NOVARTIS

Clinical Development

ABL001/Asciminib/Scemblix®

CABL001E2201/NCT03578367

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

Statistical Analysis Plan (SAP) – Final CSR
Asciminib single agent cohort analysis

Document type:	SAP Documentation
Document status:	Final
Release date:	03-Sep-2024
Number of pages:	48

Template Version 6.0, Effective from 23-Nov-2022

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
9-Oct-2018	Prior to DB lock	Creation of final version	N/A - First version	NA
11-Dec-2019	Prior to DB lock	Protocol amendment 1	Change in study design to reduce imatinib pretreatment duration, from at least 24 months to at least 12 months	Section 1.1
			Change in the study design to reduce the sample size from 120 to approximately 80	Section 1.1 Section 3.1 Section 3.2
			Addition of intolerability as a reason to stop the treatment	Section 1.1
			Addition of Interim Analysis (IA) to have early assessment of benefit (efficacy) and risk (safety) of treating patients with asciminib + imatinib arms vs continued imatinib arm and switch to the nilotinib arm. The IA will be will be performed when at least 40 (50%) patients have been randomized and have been followed for their 24 weeks visit assessment or have discontinued treatment.	Section 1.1 Section 2.1 Section 2.14
			Removal of the formal statistical hypothesis testing, replaced with a point estimate and a confidence interval	Section 2.2.1 Section 2.5.2 Section 5.5.1
			Changing the estimation of the difference in rate of $MR^{4.5}$ between asciminib + imatinib versus continued imatinib from a supportive analysis to a primary analysis	Section 2.5.4
			Change of some non-compartmental pharmacokinetics parameters	Section 2.9
			Update of the references	Section 6
		DILI Clinical Safety Guidance update	Change in the summaries produced for Liver function parameters to be in accordance with DILI Clinical Safety Guidance update	Section 2.8.3
		Data issue with serum Magnesium results from Roche Diagnostics Cobas analyzer in the UK laboratory	Clarification about how invalid laboratory samples for magnesium will be handle	Section 2.8.3

27-Aug-2020	Prior to DB lock	Changes before Interim analysis	Adding a 3-day window for the definition of the baseline for PRO. Adding a definition of the end of the efficacy assessment period.	Section 2.1.1, Table 2-2, Table 2-3
			Adding an imputation rule for dates with available day and missing month.	Section 5.1
			Adding a definition of MR^4 and derivation of MR^4 and $MR^{4.5}$ for not detectable transcripts.	Section 5.4
			Adding a definition of efficacy sets for the interim analysis.	Section 2.2, Table 2-4, Section 2.14
24-11-2021	Prior to DB lock	Changes before primary analysis	Updating Phoenix WinNonlin® software version. Updating Table 2-6 to clarify which PK parameters will be provided for the different visits.	Section 2.9, Table 2-6
			Specifying that exploratory biomarker objectives will reported in an independent report unless requested by HAs.	Section 2.12
			Adding this section about analyses to assess the impact of COVID-19 on the study.	Section 2.15
			Clarifing how the dose adjustments and discontinuation of study treatment for the combination arms	Section 2.4.1
			Specifying that the conversion factor for deriving PCR results has changed during the course of the study. It will be provided by the vendor rather than set at 1.1.	Section 5.4
03-Sep-2024	Prior to the final DB lock	Addition of the asciminib single agent cohort	Specifying analysis for asciminib single agent cohort.	

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List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
ASAC	Asciminib single agent cohort
Bid	bis in diem/twice a day
CML-CP	Chronic myelogenous leukemia in chronic phase
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
ECG	Electrocardiogram
EOT	End of treatment
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IRT	Interactive response technology
IS	International scale
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PCR	Polymerase Chain Reaction
PK	Pharmacokinetics
PRO	Patient-reported Outcomes
Qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA query
SOC	System Organ Class
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned statistical analyses for the clinical study report(s) (CSR) of study CABL001E2201, a phase 2, multi-center, open-label, randomized study of oral asciminib added to imatinib versus continued imatinib versus switch to nilotinib in patients with CML-CP who have been previously treated with imatinib first line therapy for at least one year (12 calendar months) and have not achieved deep molecular response.

The revised content of this SAP is based on protocol CABL001E2201 version 05. It aims to describe the planned statistical analyses of the asciminib single agent cohort data. This cohort was added in the protocol version 03 to assess whether asciminib single agent at the recommended dose of 80 mg QD leads to similar efficacy and safety as observed in the add-on arms of asciminib and imatinib.

All decisions regarding the planned interim, primary and Week 96 analyses as defined in the SAP, have been made prior to the respective database locks of the study data for those analyses

All decisions regarding the analysis of the asciminib single agent cohort have been made prior to the database lock of the study data for this analysis.

Data will be analyzed according to the data analysis section 12 of the study protocol version 05.

1.1 Study design

The study is a phase 2, multi-center, open-label, randomized study of 2 doses of asciminib + imatinib versus continued imatinib versus switch to nilotinib in subjects with CML-CP who have been previously treated with imatinib first line therapy for at least one year (12 calendar months) and have not achieved deep molecular response. Approximately eighty subjects will be randomized to one of the following arms in a 1:1:1:1 ratio:

- Treatment arm 1: asciminib 40 mg QD as add-on therapy to imatinib 400 mg QD, or
- Treatment arm 2: asciminib 60 mg QD as add-on therapy to imatinib 400 mg QD, or
- Treatment arm 3: to continue imatinib 400 mg QD, or
- Treatment arm 4: to switch to nilotinib 300 mg BID

Additionally, the study will estimate the safety and efficacy of the single agent asciminib. The asciminib single agent cohort will be conducted as an open label cohort. Approximately 20 eligible subjects will be enrolled to receive asciminib 80 mg QD.

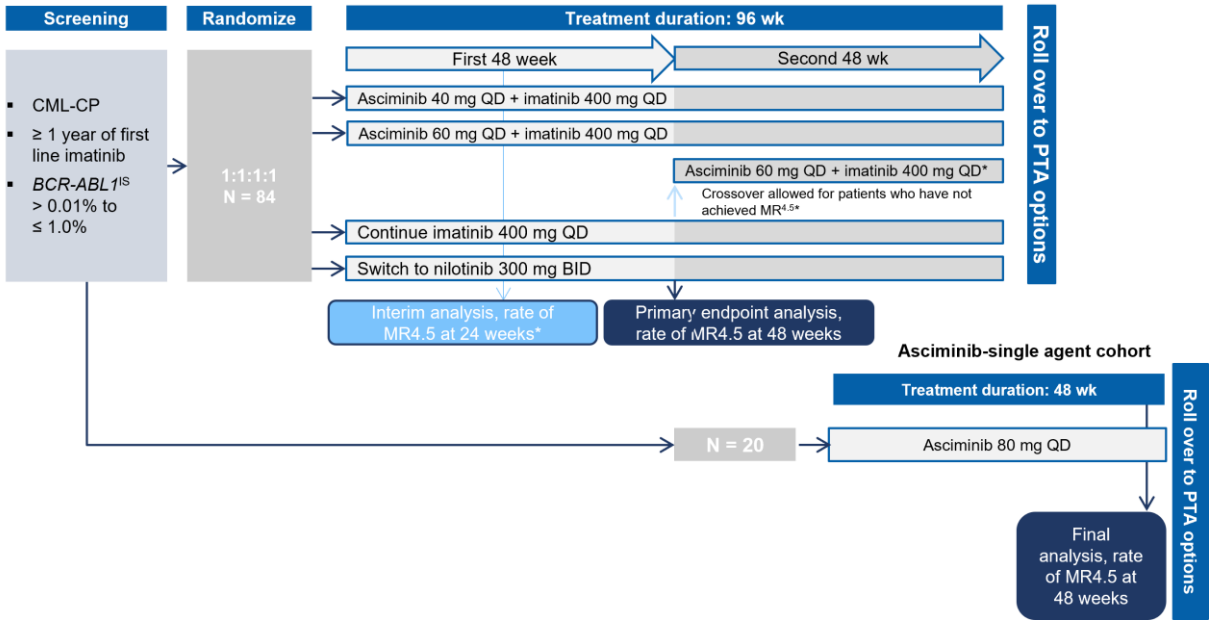
In Treatment arms 1-4, subjects were treated for up to 96 weeks after the last randomized subject received the first dose of treatment (LPFT), if they did not discontinue study treatment earlier for treatment failure or intolerability. After the last dose received, every subject were followed up for safety for 30 days.

