasons, as well as the duration of dose interruption due to any reason will be summarized. For any subject, duration of dose interruption will be calculated by adding all individual episodes of dose interruption for that subject. This includes the half days before and after the period with 0 dose if the treatment was interrupted after the morning dose and/or resumed in the evening (1 day record with QD dose administered before or after a record with 0 dose).

'Dose Changed', 'Dose Interrupted' and 'Dose Permanently Discontinued' fields from the Study Treatment eCRF and Disposition pages will be used to determine the dose changes, dose interruptions, and permanent discontinuations, respectively.

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

A dose change occurs when total daily dose is different from the most recently planned dose. Before week 48, there is only one planned dose, i.e. 80 mg/day. For subjects not in MMR at 48 weeks or losing the response after the week 48 assessments up to week 108, a dose escalation to 200 mg q.d. may be considered for subjects on 40 mg b.i.d. or 80 mg q.d., if in the investigator's opinion the subject may benefit from the escalation.

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

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

Increase: A dose change where the actual total daily dose is greater than the most recently planned dose. Therefore any dose change to correct a dosing error will not be considered a dose increase. Only dose change is collected in the eCRF, while number of increase will be derived programmatically based on the change and the direction of the change.

For the subjects with dose escalation after week 48, the subjects who are on treatment, complete treatment or have permanent discontinuations will be summarized on SAF by means of descriptive statistics seperately.

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

2.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

The number and percentage of subjects who received any prior anti-neoplastic medications will be summarized for the lowest anatomical therapeutic classification (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 and FAS 2.

The following information will also be summarized for the FAS and FAS 2:

- Prior TKI by medication (e.g. imatinib, dasatinib, nilotinib, ponatinib, bosutinib, etc.)
- Number of prior TKI (e.g. 2, 3, 4, etc.)
- Number of lines of prior TKI therapy (2, 3, 4, 5+)
  A new line of therapy is considered each time a change in TKI occured. Multiple entries for the same TKI will be counted as separate lines of therapy if a different TKI is received between the different entries.
- Time on each line of prior TKI therapy (in years)
- Time on last prior TKI (in years)
- Reason to discontinue the most recent TKI therapy at the time of screening
- Prior non-TKI therapies (Yes, No).

A Sankey-like plot showing the sequence of prior TKIs will be provided.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by the lowest anatomical therapeutic classification (ATC) class and preferred term by means of frequency counts and percentages using FAS and FAS 2.

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

Concomitant therapies

Concomitant therapies are defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a subject coinciding with the study treatment period. Concomitant therapies include medications (other than study drugs) 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 PT 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 (SAF, SAF 2) will include:

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

All concomitant therapies will be listed using the Safety Set (SAF, SAF 2). Any concomitant therapies starting and ending prior to the start of study treatment or starting beyond end of the on-treatment period will be flagged in the listing.

The prohibited concomitant medications will be summarized by lowest ATC class and preferred term up to the end of on-treatment period. Prohibited medications will be concomitant medications that led to the protocol deviation “Use of prohibited concomitant medication”.

2.5 Analysis supporting primary objective(s)

In this section, the targeted treatment effect corresponding to the primary objective as well as the primary objective is clarified using the estimand language.

The primary clinical question of interest is: What is the effect of asciminib in CML subjects in chronic phase who were resistant or intolerant to 2 or more prior TKIs, with regards to achieving MMR at 48 weeks while on study treatment regardless of dose modification, dose interruption, or any intake of concomitant medications and without intake of prohibited medications.

The primary estimand is described by the following attributes:

1. The target population comprises CML Subjects with resistance or intolerance to 2 or more prior TKI per the 2020 ELN recommendations.
2. Endpoint: Major Molecular Response (MMR) achieved at week 48 while on study treatment without meeting any treatment failure criteria prior to week 48. A subject will be counted as having achieved MMR at week 48 if he/she meets the MMR criterion (BCR::ABL1 $\leq$ 0.1% IS) at week 48 while on study treatment unless the subject met any treatment failure criteria prior to week 48.

