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ABL001/asciminib

Clinical Trial Protocol CABL001J12302

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

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Clinical Trial Protocol Template Version 5.0 dated 14-Jan-2022

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Amendment 02 (04-Sep-2024)

As of 31-Jul-2024, a total of 643 participants have been screened and 568 participants have been randomized, and recruitment is complete. The study is ongoing.

Amendment Rationale

The main purpose of this protocol amendment is to extend the duration of study treatment and add an optional Treatment Free Remission (TFR) Phase. CCI

Currently participants can be treated in the study until CCI discontinuations of study treatment due to adverse events have occurred. The amendment provides an extension of the treatment duration for a participant CCI which allows eligible participants CCI the opportunity to enter an optional TFR Phase. CCI

Additional modifications include:

- Updated with clinical and reference to non-clinical studies from the latest asciminib Investigator's Brochure (IB) Ed. 11, and template related changes impacting the Hy's law related reporting requirements, removed tubal ligation from effective methods of contraception and added bilateral salpingectomy in Exclusion criteria section 5.2 and from list of procedures exempting women from pregnancy testing section 8.4.6. Also, removed requirement for fractionated ALP (ALP isozyme) testing from section 6.5.2.1.
- Clarification of the discontinuation criterion of randomized treatment relating to detection of new *BCR::ABL1* T315I mutation or any mutation with known resistance to study treatment according to NCCN 2024 guidelines (NCCN 2024), at any time after initiation of the treatment.
- Updates to the list of concomitant medications to be used with caution (including OATP1B and BCRP substrates, and with P-gp substrates of narrow therapeutic index)
- Implementation of editorial changes throughout the protocol to correct typos and provide clarifications where required.

No change of the safety profile of asciminib has occurred that requires the protocol to be modified.

Changes to the protocol

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

The following sections, tables and figures were changed:

- CCI

- [redacted]

- [redacted]

- 

IRBs/IECs

- A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.
- The changes described in this amended protocol require IRB/IEC approval prior to implementation.
- The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 01 (13-Sep-2023)

Amendment rationale

As of 13-Sep-2023, 253 participants have been screened in the study, and 202 participants have been randomized. The study is ongoing.

The main purpose of this protocol amendment is to:

- Add a single formal interim analysis to allow for an early assessment of the tolerability of asciminib. To maintain the study power while allowing for alpha adjustment for the interim analysis the sample size is recalculated to 550 (previously 541) participants and CCI [redacted] events of discontinuation from study treatment due to adverse events. The purpose of this formal interim analysis is to allow for an early assessment of the tolerability of asciminib. The interim analysis is planned when CCI events occur. The study will continue regardless of the outcome of the interim analysis.
- Update the Schedule of Activities and Safety Assessments to clarify that additional local testing for hematology and chemistry may be performed to comply with local prescribing information.
- Update the Schedule of Activities to clarify that in case of a dry tap or missing cytogenetic analysis of previous bone marrow aspiration, cytogenetics on peripheral blood may be accepted at screening.
- Reflect the use of the same QTcF cut off value for both sexes 450ms, based on FDA guidance (E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs | FDA)
- Clarify the dose modification and dose discontinuation criteria for hepatotoxicity for both asciminib and nilotinib:
    - As the study includes patients with baseline total bilirubin elevation (< 3 x ULN are eligible), the dose modification guidelines for patients with elevated bilirubin or ALT/AST at baseline have been clarified as follows:
        1. For ALT/AST elevations (when baseline elevated): dose modification criteria have been revised to ensure that the combination of baseline values (3x, 5x etc. change from baseline) with ULN levels (5x ULN, 8X ULN etc.) are taken into consideration.
        2. Update dose modification criteria for baseline elevated total bilirubin levels. The reference to baseline elevated bilirubin levels was removed in the recommendations for dose modification in response to drug-induced elevation of bilirubin.
        3. In addition, guidance for discontinuing treatment for elevations of AST and ALT > 20 x ULN has been also clarified. Based on the current safety data on asciminib, there is a low likelihood of a >20 x ULN of AST/ALT occurrence at first presentation of a hepatic adverse event, as a conservative measure guidance for discontinuing treatment for elevations > 20 x ULN has been clarified in this protocol amendment. Of note, no patient in this study has met this criterion to

date. For additional information on liver abnormalities, please refer to ABL001 IB Ed10, section 7.2.7.

4. For isolated ALT/AST elevations (when baseline normal): Permanently discontinue if ALT/AST is >20 x ULN.

- Re-escalation rules for participants receiving asciminib have been changed to allow more than one re-escalation in case the event is considered to be significantly different than the one(s) experienced previously. Such cases may be reviewed by the study steering committee, if required.
- Update eligibility based on serologic markers for Hepatitis C to clarify that patients with no concurrent chronic hepatitis C virus (HCV) infection are eligible for enrolment. This is in line with the FDA Guidance for Industry "Cancer Clinical Trial Eligibility Criteria: Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections" (July 2020). Previously it was erroneously stated that positivity to HCV antibody (Ab) indicates active HCV infection, while HCV Ab positivity is a marker of prior contact with HCV antigens. HCV RNA allows to assess for active viral replication and is thus a marker of concurrent active infection. Patients with negative HCV RNA indicating absence of active viral replication are eligible for the trial. This has now been clarified.
- Amend the dose modifications for asymptomatic amylase and/or lipase elevation to align with the approved label/prescribing information for asciminib.
- The concomitant medications to be used with caution have been updated. OATP1B and BCRP substrates have been added to this list, based on the results of a PBPK simulation study (asciminib Investigator's Brochure Ed. 10 - Section 1.4.2).