Subjects randomized to continue on imatinib single treatment who did not achieve $MR^{4.5}$ at 48 weeks could cross over to receive the asciminib add-on treatment within 4 weeks after week 48 visit.

Subjects in the asciminib single agent cohort will continue on asciminib treatment until treatment failure, intolerability, or for up to 48 weeks after the last enrolled subject in the cohort

received the first dose of treatment. Every subject will be followed up for safety for 30 days after receiving the last dose of study treatment.

Figure 1-1 Study design



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

The interim analysis planned when at least 40 (50%) patients would have been randomized and followed for their 24 weeks visit assessment or discontinued treatment earlier was performed with the cut-off date as 22-Jul-20 This interim analysis was performed on all randomized patients at that time point.

The primary analysis including the analysis of the primary endpoint was performed with the cut-off date as 10-Jan-22 after all patients completed their Week 48 visit or discontinued treatment earlier. The primary analysis is summarized in the week 48 primary clinical study report (CSR).

The final analysis for treatment arms 1-4 (Week 96 analysis) was performed with the cut-off date as 06-Mar-2023 after all patients completed their Week 96 visit or discontinued treatment earlier. The week 96 analysis is summarized in the week 96 CSR.

The analysis of the asciminib single agent cohort will be performed when all subjects have completed their Week 48 visit or have discontinued treatment earlier. This analysis will be summarized in a final CSR.

1.2 Study objectives, endpoints and estimands

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoint for primary objective**
• To assess whether asciminib 40 mg QD + imatinib or asciminib 60 mg QD + imatinib is more effective than continued imatinib	• Molecular Response (MR)$^{4.5}$ rate at 48 weeks
Secondary objectives	**Endpoints for secondary objectives**
• - To estimate efficacy of switch to nilotinib - To estimate difference in efficacy between asciminib 60 mg + imatinib and switch to nilotinib - To estimate difference in efficacy between asciminib 40 mg + imatinib and switch to nilotinib	• - Molecular Response (MR)4.5 rate at 48 weeks - Difference in rate of MR$^{4.5}$ at 48 weeks
• To assess additional parameters of the efficacy of - asciminib 60 mg added to imatinib vs continued imatinib or switch to nilotinib - asciminib 40 mg added to imatinib vs continued imatinib or switch to nilotinib	• - Rate of MR$^{4.5}$ at 96 weeks - Rate of MR$^{4.5}$ by 48 and 96 weeks - Sustained MR$^{4.5}$ at 96 weeks - Time to MR$^{4.5}$ - Duration of MR$^{4.5}$
• To characterize the safety and tolerability profile of asciminib 60 mg or 40 mg + imatinib vs continued imatinib or switch to nilotinib	• Incidence and severity of adverse events, changes in laboratory values, clinically notable ECG abnormalities and vital signs
• To assess the pharmacokinetic profile of asciminib 60 mg or 40 mg and imatinib when administered in combination	• Plasma concentrations of asciminib and imatinib when administered in combination. PK parameters include but are not limited to C_{max}, T_{max}, C_{min}, AUC_{last} and AUC_{tau}
• To estimate efficacy of asciminib 80 mg QD	• -Molecular Response (MR)$^{4.5}$ rate at 48 weeks -Time to MR$^{4.5}$ -Duration of MR$^{4.5}$
• To characterize the safety and tolerability profile of asciminib 80 mg QD	Incidence and severity of adverse events, changes in laboratory values, clinically notable ECG abnormalities and vital signs
• To assess the pharmacokinetic profile of asciminib 80 mg QD.	• Plasma concentrations of asciminib. PK parameters include but are not limited to C_{max}, T_{max}, C_{min}, AUC_{last} and AUC_{tau}
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
• To describe the efficacy and safety of asciminib 60 mg + imatinib in subjects randomized to continued imatinib who cross over to receive asciminib 60 mg + imatinib	• - Efficacy endpoints such as time to MR$^{4.5}$ and duration of MR$^{4.5}$ - Safety endpoints such as incidence and severity of adverse events, changes in laboratory values, clinically notable ECG abnormalities and vital signs
• To assess the proportion of subjects eligible for TFR at end of the study	Subjects, with sustained MRD (Minimal Residual Disease) at the end of the study (i.e. 96 weeks after the first dose of study drug of the last randomized subject)

Objectives	Endpoints
• To explore relevant CCI [redacted] as well as CCI [redacted]	• Analysis of CCI [redacted]
• To explore CCI [redacted]	• CCI [redacted]
• To evaluate CCI [redacted]	• CCI [redacted]
• To explore the impact of treatment on patient reported outcomes (PROs) including CML-specific symptom assessment (disease and treatment), treatment satisfaction and overall impact of side effects of treatment from baseline	• Overall Scores and individual domains for EORTC QLQ-C30 plus CML24, FACIT GP5 and TSQM questionnaire

2 Statistical methods

2.1 Data analysis general information

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

Data included in the analyses

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

- Interim analysis: when at least 40 (50%) patients have been randomized and have been followed for their 24 weeks visit assessment or have discontinued treatment.
- Primary analysis: after all randomized subjects have completed Week 48 visit or have discontinued earlier.
- Week 96 analysis: once the last ongoing randomized patient has been followed up for safety for 30 days after last dose received.
- Final CSR: 48 weeks after the last enrolled subject in the asciminib single agent cohort received the first dose of study treatment (plus 30 days for the safety follow up).

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 (AE)) 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 data cut-off date and end date after the respective data cut-off date will be reported as ongoing. The same rule will be applied to events starting before or on the respective data 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 by treatment group; 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, 25th and 75th percentiles, minimum, and maximum) by treatment group. For pharmacokinetics (PK) concentration and parameters descriptive statistics also include coefficient of variation (CV)%, geo-mean and geo-CV%.

2.1.1 General definitions

2.1.2 General definitions

Investigational drug and study treatment

Investigational drug, will refer to asciminib only whereas ***study treatment*** will refer to asciminib+imatinib, imatinib, nilotinib or asciminib.

Study treatment component will refer to asciminib, imatinib or nilotinib.

Date of first administration of asciminib, imatinib or nilotinib respectively

The date of first administration of asciminib, imatinib or nilotinib is defined as the first date when a nonzero dose of asciminib, imatinib or nilotinib is administered and recorded on the Study Treatment electronic case report form (eCRF), respectively. The date of first administration of asciminib, imatinib or nilotinib will also be referred as start of asciminib, imatinib or nilotinib respectively.

Date of last administration of asciminib, imatinib or nilotinib respectively

The date of last administration of asciminib, imatinib or nilotinib is defined as the last date when a nonzero dose of asciminib, imatinib or nilotinib is administered and recorded on the Study Treatment eCRF, respectively. The date of last administration of asciminib, imatinib or nilotinib will also be referred as end of asciminib, imatinib or nilotinib respectively.

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 any component of study treatment was administered as per the Study Treatment eCRF. (Example: if 1st dose of asciminib is administered on 05-Jan-2015, and 1st dose of imatinib is administered on 03-Jan-2015, then the date of first administration of study treatment is on 03-Jan-2015). The date of first administration of study treatment will be referred to as ***start of study treatment***.

Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a non-zero dose of any component of study treatment was administered as per Study Treatment eCRF. (Example: if the last asciminib dose is administered on 15-Apr-2014, and the last dose of imatinib is administered on 17-Apr-2014, then the date of last administration of study treatment is on 17-Apr-2014).