3. Treatment of interest: the investigational treatment asciminib received for at least 48 weeks, with or without dose modification, dose interruption or any intake of concomitant medications, or intake of prohibited medications.
4. The intercurrent events are the events occurring after first dose of study drug that may impact the treatment effect. The intercurrent events of interest are:
    a) Treatment discontinuation (i.e. having performed an EOT visit) prior to week 48 due to any reason
    b) Dose modification or dose interruption, or any intake of concomitant medications
    c) Intake of prohibited medications

5. The summary measure is the MMR rate and its 95% confidence interval at week 48.

The primary analysis will be conducted after all randomized subjects have been on study treatment for 48 weeks or discontinued earlier, i.e., LPFT + 48 weeks.

2.5.1 Primary endpoint(s)

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

MMR will be considered as a binary variable with subjects achieving MMR grouped as 'responders' and subjects not achieving MMR grouped as 'non responders'. Only subjects with MMR at 48 weeks are considered responders. In other words, any subject who achieves MMR before 48 weeks, but is no longer in MMR at 48 weeks, will be considered as a non-responder in this primary analysis.

Details of derivation of Polymerase Chain Reaction (PCR) results and calculation of BCR::ABL ratio are presented in Section 5.4

2.5.2 Statistical hypothesis, model, and method of analysis

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

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

H_0: π=0.23 vs. H_1: π >0.23

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

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

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

2.5.3 Handling of intercurrent events

The approach of accounting for intercurrent events is as follows:

- **For the intercurrent events 4a:** The composite strategy will be applied for treatment discontinuation due to any reason. Treatment discontinuations due to any reason will be defined as non-responders.
- **For the intercurrent events 4b:** The treatment policy strategy will be applied. Meaning, the actual values of the variable (BCR::ABL1 % IS) will be used, regardless of whether the intercurrent event has occurred.
- **For the intercurrent events 4c:** The treatment policy strategy will be applied. Meaning, the actual values of the variable (BCR::ABL1 % IS) will be used, regardless of whether the intercurrent event has occurred.

2.5.4 Handling of missing values not related to intercurrent event

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

2.5.5 Sensitivity analyses

To explore the robustness of analysis, sensitivity analyses exploring different assumptions will be performed.

- The Exact test of MMR rate at 48 weeks will be repeated without any imputation(described in Section 2.5.4) used in the primary analysis in case of missing PCR evaluations at 48 weeks. If a subject has missing MMR at 48 weeks, then the subject will be considered as non-responder for primary analysis.
- As per the FDA guidelines "Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency", in order to assess the impact of COVID-19 (including potential missing data) on the primary endpoint, the exact test of MMR rate at 48 weeks will be repeated on the FAS excluding the subjects with missing data at week 48 due to COVID-19. MMR rate and its 95% confidence interval based on the Clopper-Pearson method on the FAS exculding subjects with missing data at week 48 due to COVID-19 will also be presented.

2.5.6 Supplementary analyses

The FAS will be used for subgroup analyses.

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

- Gender: Male and Female
- Race: Asian, Caucasian, or others

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

  Note: Only one reason for discontinuation is allowed for each prior therapy.
- Number of prior TKI therapies: 2, 3 or ≥4
- Cytogenetic response status at baseline: Major (MCyR) - 0 to 35% Ph+ metaphases; Complete (CCyR) - 0% Ph+ metaphases; Partial (PCyR) - >0 to 35% Ph+ metaphases; Minor (mCyR) - >35 to 65% Ph+ metaphases; Minimal - >65 to 95% Ph+ metaphases; or None - >95 to 100% Ph+ metaphases.
- Prior TKI treatment: imatinib, nilotinib, dasatinib, bosutinib, radotinib or ponatinib
- Prior ponatinib: Yes or No
- Mutation status at baseline: Non-mutant or mutant

For the subjects with dose escalation to 200 mg q.d. after week 48, the MMR rate and its 95% confidence interval based on the Clopper-Pearson method at week 96 and week 144 will be presented based on FAS.

2.6 Analysis supporting secondary objectives

The secondary objectives in this study are as follows:

- To evaluate the safety and tolerability of asciminib in subjects with CML-CP following two or more prior TKI treatments for SAF and SAF 2.
- To assess the rate of MMR in subjects with no evidence of MMR at baseline, at alternative time points at weeks 12, 24, 36, 72, 96 and 144 for FAS.
- To assess the rate of MMR at week 48 for subjects with MMR at baseline for FAS 2.
- To assess the time to MMR for FAS.
- To assess the rate of early responses of BCR::ABL1 ≤10% and ≤1% IS at weeks 12, 24, 36 and 48 for FAS.
- To assess the rate of deep molecular responses (MR4 and MR4.5) at weeks 12, 24, 36, 48, 72, 96 and 144 for FAS.
- To assess cytogenetic response (% Ph+ metaphases) at weeks 48 and EOT for FAS.
- To characterize the impact of additional cytogenetic abnormalities on efficacy for FAS.
- To assess cumulative molecular responses by all-time points for FAS.
- To assess duration of MMR for FAS and FAS 2.
- To assess sustained deep molecular responses as prerequisite for TFR for FAS and FAS 2.

- To assess rate of progression (PFS) for FAS.
- To assess overall survival (OS) for FAS.
- To assess time to treatment failure (TTF) for FAS.
- To evaluate patient reported outcomes and quality of life by using QoL scales for FAS and FAS 2.

2.6.1 Secondary endpoint(s)

No statistical testing of secondary efficacy endpoints will be performed.

2.6.1.1 Molecular response

MMR rates <u>at</u> all scheduled data collection time points, i.e., the protocol-planned visits except for 48 weeks which is already covered by primary endpoint. Such rates are defined as the proportion of subjects with MMR at the respective time points.

MMR rates <u>by</u> all scheduled data collection time points, i.e., the protocol-planned visits. These are cumulative MMR rates by time points and are defined as the proportion of subjects who achieve MMR at or before specified visits, i.e. if a subject achieves an MMR but then loses it before or at a specific visit, he/she will still be classed as achieving MMR by that specific time point. Subjects without any documented response for which an evaluable response assessment was never provided will be considered as non-responders for the period of time up to that time point.

Molecular response category at specific time points, i.e., the protocol-planned visits. Categories of molecular response are defined in Appendix.

Molecular response category by specific time points, i.e., the protocol-planned visits. This is defined as the molecular response category up to the specific time points.

Time to MMR (in weeks) is defined as: (date of first documented MMR - date of randomization + 1)/7.

Duration of MMR is defined in protocol section 8.3.1.1 as the time from the date of first documented MMR to the earliest date of confirmed loss of MMR, progression to accelerated phase (AP) or blast crisis (BC), or CML-related death. Loss of MMR and progression to accelerated phase (AP)/blast crisis (BC) are defined in Appendix.

The duration of MMR (in weeks) is calculated as: (end date or censoring date of MMR - date of first MMR + 1)/7.

2.6.1.2 Cytogenetic response

At each assessment time point the cytogenetic response status of each subject is classified as complete, partial, major, minor, minimal response and none (a review of a minimum of 20 metaphases is required):

- Complete response (CCyR): 0% Philadelphia chromosome positive (Ph+) metaphases
- Partial response (PCyR): >0 to 35% Ph+ metaphases

- Major response (MCyR = CCyR + PCyR): 0 to 35% Ph+ metaphases
- Minor response (mCyR): >35 to 65% Ph+ metaphases
- Minimal response: >65 to 95% Ph+ metaphases
- None: >95 to 100% Ph+ metaphases.

Bone marrow aspirate for cytogenetic analyses will be performed at screening/baseline (performed up to 56 days prior to Week 1 Day 1), at Week 48 and at EOT (only required if the subject discontinues from the study early due to lack/loss of response). In case no bone marrow aspirate was performed but the subject is in MMR at a specific time-point, the subject is considered to have achieved CCyR at that time-point. The date of CCyR is imputed by the date of MMR at the same scheduled time-point.

CCyR rates at Week 48 and EOT. Such rates are defined as the proportion of subjects in CCyR at the respective time points, which excludes subjects who are in CCyR at baseline.

2.6.1.3 Other secondary efficacy endpoints

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

- BCR::ABL1 >1% IS at 48 weeks after initiation of therapy or no complete cytogenetic response at 48 weeks.
- Subject demonstrates new T315I mutation
- Subject shows lack or loss of response such as "Loss of CHR, CCyR or PCyR at any time after initiation of therapy OR confirmed loss of MMR"
- Progression to AP/BC

For subjects who have not reached treatment failure, their TTFs will be censored at the time of last study assessment (PCR, cytogenetic, hematologic or extramedullary) before the cut-off date.