For patients randomized to the continued imatinib arm, who cross over to receive asciminib + imatinib, the date of last administration of imatinib is derived as the last date when a non-zero dose of imatinib was administered before the first date when a non-zero dose of asciminib was administered as per the Study Treatment eCRF.

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, pk etc.) is the start of study treatment.

The reference start date ***for all other, non-safety assessments*** (i.e., response assessment, and patient reported outcomes (PRO)) is the date of randomization/enrollement.

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

For patients who cross over to receive asciminib + imatinib, the reference start date will be reset to the date of first administration of asciminib once they cross over.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). 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.

Baseline

For ***efficacy and other non safety evaluations***, the last non-missing assessment, including unscheduled assessments on or before the date of randomization/enrollement is taken as "baseline" value or "baseline" assessment. For PROs the last non-missing assessment, including unscheduled assessments on or before the date of randomization + 3 days, but no later than the treatment start date, is taken as "baseline" value or "baseline" assessment.

For ***safety evaluations***, the last available assessment on or before the date of start of study treatment is taken as ‘‘baseline” assessment.

For patients who cross over to receive asciminib+imatinib, the last available assessment on or before the date of first administration of asciminib is taken as “baseline” value or “baseline” assessment for the cross over period.

In case time of assessment and time of treatment start are captured (e.g. pre-dose electrocardiogram (ECG)), the last available assessment before the treatment start date/time is used for baseline.

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

In rare cases where multiple laboratory measurements meet the baseline definition, with no further flag or label that can identify the chronological order then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory (local or central) then the value with the last sequence/repeat number 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 four mutually exclusive segments:

- ***pre-treatment period***: from day of patient’s informed consent to the day before first administration of study treatment,
- ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date) (For patients who cross over to receive asciminib+imatinib, the on-treatment period will be from the date of first administration of study treatment to the day before the first administration of asciminib),
- ***cross-over period***: (for subjects who cross over to receive the asciminib add-on treatment), from the date of first administration of asciminib to 30 days after last administration of asciminib or imatinib, whichever is the latest.
- ***post-treatment period***: starting at day 30+1 after last administration of study treatment (For patients who cross over to receive asciminib+imatinib, the post-treatment period will start 31 days after last administration of asciminib or imatinib, whichever is the latest).

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

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

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment, the cross-over and post-treatment period will be flagged.

Efficacy summaries include data from baseline up to either the last assessment on or before the end of treatment visit or before or on treatment discontinuation, whichever is the earliest.

Windows for multiple assessments

In order to summarize molecular response, ECG, and PRO measures data collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the average of the 2 assessments will be used. If multiple assessments on the same date then the average case 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 4*	28	Day 2 to day 38
Week 8*	56	Day 39 to day 66
Week 12	84	Day 67 to day 122
Week k (k=24, 36, 48, …)	7k	From Day 7k-45 to Day 7k+38

Day 1 = Date of randomization for randomized subjects/ date of first administration of study treatment for subjects in the asciminib single agent cohort

* Not mandatory for subjects in imatinib and nilotinib arm

EOT assessments are mapped to the time points as needed.

Table 2-2 Time windows for ECG assessments

Assessment	Target day of assessment	Time Interval
Baseline	≤ 1 (On or before Day 1)	≤ Day 1 #
Week 2*	14	Day 2 to day 17
Week 4*	28	Day 18 to day 52
Week 12	84	Day 53 to day 122
Week 24	168	Day 123 to day 248
Week 48	336	Day 249 to day 500
Week 96	672	Day 501 to day 836
Week k (k=144, …)	7k	From Day 7k-171 to Day 7k+164

Day 1 = Date of start of study treatment

* Not mandatory for subjects in imatinib and nilotinib arm

EOT assessments are mapped to the time points as needed.

Time windows for PRO assessments

Time windows will be defined for descriptive summary of PRO data by visit and longitudinal data analysis. 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. Data obtained at the end of treatment will be classified as other assessment in the corresponding time window. The end of treatment assessment will be included if collected within 7 days of the last dose intake.

Table 2-3 Time windows for PRO assessments

Assessment	Target day of assessment	Time Interval
Baseline	1	≤ Day 1 +3, no later than treatment start date [#]
Week 4	28	Day 4 to day 52
Week 12	84	Day 53 to day 122
Week 24	168	Day 123 to day 248
Week 48	336	Day 249 to day 500
Week 96	672	Day 501 to day 700

[#] Day 1 = Date of randomization for randomized subjects/ date of first administration of study treatment for subjects in the asciminib single agent cohort

2.2 Analysis sets

Randomized phase

Full analysis set

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

Safety set

The **Safety Set** includes all subjects who received any study treatment (i.e at least one dose of any component of the study treatment). Subjects will be analyzed according to the study treatment actually received.

The actual treatment received corresponds to:

- the randomized treatment if the subject took at least one dose of that treatment;
- the first treatment received if the randomized treatment was never received.

Pharmacokinetic Analysis Set

The **Pharmacokinetic analysis set (PAS)** includes all subjects randomized to the asciminib + imatinib arm who received at least one dose of asciminib or imatinib and provide at least one evaluable PK concentration. For a concentration to be evaluable, subjects are required to:

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

Other analysis sets

$MR^{4.5}$ Responder set: this set consists of the subjects in the FAS who achieved $MR^{4.5}$ under randomized treatment by the corresponding cut-off date. It will be used for the time to $MR^{4.5}$ and duration of $MR^{4.5}$ analyses.

Crossover set: this set consists of the subjects randomized to the continued imatinib arm who crossed over to receive the asciminib add-on treatment after 48 weeks of study treatment. This will be used in the analyses of the data after crossover.

Interim analysis efficacy set: At the time of the interim analysis, many patients will be ongoing on study treatment and will not have completed all the visits. Thus, for any efficacy analysis at interim, only the subset of patients with adequate follow-up will be considered.

1. For any efficacy analysis up to and including week 24 (e.g. MR4.5 at week 24), this subset will include only patients who were randomized at least 24 weeks prior to the cut-off date.
2. For any efficacy analysis for week 48 (e.g. MR4.5 at week 48), this subset will include only patients who were randomized at least 48 weeks prior to the cut-off date.

Asciminib single agent cohort (ASAC)

Full analysis set - ASAC

The **Full Analysis Set - ASAC (FAS-ASAC)** comprises all subjects assigned to the asciminib single agent cohort.

Safety set - ASAC

The **Safety Set** - ASACincludes all subjects assigned to the asciminib single agent cohort who received at least one dose of asciminib 80 mg QD.

Pharmacokinetic Analysis Set - ASAC

The **Pharmacokinetic analysis set – ASAC (PAS- ASAC)** includes all subjects assigned to the asciminib single agent cohort who received at least one dose of asciminib 80 mg QD and provide at least one evaluable PK concentration. For a concentration to be evaluable, subjects are required to:

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

Other analysis sets

$MR^{4.5}$ Responder set - ASAC: this set consists of the subjects in the FAS - ASAC who achieved $MR^{4.5}$ under treatment by the cut-off date. It will be used for the time to $MR^{4.5}$ and duration of $MR^{4.5}$ analyses.

Patient Classification

Subjects may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific subject classification rules defined in Table 2-4.

Table 2-4 Subject classification based on protocol deviations and non-PD criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written inform consent	Not applicable
Safety set	No written inform consent	No dose of study medication
PK Analysis set	No written inform consent	See definition of PAS
Interim analysis efficacy set	No written inform consent	See definition of Interim analysis efficacy set for selection of subject subsets
$MR^{4.5}$ Responder set	Not applicable	See definition of $MR^{4.5}$ Responder set
Crossover set	Not applicable	See definition of Crossover set
FAS - ASAC	No written inform consent	Not applicable
Safety set – ASAC	No written inform consent	No dose of asciminib
PK Analysis set - ASAC	No written inform consent	See definition of PAS - ASAC
$MR^{4.5}$ Responder set - ASAC	Not applicable	See definition of $MR^{4.5}$ Responder set - ASAC

Withdrawal of Informed Consent

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

2.2.1 Subgroup of interest

Subgroup analyses will use the same method as for the analysis in the respective overall analysis set.