TTF (in months) is calculated as: (date of treatment failure or censoring date (see Section 2.6.2) - date of randomization + 1)/30.4375.

Progression-Free-Survival (PFS) is defined as the time from the date of randomization to the earliest occurrence of documented disease progression to AP/BC or the date of death from any cause before the cut-off date. The time will be censored at the date of last study assessment (PCR, cytogenetic, hematologic or extramedullary) or last post-treatment follow-up for subjects without event.

PFS (in months) is calculated as: (date of disease progression/death or censoring date (see Section 2.6.2) - date of randomization + 1)/30.4375.

Overall survival (OS) is defined as the time from the date of randomization to the date of death. Subjects who are alive at the time of the analysis data cutoff date will be censored at the date of last contact (see Section 2.1.1) before the cut-off date. OS (in months) is calculated as: (date of death or censoring date (see Section 2.6.2) - date of randomization + 1)/30.4375.

2.6.2 Statistical hypothesis, model, and method of analysis

No statistical testing of secondary efficacy endpoints will be performed .

Molecular response at and by time points

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

Frequency and percentage of all molecular response categories (defined in Appendix) using FAS or FAS 2 will be presented for each time point.

For each endpoint above, the rate and the associated 95% confidence interval based on the Clopper-Pearson method will be presented. For the at-time-points summary, subjects discontinuing the treatment prior to a specific time point due to any reason or subjects without an available assessment at that time point will be considered as non-responders for that time point. For the by-time-points summary, subjects without any documented response for which an evaluable response assessment was never provided will be considered as non-responders for the period of time up to that time point.

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

Additional chromosomal abnormalities and occurrence of high-risk ACAs

The number and percentage of subjects achieving MMR at week 48 and week 96, and CCyR at week 48 will be presented by ACA status at baseline. Per NCCN 2024 guideline and ELN 2020 guideline, the major route ACA/Ph+ including trisomy 8, isochromosome 17q, second Ph, trisomy 19, and chromosome 3 abnormalities are considered as presence of ACA at baseline.

Time to MMR

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

The FAS will be also used to perform similar Time-to-Event analyses as described below for duration of MMR.

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

- If a subject does not achieve the specified response before the cut-off date for the analysis, censoring time will be the last molecular assessment (PCR) date on treatment prior to the cut-off date or the EoT visit, whichever comes first.
- If a subject discontinues study treatment prior to achieving a response for a reason other than disease progression or death, then the subject will be censored at the last molecular assessment (PCR) date on treatment prior to the cut-off date or the EoT visit, whichever comes first.
- If a subject discontinues study treatment prior to achieving a response due to progression or death, then the censoring time will be set to the longest follow-up time in the treatment group, that is, consider the response is impossible to reach.
- In case no on-treatment response assessment was performed, the subject will be censored at day 1.

The estimated cumulative incidence rates and 95% confidence intervals at 12, 24, 48, 72, 96 and 144 weeks will be presented. The cumulative incidence curve will be plotted.

Duration of MMR

Duration of MMR is defined in protocol Section 8.3.1.1 as the time from the date of first documented MMR to the earliest date of confirmed loss of MMR, progression to AP or BC, or CML-related death. The time will be censored at the last molecular assessment (PCR) date while on treatment for subjects who have not experienced any of the above events. The duration of MMR will be analyzed for the subjects in FAS who achieve MMR at any time.

Duration of MMR will be analyzed by K-M method and presented by K-M plots. The survival distribution of duration of MMR will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals [Brookmeyer and Crowley 1982] of the medians, along with the proportion of subjects who are still in MMR at 24, 48, 72, 96 and 144 weeks and the associated 95% confidence intervals, will be presented.

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

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

CCyR rates at time points

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

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

TTF, PFS and OS

For each endpoint the survival distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals [Brookmeyer and Crowley

1982] of the medians, along with the proportion of subjects who have not experienced the respective events at 1, 2 and 3 years and the associated 95% confidence intervals, will be presented.

TTF: For subjects in the FAS who have not reached treatment failure, their TTFs will be censored at the time of their last study assessment (PCR, cytogenetic, hematologic or extramedullary) before the cut-off date.

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

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

2.6.3 Handling of intercurrent events

Not applicable.

2.6.4 Handling of missing values not related to intercurrent event

Not applicable.

2.6.5 Sensitivity analyses

Not applicable.