Summary tables will only be generated if at least 5 patients are present in each subgroup.

Efficacy

The primary efficacy endpoint will be summarized by the following subgroups to examine the consistency of the rate of $MR^{4.5}$ at 48 weeks across the different subgroups:

- prior imatinib duration: < 5 years versus ≥ 5 years
- molecular response at screening: 0.1%<BCR::ABL1≤1.0% versus 0.01%<BCR::ABL1≤ 0.1%

No formal statistical test of hypotheses will be performed for the subgroups, only point estimates of the treatment effect and 90%-confidence intervals will be provided (see Section 2.5.2 for further analysis details). The objective of the efficacy subgroup analysis is to demonstrate homogeneity of treatment effect in the above subgroups.

Safety

There is no plan to summarize safety by any subgroup.

2.3 Patient disposition, demographics and other baseline characteristics

The FAS will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries will be reported by treatment arm and for all subjects, and listings will be reported by treatment arm to assess baseline comparability. No inferential statistics will be provided.

2.3.1 Patient disposition

Randomized phase

Enrollment by country and center will be summarized for all screened subjects and also by treatment arm using the FAS. The number (%) of randomized subjects included in the FAS will be presented overall and by treatment arm. The number (%) of screened and not - randomized subjects and the reasons for screening failure will also be displayed. The number (%) of subjects in the FAS who are still on randomized treatment, who discontinued the study phases (randomized treatment period and safety follow-up) and the reason for discontinuation will be presented overall and by treatment arm. The number (%) of subjects in the FAS randomized to the imatinib arm who crossed over to receive asciminib add-on treatment, who are still on asciminib add-on treatment, who discontinued asciminib add-on treatment and the reason for discontinuation of asciminib add-on treatment after cross-over will also be presented.

The following summaries will be provided (with % based on the total number of FAS 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 the Disposition eCRF page for event “Treatment disposition”)
- 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 randomized treatment (based on the Disposition eCRF page for event “Treatment disposition” not completed)
- Number (%) of subjects who completed the randomized treatment phase (based on the Disposition eCRF page for event “Treatment disposition”)
- Number (%) of subjects who discontinued the randomized treatment (based on the Disposition eCRF page for event “Treatment disposition”)
- Primary reason for randomized treatment discontinuation (based on the Disposition eCRF page for event “Treatment disposition”)
- Number (%) of subjects who crossed over from imatinib arm and received asciminib + imatinib (based on the Study Treatment eCRF page for study treatment “Asciminib” completed with non-zero dose administered)

- Number (%) of subjects who crossed over from imatinib arm to receive asciminib + imatinib and are still receiving asciminib + imatinib (based on the Disposition eCRF page for event "Crossover treatment disposition" not completed)
- Number (%) of subjects who crossed over from imatinib arm to receive asciminib 60 mg + imatinib and discontinued asciminib + imatinib (based on the Disposition eCRF page for event "Crossover treatment disposition")
- Primary reason for cross-over phase discontinuation (based on the Disposition eCRF page for event "Crossover treatment disposition")

Asciminib single agent cohort

Enrollment by country and center will be summarized for all screened subjects and also for the asciminib single agent cohort using the FAS-ASAC. The number (%) of subjects enrolled in the FAS - ASAC will be presented. The number (%) of screened and not – enrolled subjects and the reasons for screening failure will also be displayed. The number (%) of subjects in the FAS - ASAC who are still on treatment, who discontinued the study phases (treatment period and safety follow-up) and the reason for discontinuation will be presented.

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

- Number (%) of subjects who were enrolled (based on data from IRT system)
- Number (%) of subjects who were enrolled but not treated (based on Study Treatment eCRF page not completed)
- Primary reason for not being treated (based on the Disposition eCRF page for event "Treatment disposition")
- Number (%) of subjects who were treated (based on Study Treatment eCRF pages of study treatment completed with non-zero dose administered)
- Number (%) of subjects who are still on treatment (based on the Disposition eCRF page for event "Treatment disposition" not completed)
- Number (%) of subjects who completed the treatment phase (based on the Disposition eCRF page for event "Treatment disposition")
- Number (%) of subjects who discontinued the treatment (based on the Disposition eCRF page for event "Treatment disposition")
- Primary reason for treatment discontinuation (based on the Disposition eCRF page for event "Treatment disposition")

Protocol deviations

Randomized phase

The number (%) of subjects in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the Study Specification Document) overall and by treatment arm for the FAS. All protocol deviations will be listed.

Asciminib single agent cohort

The number (%) of subjects in the FAS - ASAC with any protocol deviation will be tabulated by deviation category (as specified in the Study Specification Document). All protocol deviations will be listed.

Analysis sets

Randomized phase

The number (%) of subjects in each analysis set (defined in Section 2.2) will be summarized by treatment arm. Reasons leading to exclusion from analysis sets will be listed by treatment arm as well as tabulated overall and by treatment arm.

Asciminib single agent cohort

The number (%) of subjects in each ASAC analysis set (defined in Section 2.2) will be summarized. Reasons leading to exclusion from analysis sets will be listed and tabulated.

2.3.2 Demographics and other baseline characteristics

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by treatment arm and for the asciminib single agent cohort. Categorical data (e.g. gender, age groups: 18 - <65, 65 - <85, and ≥ 85 years, race, ethnicity) 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, 25^{th} and 75^{th} quantile, minimum and maximum). BMI (kg/m^2) will be calculated as weight[kg] / (height[m]^2) using weight at screening. Demographic and baseline disease characteristics data will also be summarized using the crossover set.

Diagnosis and extent of cancer

All diagnosis and extent of cancer data will be summarized and listed by treatment arm and for the asciminib single agent cohort. One summary table will include time (years) since initial diagnosis (descriptive statistics with N, mean, median, standard deviation, 25^{th} and 75^{th} quantile, minimum and maximum) and extramedullary involvement (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 by treatment arm and for the asciminib single agent cohort. The summary will be presented by primary system organ class (SOC), preferred term (PT) and treatment arm. Medical history and current medical conditions will be coded using the Medical Dictionary for 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.

Other

All 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

Randomized phase

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment arm, separately for each component of study treatment. For the asciminib + imatinib arms, the duration of exposure will also be presented overall. 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 by treatment arm and component.

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

The safety set will be used for all summaries and listings of randomized study treatment.

Asciminib single agent cohort

Duration of exposure, actual cumulative 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, including the reasons for them, will be summarized. Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set – ASAC will be used for all summaries and listings of the asciminib single agent cohort data

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to any component of the study treatment, if applicable:

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

The date of last administration of study treatment and the date of first administration of study treatment are defined in Section 2.1.1.

Summary of duration of exposure to study treatment in appropriate time units will include categorical summaries and continuous summaries (i.e. mean, standard deviation etc.) using appropriate units of time .

Duration of exposure to each of the study treatment components

Duration of exposure to one component of study treatment (days) = (last date of exposure to the considered component of study treatment) – (date of first administration of the considered component of study treatment) + 1.

The date of last administration of each study treatment components and the date of first administration of each study treatment components are defined in Section 2.1.1.

Summary of duration of exposure to each of the study treatment components in appropriate time units will include categorical summaries and continuous summaries (i.e. mean, standard deviation etc) using appropriate units of time.

Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment components.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the date of last administration of study treatment as defined in Section 2.1.1.

The calculation for the five study treatment components are:

- Asciminib: 60 mg/administration × 1 (administration/day) × duration of exposure to study treatment (days)
- Asciminib: 40 mg/administration × 1 (administration/day) × duration of exposure to study treatment (days)
- Imatinib: 400 mg/administration × 1 (administration/day) × duration of exposure to study treatment (days)
- Nilotinib: 300 mg/administration × 2 (administration/day) × duration of exposure to study treatment (days)
- Asciminib: 80 mg/administration × 1 (administration/day) × duration of exposure to study treatment (days)

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 doses recorded over the dosing period. For subjects who did not take any drug, the actual cumulative dose is by definition equal to zero.