2.6.6 Supplementary analyses

Not Applicable.

2.7 Safety analyses

For all safety analyses, the Safety set (SAF, SAF 2) will be used, except where stated otherwise.

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

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

1. Pre-treatment period: from day of participant's informed consent to the day before first dose of study medication
2. On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. Post-treatment period: starting at day 31 after last dose of study medication.

The following will also be summarized for a) **all** subjects using combined sets (SAF and SAF 2), for b) SAF 2 only, for c) subjects by dose escalation status (with or without dose escalation) and for d) only for subjects with dose escalation (prior to and after dose escalation):

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

Analysis of ECG data, for dose escalation is mentioned in section 2.7.4.1.

2.7.1 Adverse events (AEs)

All the summary tables for adverse events (AEs) will be tabulated by randomized groups. AE summaries will include all AEs occurring during 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. AE relationship to study drug, AE outcome, etc. AEs with start date outside of the on-treatment period will be flagged in the listings.

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

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sorting order for the preferred term will be based on their frequency in the asciminib 40 mg b.i.d. group.

The following adverse event summaries will be produced: overview of adverse events and deaths, AEs by SOC and PT, summarized by relationship, seriousness, leading to treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy, and leading to fatal outcome. The study treatment-related AEs/SAEs/AEs leading to treatment discontinuation as well as SAE with fatal outcome are summarized for the corresponding Safety set.

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

2.7.1.1 Adverse events of special interest / grouping of AEs

Data analysis of AESIs

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 groupings are defined using

MedDRA terms, SMQs (standardized MedDRA queries), HLGTs (high level group terms), HLT (high level terms) and PTs (preferred terms). 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 an existing SMQ, narrow or broad. The latest approved version of CRS (Case Retrieval Strategy) prior to the respective database lock will be used.

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

Summaries of these AESIs will be provided (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, death, etc.). If sufficient number of events occurred, analysis of time to first occurrence will be applied.

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

2.7.2 Deaths

Separate summaries for on-treatment and all deaths *(including post-treatment deaths)* will be produced on the corresponding Safety set (SAF, SAF 2) by randomized groups, system organ class and preferred term.

All deaths will be listed, where deaths occurring during the post-treatment period will be flagged.

2.7.3 Laboratory data

Clinical laboratory evaluations

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

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. Details of CTCAE grading and imputation rules are presented in Appendix 5.3.

For laboratory tests where grades are not defined by CTCAE version 5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

On analyzing laboratory data, all sources (central and local laboratories) will be combined. 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 will be generated on the corresponding Safety set (SAF, SAF 2) separately for hematology, and biochemistry laboratory data (by laboratory parameter):

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline in the on-treatment period.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

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

- Listings of all laboratory data, with CTCAE grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTCAE grade 3 or 4 laboratory toxicities

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 subjects 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).

The following summaries will be produced:

- ALT or AST > 3x upper limit of norm (ULN)
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP >= 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

ECG

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

The echocardiogram will be performed and evaluated locally to assess the left ventricular ejection fraction (LVEF).

Data handling

The average of the triplicate ECG parameters at each time point 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 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 subjects will be considered as an unscheduled measurement in case it occurs outside a scheduled visit.

Data analysis

The number and percentage of subjects with notable ECG values will be presented for the corresponding Safety set (SAF, SAF 2). 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 to ≤ 60ms
  - 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
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

A listing of all ECG assessments will be produced and notable values will be flagged. A separate listing of only the subjects with notable ECG values will also be produced. In each listing the assessments collected during the post-treatment period will be flagged.

Change from baseline ECG parameters by timepoint will also be summarized.

A listing of all LVEF assessments will be produced. In the listing, the assessments collected outside of on-treatment period will be flagged.

A summary table with descriptive statistics for LVEF at different timepoints (screening/baseline, Week 48 (+/- 4 weeks) and end of treatment visit) and for change from baseline will be presented. A shift table for LVEF categories (≤40%, 41-49%, ≥50%) at baseline versus worst value on treatment will also be presented.

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

For subjects with dose escalation, ECG assessments will be performed at:

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

The above described analyses for ECG data will also be performed seperately for a) subjects by dose escalation status (with or without dose escalation) and for b) only for subjects with dose escalation (prior to and after dose escalation).