Dose intensity and relative dose intensity

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 follows:

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

Relative dose intensity (RDI) is defined as follows:

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

DI and RDI will be summarized separately for each of the study treatment components, using the duration of exposure of each of the components (see Section 2.1.1).

Dose reductions, interruptions or permanent discontinuation

The number of subjects who have dose reductions, dose interruptions or permanent discontinuation, the reasons, and the number and duration of dose reductions and dose interruptions per subject will be summarized separately for each of the study treatment components.

'Dose changed', 'Dose interrupted', and Dose permanently discontinued' fields from the Study Treatment CRF pages will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

The field 'Reason for change' will be used to summarize the reasons.

Dose changed is either 'change in prescribed dose level' or 'dosing error' where actual dose administered/total daily dose is different from the prescribed dose.

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 this 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 planned daily dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the CRF, number of reductions will be derived programmatically based on the change and the direction of the change.

Dose adjustments and discontinuation of study treatment will be summarized by treatment arm and component. A dose adjustment for the combination arms is a dose adjustment in one of the two drugs. A discontinuation of study treament for the combination arms is a discontinuation of study treatment of one of the tow drugs.

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 by treatment arm as well as for the asciminib single agent cohort and also by lowest ATC class and preferred term. Summaries will include total number of regimens.

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

The above analyses will be performed using the FAS and FAS-ASAC.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by ATC class, preferred term, overall, by treatment arm and for the asciminib single agent cohort by means of frequency counts and percentages using FAS and FAS-ASAC.

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.

Concomitant therapies

Concomitant therapies are defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient 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 Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries will include:

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

All concomitant therapies will be listed. Data after crossover will be flagged. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last dose of study treatment will be flagged in the listing. The safety set will be used for all concomitant therapies tables and listings.

2.5 Analysis supporting primary objective(s)

The primary objective of the study is to assess whether asciminib 40 mg + imatinib or asciminib 60 mg + imatinib is more effective than continued imatinib in subjects with CML-CP who have received imatinib for at least one year (12-calendar months) and have not achieved DMR.

2.5.1 Primary endpoint(s)

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

2.5.2 Statistical hypothesis, model, and method of analysis

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

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

2.5.3 Handling of missing values/censoring/discontinuations

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

2.5.4 Supportive analyses

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

1. The rate of $MR^{4.5}$ at 48 weeks and its 90% confidence interval based on the Clopper-Pearson method will be presented by treatment arm (asciminib 60 mg + imatinib, asciminib 40 mg + imatinib and continued imatinib) for the following subgroups if, within each treatment arm, each subgroup includes at least 5 subjects:
    - prior imatinib duration < 5 years *versus* ≥ 5 years
    - molecular response at screening (0.1% < BCR::ABL1 ≤ 1.0% *versus* 0.01% < BCR::ABL1 ≤ 0.1%)

No formal statistical test of hypotheses will be performed. No inferential statistics (p-values) will be produced for the subgroups.

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

2.6 Analysis supporting secondary objectives

The secondary objectives are:

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

2.6.1 Secondary endpoint(s)

The secondary efficacy endpoints of this study are:

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

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

Randomized phase

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

In addition, the difference in efficacy will be estimated between

- asciminib 60 mg + imatinib and switch to nilotinib

and between

- asciminib 40 mg + imatinib and switch to nilotinib

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

Asciminib single agent cohort

To estimate the efficacy of asciminib 80 mg QD, the rate of $MR^{4.5}$ at 48 weeks and its 2 sided 90% confidence interval based on the Clopper-Pearson method will be presented using the FAS–ASAC. No formal comparison or estimate of the difference with the other treatment arms will be performed for this additional cohort.

2.6.1.2 Rate of Sustained $MR^{4.5}$ at 96 weeks

Randomized phase

The rate of sustained $MR^{4.5}$ at 96 weeks is defined as the proportion of subjects who are in $MR^{4.5}$ at both 48 and 96 weeks (considering window) under randomized treatment and who have no loss of $MR^{4.5}$ in between those two time points among all subjects randomized to the respective treatment arm.

Loss of $MR^{4.5}$ is defined as an increase of the BCR::ABL ratio to >0.0032% in a single blood sample, by International Scale.

Asciminib single agent cohort

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

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

Randomized phase

The rate of $MR^{4.5}$ at 96 weeks is defined as the proportion of subjects who have been treated with the randomized treatment for at least 96 weeks and are in $MR^{4.5}$ at 96 weeks, among all subjects randomized to the respective treatment arm.

Asciminib single agent cohort

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

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

Randomized phase

The rate of $MR^{4.5}$ by 48 weeks (respectively 96 weeks) is defined as the proportion of subjects who have ever reached $MR^{4.5}$ under the randomized treatment up to 48 weeks (resp. 96 weeks), among all subjects randomized to the respective treatment arm.

Asciminib single agent cohort

The rate of $MR^{4.5}$ by 48 weeks is defined as the proportion of subjects who have ever reached $MR^{4.5}$ under treatment up to 48 weeks, among all subjects enrolled to the asciminib single agent cohort.

2.6.1.5 Time to $MR^{4.5}$

Randomized phase

Time to $MR^{4.5}$ in weeks is defined for subjects in the $MR^{4.5}$ Responder set at the corresponding cut-off as: (date of first $MR^{4.5}$ – date of randomization + 1)/7.

Asciminib single agent cohort

Time to $MR^{4.5}$ in weeks is defined for subjects in the $MR^{4.5}$ Responder set – ASAC at the corresponding cut-off as: (date of first $MR^{4.5}$ – date of first administration of asciminib + 1)/7

2.6.1.6 Duration of $MR^{4.5}$

Duration of $MR^{4.5}$ is defined as the time between the date of first documented $MR^{4.5}$ and the end date of $MR^{4.5}$, i.e. the earliest date of loss of $MR^{4.5}$ or CML-related death.

Loss of $MR^{4.5}$ is defined in Section 2.6.1.2.

For patients for whom none of the events above is reported, the duration will be censored (see Section 2.6.3).

The duration of $MR^{4.5}$ (in weeks) is calculated as: (end date or censoring date of $MR^{4.5}$ - date of first $MR^{4.5}$ + 1)/7

A sensitivity analysis of duration of $MR^{4.5}$ is produced where duration of $MR^{4.5}$ is defined as the time between the date of first documented $MR^{4.5}$ and the end date of $MR^{4.5}$, i.e. the earliest date of confirmed loss of $MR^{4.5}$ or CML-related death.

Confirmed loss of $MR^{4.5}$ is defined as an increase of the BCR::ABL1 ratio to >0.0032% in two consecutive blood samples, by International Scale.

Randomized phase

Duration of $MR^{4.5}$ is defined for subjects in the $MR^{4.5}$ Responder set.

Asciminib single agent cohort

Duration of $MR^{4.5}$ is defined for subjects in the $MR^{4.5}$ Responder set – ASAC.

2.6.2 Statistical hypothesis, model, and method of analysis

Rates of $MR^{4.5}$ at and by time points

Randomized phase

These endpoints will be calculated based on the FAS. For each time point, the rate of $MR^{4.5}$ and its 90% confidence interval based on the Clopper-Pearson method will be presented by treatment arm.

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

Asciminib single agent cohort

These endpoints will be calculated based on the FAS-ASAC. For each time point, the rate of $MR^{4.5}$ and its 90% confidence interval based on the Clopper-Pearson method will be presented by treatment arm.

The cumulative incidence of $MR^{4.5}$ will also be graphically displayed by an increasing step-function. This curve will increase each time (after first dose of treatment) 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 $MR^{4.5}$).

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

Randomized phase

Using the FAS, the rate of sustained $MR^{4.5}$ at 96 weeks and its 90% confidence interval based on the Clopper-Pearson method will be presented by treatment arm.

Asciminib single agent cohort

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

Time to $MR^{4.5}$

Randomized phase The $MR^{4.5}$ Responder set will be used. Descriptive statistics (range, median, quartiles, mean, SD) of time to $MR^{4.5}$ will be provided for the 4 treatment arms separately.

Asciminib single agent cohort

The $MR^{4.5}$ Responder set – ASAC will be used. Descriptive statistics (range, median, quartiles, mean, SD) of time to $MR^{4.5}$ will be provided for asciminib single agent cohort.

Duration of $MR^{4.5}$

Randomized phase

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

Asciminib single agent cohort

The $MR^{4.5}$ Responder set – ASAC will be used. Descriptive statistics (range, median, quartiles, mean, SD) of time to $MR^{4.5}$ will be provided for asciminib single agent cohort.

2.6.3 Handling of missing values/censoring/discontinuations

Rates of $MR^{4.5}$ at a specific time point

Randomized phase

All randomized subjects will be included in the denominator. In the analysis "at" a specific time point, only subjects with $MR^{4.5}$ under randomized treatment at this specific time point are considered as responders. A subject who has achieved $MR^{4.5}$ before this specific time point, but who is no longer in $MR^{4.5}$ at this specific time point, will be considered as a non-responder at this specific time point. Subjects who discontinue the randomized treatment for any reason prior to a specific time point will be considered as non-responders for that time point.

Asciminib single agent cohort

All subjects enrolled in the asciminib single agent cohort will be included in the denominator. In the analysis "at" a specific time point, only subjects with $MR^{4.5}$ under asciminib 80 mg QD at this specific time point are considered as responders. A subject who has achieved $MR^{4.5}$ before this specific time point, but who is no longer in $MR^{4.5}$ at this specific time point, will be considered as a non-responder at this specific time point. Subjects who discontinue asciminib 80 mg QD for any reason prior to a specific time point will be considered as non-responders for that time point.

Rates of $MR^{4.5}$ by a specific time point

Randomized phase

All randomized subjects will be included in the denominator. In the analyses "by" a specific time point, subjects who had achieved $MR^{4.5}$ under randomized treatment at or before the time point will be displayed as responders, whether they lost the response/discontinued treatment or not. Therefore this response rate represents the best observed rate of $MR^{4.5}$ under randomized treatment up to that specific time point. Response assessments after discontinuation of the randomized treatment or after a specific time point will be ignored for that time point.

Asciminib single agent cohort

All subjects enrolled in the asciminib single agent cohort will be included in the denominator. In the analyses "by" a specific time point, subjects who had achieved $MR^{4.5}$ under asciminib 80 mg QD at or before the time point will be displayed as responders, whether they lost the response/discontinued treatment or not. Therefore, this response rate represents the best observed rate of $MR^{4.5}$ under asciminib 80 mg QD up to that specific time point. Response assessments after discontinuation of asciminib 80 mg QD or after a specific time point will be ignored for that time point.

Sustained rate of $MR^{4.5}$ at 96 weeks

Randomized phase

All randomized subjects will be included in the denominator. Subjects who discontinue the randomized treatment for any reason prior to 96 weeks will be considered as non-responders.

Asciminib single agent cohort

Not applicable for the asciminib single agent cohort.

Time to $MR^{4.5}$

Subjects who have not reached $MR^{4.5}$ under treatment will be excluded from the time to $MR^{4.5}$ analyses. Response assessments after discontinuation of the treatment will be ignored. Censoring will not be needed.

Duration of $MR^{4.5}$

Subjects who have not reached $MR^{4.5}$ under treatment will be excluded from the duration of $MR^{4.5}$ analyses. Subjects with missing date of loss of $MR^{4.5}$ or CML-related death will be censored.

The duration of $MR^{4.5}$ will be censored at the last molecular assessment (RQ-PCR) date while on treatment for subjects who have not experienced loss of $MR^{4.5}$ or CML-related death.

2.7 Safety analyses

All safety analyses will be based on the safety set. All listings and tables will be presented by treatment arm. Data after crossover will be summarized separately for subjects in the crossover set who received at least one dose of asciminib (see Section 2.12.2). Data from the asciminib single agent cohort will be summarized separately for the subjects in the safety set – ASAC.

2.7.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on treatment period. All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings. AEs will be summarized by number and percentage of 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 for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

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 sort order for the preferred term will be based on their frequency in the asciminib 60 mg + imatinib arm.

The following adverse event summaries will be produced by treatment arm: 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.

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

2.7.1.1 Adverse events of special interest / grouping of AEs

Data analysis of AESIs

An adverse event of special interest 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), HGLTs (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 case retrieval strategy (CRS) 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 on treatment period will be summarized.

Summaries of these AESIs will be provided by treatment arm, (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, hospitalization, death etc.).

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

2.7.2 Deaths

Separate summaries for on-treatment and all deaths (including post-treatment death) will be produced by study treatments, system organ class and preferred term.

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

2.7.3 Laboratory data

On analyzing laboratory data, data from 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 or one day before the first administration of asciminib for patients who cross over to receive asciminib + imatinib (see Section 2.1.1).

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

- Worst post-baseline CTC grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTC 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 for the laboratory data:

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

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT, AST and alkaline phosphatase (ALP). The number (%) of subjects with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized:

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- ALP > 1.5xULN
- TBL > 1.5xULN
- TBL > 2xULN
- ALT or AST > 3xULN & TBL > 1.5xULN
- ALT or AST > 3xULN & TBL > 2xULN

Risk Handling for Q2 Roche Magnesium Testing

Q2 solutions identified an issue with serum Magnesium (Mg) results from Roche Diagnostics Cobas analyzer in the UK lab (only) from 05 Jun- 09 Jul 2018 and 22 Nov 2018- 02 Jan 2019. Some magnesium values for three patients (7500001, 4200001, 4200002) were not valid; one of these patients (4200002) was a screen failure not linked to the magnesium testing, and finally randomized. The invalid values are flagged in the database 3; these values will be excluded from the analysis but listed in the CSR to discuss potential impact.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

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

Data handling

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

Data analysis

The number and percentage of subjects with notable ECG values will be presented by study treatments. 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 ≤ 60 ms
    - Increase from baseline of > 60 ms
- RR
    - 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

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

A listing of all ECG assessments will be produced by study treatments 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.

2.7.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters will be 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 the on-treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-5 below.

Table 2-5 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase > 10% from Baseline	decrease > 10% from Baseline
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%
Body temperature	>= 39.1	-

The number and percentage of subjects with notable vital sign values (high/low) will be presented by study treatments.

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

2.8 Pharmacokinetic endpoints

PK parameters

The PK parameters that will be determined are shown in Table 2-6. For imatinib metabolite (N-desmethyl imatinib (CGP74588)), only C_{max}, T_{max}, AUC_{last} and the metabolite-to-parent AUC ratio will be calculated. The PK parameters are derived based on the non-compartmental methods using Phoenix WinNonlin® software version 8.

Table 2-6 Non-compartmental PK parameters

AUC_{tau}	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1) (only for Week 2 Day 14)
AUC_{last}	The AUC from time zero to the last measurable plasma concentration sampling time (Tlast) ($ng*hr*mL^{-1}$) (only for Week 2 Day 14)
C_{max}	The maximum (peak) observed plasma concentration (ng/mL) (Week 2 Day 14 and Week 4 Day 28)
T_{max}	The time to reach maximum (peak) plasma concentration (hr) (Week 2 Day14 and Week 4 Day 28)
T_{last}	Time of last measurement (time) (Week 2 Day 14 and Week 4 Day 28)

Descriptive statistics (n, arithmetic mean, CV% mean, standard deviation (SD), median, geometric mean, CV% geo-mean, minimum and maximum) will be presented by treatment for Pharmacokinetic analysis sets for all PK parameters defined Table 2-6 in except Tmax, where only n, median, minimum and maximum will be presented.

All individual PK parameters will be listed by treatment for the Pharmacokinetic analysis sets.

Descriptive statistics (n, m (number of non-zero concentrations), mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum) for asciminib and imatinib concentrations will be presented at each scheduled time point by treatment for the Pharmacokinetic analysis sets.