2.7.4.2 Cardiovascular risk factor assessment

At the screening/baseline and at the end of treatment, for each subject information of the following risk factors is collected: smoking, low physical activity, unhealthy diet, and other. A listing will be presented.

Family medical history of each subject for ischemic heart disease, cardiac arrhythmia, sudden death, high cholesterol, diabetes mellitus, heart defects (congenital heart disease), and heart failure is also collected at the screening visit. A listing will be presented.

2.7.4.3 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 (mmHg).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

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

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

2.7.4.4 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.

2.8 Pharmacokinetic endpoints

Not applicable.

2.9 PD and PK/PD analyses

Not Applicable.

2.10 Patient-reported outcomes

The patient reported outcomes (PRO) objectives are to compare the impact of treatment on PROs including CML-specific symptoms and health related patient quality of life from baseline through end of treatment in all subjects by using FAS except stated otherwise. The M.D. Anderson Symptom Inventory – Chronic Myeloid Leukemia (MDASI-CML) questionnaire is planned to be administered during screening, at weeks 4, 12, 24, 48, 72, 96, 120 and end of treatment.

The MDASI-CML is a 26 item self-administered questionnaire for adult CML patients. Twenty of the items measure the severity of disease-related symptoms and are scored from 0 (Not present) to 10 (As bad as you can imagine) and 6 items that measure symptom interference with daily life scored from 0 (Did not interfere) to 10 (Interfered completely).

The severity score will be calculated when a subject scores at least 11 items out of the 20 severity items using the formula: (sum of scores for the items answered) / (number of items answered). If a subject scores fewer than 11 items, the severity score will be missing.

The interference score will be calculated when a subject scores at least 4 items out of the 6 interference items using the formula: (sum of scores for the items answered) / (number of items answered). If a subject scores fewer than 4 items, the interference score will be missing.

For the severity score and interference score, descriptive statistics (n, mean, SD, median, 25th and 75th percentiles) will be provided for the actual scores and changes from baseline scores at each scheduled assessment time point.

Subjects with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses. Missing data items in a scale will be handled according to the manual for each instrument. No imputation will be applied if the total or subscale scores are missing at a visit.

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

2.11 Biomarkers

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

2.12 Other Exploratory analyses

Not applicable.

2.13 Interim analysis

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

- 48-week primary analysis: Formal testing of the primary endpoint will be performed. Analyses of other efficacy endpoints at and by week 48 and safety analyses will also be performed.
- 96-week analysis: Analyses of efficacy endpoints at and by week 96 and safety analyses will be performed.
- End of study treatment analysis similar to the 96-week analysis without formal statistical testing. All efficacy and safety analyses will be included.

3 Sample size calculation

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

The MMR rate (95% CI) at Week 48 in Bosutinib arm of ASCEMBL trial (at ASCEMBL study Week 24 primary CSR (Data cut-off date of 25-May-2020, Table 14.2-1.1.1)) was 11.1 % (4.2% – 22.6%); 54 subjects were eligible for this sample size computation.

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

4 Change to protocol specified analyses

Not applicable.

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 component.

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

The subject 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.

- All other cases should be considered as a data issue and the statistician should contact the data manager of the study.
- After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

  Use the treatment start date

Subjects with missing start dates are to be considered 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, ConMeds and safety assessment date imputation

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

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

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates
day, month	• If available year = year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY o 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
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o 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 (AE, CM) and assessments (eg: LB, EG, VS)

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, ConMeds or assessments with partial/missing dates will be displayed as such in the data listings.

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

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

5.2 AEs coding/grading

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

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

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

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters (embedded below). The latest available version of the document based on the underlying CTCAE version v5 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.

EASE LAB - CTC grades in Novartis Or

Imputation Rules

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 was performed but no data is transferred for immature cells, this means there was no immature cells and their values can be imputed to 0. Note that there should not be any imputation in case the automatic testing was not 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 couldn't).

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) * (%value / 100)

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

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

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

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

5.4 Efficacy variables

5.4.1 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::ABL and the control gene ABL is calculated and multiplied by the lab-specific conversion factor ([Branford and Hughes 2006]). Therefore, using the international unit, the BCR::ABL ratio will be presented in %. The MRDx assay using PAXgene^{TM} Blood RNA tubes from MMD laboratory will be used in this study. The lab conversion factor for this assay was 1.1 until 1 June 2020 and 1 thereafter.