Individual concentration-time profiles for asciminib and imatinib concentrations with median will be displayed graphically by treatment and visit/sampling time point (Week 2 Day 14 and Week 4 Day 28) for the Pharmacokinetic analysis sets on the semi-log view.

In addition, the mean (+/- SD) and geometric mean concentration-time profiles for asciminib and imatinib by treatment over time will be displayed graphically for the Pharmacokinetic analysis sets on the linear and semi-log view.

All individual plasma asciminib and imatinib concentration data will be listed for patients from the asciminib + imatinib arms in the Safety set and from the asciminib single agent cohort in the Safety set - ASAC.

Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ) (<1.00 ng/mL for asciminib and imatinib and <20.0 ng/mL for N-desmethyl imatinib) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing values for any PK data will not be imputed and will be treated as missing.

2.9 PD and PK/PD analyses

The potential relationship between asciminib exposure (e.g. trough concentration) and primary efficacy endpoint or most critical safety endpoints may be assessed by graphic exploration

and/or statistical modeling as appropriate. If applicable, the details of the analyses and results will be described in a separate analysis plan and reported separately.

2.10 Patient-reported outcomes

The potential relationship between asciminib exposure (e.g. trough concentration) and primary efficacy endpoint or most critical safety endpoints may be assessed by graphic exploration and/or statistical modeling as appropriate. If applicable, the details of the analyses and results will be described in a separate analysis plan and reported separately.

2.11 Biomarkers

Randomized phase

As a project standard, only biomarkers collected in the clinical database will be analyzed. For exploratory markers, since the studies are not adequately powered to assess specific biomarker–related hypotheses, the goal of these exploratory statistical analyses should be considered as the generation of new scientific hypotheses. No adjustment for multiple comparisons is usually planned for exploratory analyses. Furthermore, additional post hoc exploratory assessments are expected and may be performed.

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue their analysis due to either practical or strategic reasons. Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

The FAS will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data.

Exploratory biomarker objectives

- To explore mechanisms of resistance associated with asciminib 60 mg or 40 mg via CCI [redacted]
- To explore CCI [redacted]
- To evaluate the CCI [redacted]

If requested by health authorities, some analyses for the first exploratory biomarker objective about CCI [redacted] listed above are described in this SAP and the results will be included in the CSRs. Additional analyses for this and the other exploratory biomarker objectives will be described in separate analyses plans, with results reported separately.

List of biomarkers evaluated and the collection time points

The biomarkers evaluated in the study are listed in Table 2-7 below.

Table 2-7 Sample biomarker summary table

Biomarker	Time point	Sample	Method	Dataset
CCI		*Whole blood*	CCI	
		Whole blood		
		Whole blood		

General Data Handling and preprocessing

When more than one biomarker data value are available for a subject at any time point, the mean of the replicate values will be used for all statistical analyses.

2.11.1 Somatic mutation biomarker data handling and analysis

Randomized phase

Handling of somatic biomarker data

Overall, somatic mutation status will be derived from the interrogated exons for the BCR::ABL1 gene. These may be non-exclusive and the presence of mutation across more than one exon will be reported in separate categories.

Mutation summary statistics

All somatic mutation data will be reported using counts and percentages in the form of contingency tables with the rows containing the different mutations assayed, and the treatment groups in the columns. A summary table will be presented for baseline mutations and another summary table for post-baseline new mutations (not present at baseline).

All the mutation data will be listed for each subject ordered by treatment group.

Association between biomarkers and clinical outcome

CCI data and outcome data (with or without $MR^{4.5}$ at and by 48 and 96 weeks using FAS) will be listed for each subject listed by treatment group.

Asciminib single agent cohort

Biomarker sample will not be collected for the asciminib single agent cohort.

2.12 Other Exploratory analyses

2.12.1 Proportion of subjects eligible for TFR at end of study

The proportion of subjects eligible for TFR at end of study is defined as the proportion of subjects who have been treated with the randomized treatment up to the end of study and achieved sustained MRD (Minimal Residual Disease) based on the last 5 quarterly performed PCR assessments, i.e. (1) both first and last assessments are $MR^{4.5}$, (2) no assessment is worse than MR^4, and (3) no more than two assessments are between MR^4 and $MR^{4.5}$, among all patients randomized to the respective treatment arm.

Using the FAS, the proportion of subjects eligible for TFR at end of study and its 90% confidence interval based on the Clopper-Pearson method will be presented by treatment arm.

All randomized subjects will be included in the denominator. Subjects who discontinue the randomized treatment for any reason prior to end of study will be considered as non-eligible for TFR.

2.12.2 Efficacy and safety evaluation after cross-over

Separate analyses of efficacy and safety events will be conducted for patients randomized to the imatinib arm who will cross-over to receive asciminib 60mg + imatinib, i.e. crossover set.

Efficacy

Time to $MR^{4.5}$from first administration of asciminib is defined as: date of first $MR^{4.5}$ on asciminib treatment– date of first administration of asciminib + 1.

Using the subset of subjects in the crossover set who will achieve $MR^{4.5}$ under asciminib + imatinib during the crossover period, descriptive statistics (range, median, quartiles, mean, sd) of time to $MR^{4.5}$ will be provided.

Subjects who will not have reached $MR^{4.5}$ under asciminib + imatinib during the crossover period will be excluded from this time to $MR^{4.5}$ analysis. Response assessments after discontinuation of asciminib will be ignored. Censoring will not be needed.

Safety

Safety analyses will be based on the subjects in the crossover set who will have received at least one dose of asciminib.

AE summaries will include all AEs occurring during the cross-over period (see Section 2.1.1).

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 following summaries will be produced separately for hematology and biochemistry laboratory data (by laboratory parameter and treatment) (see Section 2.7.3):

- Worst post-baseline CTC grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline.

- Shift tables using CTC grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

They will include all assessments available for the lab parameter collected from the first administration of asciminib to 30 days after the last administration of asciminib + imatinib (see Section 2.1.1).

Specific summaries for the liver function parameters will also be produced (see Section 2.7.3).

The following summaries for ECG and vital signs data will be produced:

- Number and percentage of subjects with notable ECG values
- Number and percentage of subjects with notable vital sign values (high/low)

2.12.3 Patient-reported outcomes

The EORTC QLQ-C30 questionnaire along with the disease-specific chronic myeloid leukemia module (EORTC QLQ-CML24), TSQM and FACIT GP5 will be used to collect data on the patient-reported outcome measures of health-related quality-of life, treatment satisfactions and treatment-related side effects from baseline to EOT. All tools require patient's direct completion and will be administered utilizing electronic device for data collection at scheduled time points from baseline to end of treatment.

The compliance to the schedule of administration of PRO will be summarized by study treatments, for baseline and post-baseline on-treatment time points.

The following categories, as collected on the eCRF, will be used to describe whether the questionnaire was completed at a specific time point:

- yes, fully completed
- yes, partly completed
- no, patient refused due to poor health
- no, patient refused (unrelated to health)
- no, questionnaire not available in appropriate language
- no, institutional error
- no, technical issues
- no, other.

The FAS and FAS-ASAC will be used for analyzing PRO data unless specified differently.

Descriptive statistics (n, mean, SD, median, 25^{th} and 75^{th} percentiles) will be used to summarize all scores by study treatments over time using time windows as described in Section 2.1.1. Additionally, change from baseline in the scores at the time of each scheduled assessment will be summarized. No formal statistical tests will be performed.

The scoring system for each PRO is described in the Appendix. Baseline is defined in Section 2.1.1. Patients with an evaluable baseline score and at least one evaluable post-baseline score during the treatment period will be included in the change from baseline analyses. 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.

Results from the qualitative subject interview will be analyzed and reported separately.

2.13 Interim analysis

An interim analysis will be performed in order to have an early assessment of benefit and risk of treating patients with asciminib + imatinib arms vs continued imatinib arm and switch to the nilotinib arm in Ph+CML-CP patients. This interim analysis will be performed on all randomized patients when at least 40 (50%) patients have been randomized and have been followed for their 24 weeks visit assessment or have discontinued treatment.. The interim analysis will include all randomized patients data until the date of data cutoff. All patients in the safety set will be used for safety analysis. The interim analysis efficacy set will be used for efficacy analysis as defined in Section 2.2.

No formal comparison is planned between the treatment arms at the time of the interim analysis, and only descriptive analyses will be conducted. The following summaries will be provided by treatment arm:

- Patient disposition, baseline and disease characteristics as well as treatment exposure will be summarized..
- Descriptive summaries of BCR::ABL1 levels over time will be provided, as well as MR^4 and $MR^{4.5}$ rates over time with 90% confidence intervals . In addition, patient-level listings as well as lasagna plots will also be produced to visualize each subject's trajectory of the molecular response status (based on BCR::ABL1 levels) over time.
- Adverse event summaries will be produced by SOC, PT and worst grade (separately for all AEs and for AEs suspected to be related to study treatment). For hematology and biochemistry laboratory data the worst post-baseline CTC grade will be summarized. Listings of all adverse events, deaths, hematology and biochemistry values will also be provided.

An interim CSR will not be produced based on this interim analysis.

2.14 COVID-19 related analysis

Additional analyses may be performed to assess the impact of COVID-19 pandemic on the study (reporting of adverse events, missing visits, protocol deviations, etc.).

3 Sample size calculation

3.1 Primary objective

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

With 20 subjects per arm enrolled in the two asciminib + imatinib arms and the continued imatinib arm, the precision of the estimates of the difference between 1) asciminib 60 mg +

imatinib *versus* continued imatinib and 2) asciminib 40 mg + imatinib *versus* continued imatinib for different scenarios is shown in Table 3-1.

Table 3-1 90% Confidence intervals for 30% difference rate between the arms

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

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

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

These calculations were made using the software package PASS 11.

There will however be no adjustment for repeated hypothesis testing due to the interim analysis as there is no formal comparison to be performed between the treatment arms, and only the estimation of effect sizes is planned.

3.2 Secondary objective

Randomized phase

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

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

These calculations were made using the software package PASS 11.

Asciminib single agent cohort

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

These calculations were made using the software package PASS 11.

4 Change to protocol specified analyses

No change to protocol specified analyses was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Missing dates for study drug administration should be queried and will not be imputed.

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made.

5.1.2 AE, ConMeds and safety assessment date imputation

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

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

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

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

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

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

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

Missing Element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

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

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

For the imputation of dates with day available and month missing, the day available will be ignored and the imputation rule for when day and month are missing will be used.

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 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version v5.0 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE v5.0, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

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

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

Imputation Rules

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

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

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

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

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

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

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

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

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

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

5.4 Derivation of PCR results and loss of response

Scaling towards an international standard will be performed for all molecular results using laboratory specific conversion factors. In this process, the raw ratio between BCR::ABL1 and the control gene ABL is calculated and multiplied by the lab-specific conversion factor ([Branford and Hughes 2006]). Therefore, using the international unit, the BCR::ABL1 ratio will be presented in %. The MRDx assay using PAXgene™ Blood RNA tubes from MMD laboratory will be used in this study. The conversion factor will be provided by the lab for each sample.

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

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

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

BCR::ABL1 Log-Reduction = $-\log_{10}$ (BCR::ABL1 ratio in %)

For example, -log10 (0.001) = 3 log reduction for a ratio of 0.1%.

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

Table 5-3 Response categories for molecular response

Molecular response		BCR::ABL1 ratio	Log-reduction category
$MR^{4.5}$	Yes	≤ 0.0032%	≥ 4.5-log reduction
	No	>0.0032%	<4.5-log reduction
MR^{4}	Yes	≤ 0.01%	≥ 4-log reduction
	No	>0.01%	<4-log reduction

Loss of $MR^{4.5}$ is defined in Section 2.6.1.2.

5.5 Statistical models

5.5.1 Analysis supporting primary objective(s)

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

The rate of $MR^{4.5}$ at 48 weeks and its 2-sided 90% confidence interval will be provided for each treatment arm using exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table (Clopper and Pearson 1934) for all patients and by subgroups (described in Section 2.5.4). The 2-sided 95% confidence interval within each treatment arm will also be computed using the same technique but for information purposes only.

The 2-sided 90% confidence interval for the difference in rate of $MR^{4.5}$ at 48 weeks between 1) asciminib 60 mg + imatinib *versus* continued imatinib and 2) asciminib 40 mg + imatinib *versus* continued imatinib will be provided using the Wald method (implemented via SAS procedure FREQ with RISKDIFF option in the TABLES statement, under the default CL =WALD and VAR=SAMPLE). If the 2x2 table is with asciminib + imatinib in row 1, continued imatinib in row 2, $MR^{4.5}$ in column 1 and No $MR^{4.5}$ in column 2, then the SAS output will give the estimate of (risk for $MR^{4.5}$ at 48 weeks in asciminib + imatinib – risk for $MR^{4.5}$ at 48 weeks in continued imatinib). The 2-sided 95% confidence intervals for these two differences will also be computed using the same technique but for information purposes only.

A logistic regression of $MR^{4.5}$ status at 48 weeks on treatment arm (asciminib 60 mg + imatinib, asciminib 40 mg + imatinib and continued imatinib), prior imatinib duration category and molecular response status at screening will be performed. An adjusted odds ratio for the treatment effect will be derived from the logistic regression model (implemented using SAS procedure LOGISTIC, with treatment, prior imatinib duration category and molecular response status at screening specified as explanatory variables in the CLASS statement) which allows for including adjustments for covariates (both categorical and continuous).

The odds ratio will be determined using exact logistic regression, and the odds ratio presented with exact 90% confidence limits. In these cases, SAS PROC LOGISTIC with EXACTONLY option will be used. The 2-sided 95% confidence interval will also be computed using the same technique but for information purposes only.

5.6 Scoring system for PROs

5.6.1 EORTC QLQ-C30

The EORTC QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than o ne scale.

EORTC QLQ-C30 subscale scores will be calculated by first obtaining the raw scores through adding up the item responses on the questions which make up each scales and then applying the linear transformation to the raw scores in accordance with the respective scoring manual provided by the developer (Fayers 2001). If at least half of the items comprising the scale have been answered, the score for this scale will be calculated. For single item scales with missing responses and scales where less than half of the items have been answered, the score for these scales will be set to missing.

5.6.2 EORTC QLQ-CML24

The **Chronic Myeloid Leukemia Module** is a supplementary questionnaire module to be employed in conjunction with the QLQ-C30. It consists of four multi-item scales to assess symptom burden, impact on worry/mood, impact on daily life, and satisfaction with care and information. In addition, two single items assess body image problems and satisfaction with social life.

The scoring approach for the QLQ-CML24 is identical in principle to that for the symptom scales/single-items of the QLQ-C30. All scoring information specific to the QLQ-CML24 is presented in the EORTC QLQ-CML Scoring Manual (Efficace 2014).

5.6.3 FACIT-GP5

This is a single item scale. Then, the score for this scale will be either set to the item response or set to missing in case the response is missing.

5.6.4 TSQM

Version 1.4 of the TSQM consists of 14 items that results in four specific domains: Effectiveness, Side Effects, Convenience, and one global scale item, Global Satisfaction. TSQM scale scores for each domain will be computed by adding the TSQM items in each domain and then transforming the composite score into a value ranging from from 0 to 100 according to the rules defined in the TSQM user manual (The lowest possible score is subtracted from the composite score and divided by the greatest possible score range. This provides a transformed score between 0 and 1 that is then multiplied by 100.). A score can be computed for a domain only if no more than one item is missing from that domain.

6 Reference

References are available upon request

Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.

Efficace F, Baccarani M, Breccia M, et al (2014) International development of an EORTC questionnaire for assessing health-related quality of life in chronic myeloid leukemia patients: the EORTC QLQ-CML24. Qual Life Res p. 825-36.

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