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

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

The BCR::ABL ratio in IS% provided by the central laboratory will be use in the analyses. However, to calculate the fold change in BCR::ABL1/ABL used to derive the loss of MMR criteria, in case the BCR::ABL number of copies is reported as a 0 value and the subject doesn't have atypical transcript at baseline, then the value will be replaced by 1, and the BCR::ABL ratio will be calculated.

Molecular response is categorized as follows:

- 10% > BCR::ABL ratio
- 1% < BCR::ABL ratio ≤ 10%
- 0.1% < BCR::ABL ratio ≤ 1%
- 0.01% < BCR::ABL ratio ≤ 0.1%
- 0.0032% < BCR::ABL ratio ≤ 0.01%
- BCR::ABL ratio ≤ 0.0032%

If the BCR::ABL number of copies or BCR::ABL ratio is reported as "Not Detected", then the BCR::ABL ratio will be imputed to 0.

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

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

- Rate of MMR where MMR is defined as a ≥ 3.0 log reduction in BCR::ABL1 transcripts compared to the standardized baseline equivalent to ≤0.1 % BCR::ABL1/ABL1 % by IS as measured by RQ-PCR, confirmed by duplicate analysis of the same sample,
- Time to MMR defined as the time from the date of randomization to the date of the first documented MMR,

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

Loss of MMR is defined as increase of BCR::ABL1/ABL to > 0.1% by international scale (IS) in association with a ≥ 5-fold rise in BCR::ABL1 from the lowest value achieved on study treatment and replicated by a second analysis of the same sample. Confirmed loss of MMR by subsequent sample analysis within 4 to 6 weeks showing loss of MMR associated with a ≥ 5-fold rise in BCR::ABL1 from the lowest value achieved on study treatment, unless it is associated with confirmed loss of CHR or loss of CCyR or progression to AP/BC or CML-related death.

5.4.2 Cytogenetic response

Cytogenetic response will be based on the percentage of Ph+ metaphases in the bone marrow. Cytogenetic evaluations will be considered for response assessment only if the number of metaphases examined is ≥ 20 in each bone marrow sample.

Cytogenetic response is categorized as follows (a review of a minimum of 20 metaphases is required):

- Complete response (CCyR): 0% Philadelphia chromosome positive (Ph+) metaphases
- Partial response (PCyR): >0 to 35% Ph+ metaphases
- Major response (MCyR = CCyR + PCyR): 0 to 35% Ph+ metaphases
- Minor response (mCyR): >35 to 65% Ph+ metaphases
- Minimal response: >65 to 95% Ph+ metaphases
- None: >95 to 100% Ph+ metaphases.

If bone marrow aspirate blast percentage is provided as '<X' (i.e. below limit of detection), the numeric value is set to X for summary tables. In the listing '<X' will be presented.

Complete cytogenetic response (CCyR)

CCyR is defined as a value of 0% Ph+ metaphases in bone marrow.

CCyR will be considered as a binary variable with subjects achieving CCyR grouped as 'responders' and subjects not achieving CCyR, subjects with missing cytogenetic evaluations grouped as 'non-responders'. In case no bone marrow aspirate was performed but the subject is in MMR at a specific time-point, the subject is considered to have achieved CCyR at that time-point. The date of CCyR is imputed by the date of MMR at the same scheduled time-point.

5.4.3 Hematologic response

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)

Loss of CHR must have led to treatment discontinuation because of lack of efficacy.

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).

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. As extramedullary disease is evaluated less frequently than hematology, the results of these evaluations are carried forward until the next assessment (unless extramedullary disease was not present at the current assessment but present at the next).

5.4.4 Treatment Failure

In the event of treatment failure the subject should be discontinued from the study treatment. The ELN criteria 2020 do not make provisions for treatment failure in 3rd line however they define that a level of BCR::ABL1 > 1% IS and failure to achieve CCyR is not sufficient for optimal survival. The following events will constitute 'treatment failure':

- BCR::ABL1 >1% IS at 48 weeks after initiation of therapy or no complete cytogenetic response at 48 weeks.
- Subject demonstrates new T315I mutation.
- Subject shows lack or loss of response such as "Loss of CHR, CCyR or PCyR at any time after initiation of therapy OR confirmed loss of MMR".
- Progression to AP/BC.
- Subjects fulfilling treatment failure criteria above but without alternative treatment options may however be continued on study drug if in the investigators opinion they are obtaining benefit from the drug. Subjects with BCR::ABL 1 greater than 10%

after 48 weeks of treatment or subjects with signs of progression to AP and BC must however be discontinued.

- Subjects with newly emerging T315I mutation and lack or loss of response. While asciminib has known activity against CML with additional T315I mutation, the recommended dose of 200 mg bid for the treatment of T315I is not in use in the study. In case a subject demonstrates a new T315I mutation on asciminib, subjects should not continue in the study.

5.4.5 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
- Thrombocytopenia (<100 x 10^9/L) that is unrelated to therapy*

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).

The second bullet for BC cannot be considered in this study as this information was not collected.

5.4.6 CML-related deaths

CML-related death is considered as any death during treatment or follow-up

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

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.

5.4.7 Disease progression

The following events are considered disease progression

- CML-related death (any death during treatment or follow-up if the principal cause of death is marked as “study indication” in the eCRF by the investigator, or if the death occurred subsequent to documented progression to AP/BC and the cause of

death is reported as “unknown” or not reported by the investigator)

- Accelerated phase (AP) as defined by any of the following:
  - ≥ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate
  - ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate
  - ≥ 20% basophils in the peripheral blood
  - Thrombocytopenia (<100 x 109/L) that is unrelated to therapy
- Blast crisis (BC) as defined by any of the following:
  - ≥ 30% blasts in peripheral blood or bone marrow aspirate
  - Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma).

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

5.4.8 Overall survival

This includes all deaths.

5.5 Derivation of response rates and categories

5.5.1 Response rate at a specific time point

The molecular and cytogenetic response evaluations will be summarized by the following mutually exclusive categories which are based on the respective assessment within the time window:

- **Response categories** (sections 5.4.1 and 5.4.2)**:** Subjects with an available assessment at that time point (+/- time window) indicating any of the response categories.
- **No response:** Subjects with assessment at that time point (+/- time window) indicating 'no response'
- **Missing:** Subjects without an evaluable response assessment at that time point (+/- time window). This category is then further split into subjects who are ongoing without treatment failure at the beginning of the relevant time window, subjects who are ongoing with treatment failure at the beginning of the relevant time window, subjects who discontinued due to lack of efficacy, disease progression (PD) or death and subjects who discontinued due to other reasons.

5.6 Statistical models

5.6.1 Analysis supporting primary objective(s)

The null hypothesis that proportion of subjects who achieve MMR equals to 0.23 at 48 weeks will be tested against one-sided alternative.

The statistical hypotheses are:

$$H_0: \pi=0.23 \text{ vs. } H_1: \pi > 0.23$$

where π is the proportion of subjects who achieve major molecular response (BCR::ABL1 ≤0.1% IS) rate at Week 48. MMR rate and its 95% confidence interval based on the Clopper-Pearson method will also be presented.

The proportion test will implemented via SAS procedure FREQ with binomial option in the TABLES statement. The p-value corresponding to the proprtion test will be used which follows a standard normal distribution.

The setup of the data is important. PROC FREQ will run a binomial test assuming that the probability of interest is the first level of the variable (in sorting order) in the TABLES statement. For example, the above statements run a binomial test on MMR flag, which takes one of two numeric values – 1 (Yes) or 0 (No). The binomial test is applied to MMR flag values of 1 because it is the first sorted value for that variable.

Confidence interval for MMR rate

MMR will be summarized in terms of percentage rates with 95% confidence interval using exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table ([Clopper and Pearson 1934]).

5.6.2 Analysis supporting secondary objective(s)

Kaplan-Meier estimates

An estimate of the survival function will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

Cumulative incidence

The cumulative incidence proportion (CIP) will be estimated using competing risk analysis via SAS procedure LIFETEST or PHREG with EVENTCODE=Code for event of interest (e.g. MMR) as option in the MODEL statement, whereas code=0 for censored subjects and any other code (e.g. code=2) for subjects who dropped out due to a competing risk. The estimated CIP at the defined time points will be presented with 95% CI together with number of subjects with events, number of subjects with competing risks, and number of subjects censored.

6 Reference

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