In addition, the following clarifications were implemented throughout the protocol:

- Clarification that competing risk analysis will be performed for the secondary endpoint time to first MMR/MR4.0/MR4.5
- Clarification of the primary clinical question and the summary measure.
- Clarification on the window for completion of the ePRO assessments
- Update on the duration of the storage of source documents and ICF documents to 15 years.
- Clarification to the ELN treatment failure criteria at 3 months and 12 months for greater alignment with ELN 2020 recommendations and clarification on when the treatment discontinuation visit should occur.
- Clarify that smoking history should be collected at screening as a part of baseline medical and cardiovascular history.
- Clarify the duration of the adverse event 30-day safety follow up period.
- Clarify the duration of pregnancy monitoring to include the 30-day safety follow up timepoint.
- Clarification on the definition of confirmed loss of MMR. This update does not change the collection of data or analysis of this molecular response parameter.
- Clarification on the rationale for an open label study.

- Clarification that pseudohyperkalemia in case of thrombocytosis is not an exclusion criterion.
- Clarification in the laboratory assessments that Hepatitis C RNA testing will be performed if the Hepatitis C antibody test is positive.
- Clarification that participants in the nilotinib arm who require a dose reduction may require a new capsule strength in order to appropriately reduce their dose and this should be done at the earliest opportunity.
- Implement editorial changes throughout the protocol to correct typos and provide clarifications where required.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

The main changes made to the protocol are as follows:

- 

- [redacted]

- [redacted]

- 

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

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The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

1 Protocol summary

1.1 Summary

Protocol Title:

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

Brief Title:

A study to investigate tolerability and efficacy of oral asciminib versus nilotinib in adult patients with newly diagnosed Philadelphia Chromosome Positive Chronic Myelogenous Leukemia in Chronic Phase

Purpose:

Considerable advancements in treatment of patients with CML-CP have increased the life expectancy of patients making it a chronic disease requiring long term medication. This emphasizes the need for treatments that combine high efficacy with a favorable safety profile as improving over the currently available options (refer to Section 2.2.2). There remains an unmet medical need for newly diagnosed patients with CML-CP requiring chronic treatment and for a specific targeted treatment option that is highly efficacious while minimizing adverse events.

To assess if asciminib may address these needs, the ongoing Phase III study CABL001J12301 sets out to evaluate primarily the efficacy of asciminib in newly diagnosed Chronic Myelogenous Leukemia (CML) patients.

The primary purpose of this Phase IIIb study CABL001J12302 is to focus on the patient relevant outcomes and to assess the tolerability of asciminib, as it translates in study treatment discontinuations due to adverse events (AEs), in comparison with that of the second generation (2G) Tyrosine Kinase Inhibitor (TKI) nilotinib, in adult patients with newly diagnosed Ph+ CML-CP. The study also aims to assess treatment impact on quality of life. Generating such data is patient relevant as well as deemed important for Health Technology Assessment (HTA) bodies' decision making.

Treatment-free remission (TFR) is evolving as one of the main goals of frontline therapy providing the opportunity of functional cure to patients with CML-CP. There remains an unmet need for treatments that are well tolerated and highly efficacious which support increased and earlier eligibility and successful TFR. CCI [redacted].

Study Indication /Medical Condition:

Philadelphia Chromosome–Positive Chronic Myeloid Leukemia

Treatment Type

Drug

Study Type

Interventional

Objectives, Endpoints, and Estimands:

Objective(s)	Endpoint(s)
Primary Objective(s) • The primary objective of the study is to assess the tolerability of asciminib versus nilotinib, in participants with newly diagnosed CML-CP, with respect to the time to discontinuation of study treatment due to adverse event (TTDAE). The primary clinical question of interest is: What is the safety/tolerability of asciminib (80 mg QD) compared to nilotinib (300 mg BID); with respect to the time to discontinuation of study treatment due to AE (TTDAE), where study treatment discontinuation due to other reasons is considered a competing risk event, in newly diagnosed CML-CP patients; *regardless of* dose interruptions/reductions; *regardless of* dosing errors, and any concomitant medication.	**Endpoint(s) for primary objective(s)** • Time to discontinuation of study treatment due to adverse event (TTDAE). TTDAE is defined as the time from the date of first dose of study treatment to the date of discontinuation of study treatment due to adverse event (AE).
Secondary Objective(s) • **Secondary objective on efficacy** • To compare the efficacy of asciminib versus nilotinib at and by all scheduled data collection time points. • Time to Treatment Discontinuation (TTD) for selected reasons of discontinuation. • **Secondary objectives on PRO** • To assess the effect of asciminib versus nilotinib on patient-reported disease-related symptoms, functioning, and health-related quality of life (HRQoL).	**Endpoint(s) for secondary objective(s)** • MMR **at** all scheduled data collection time points. • MMR **by** all scheduled data collection time points. • MR4.0 and MR4.5 **at** and **by** all scheduled data collection time points. • Complete Hematological Response (CHR) **at** and **by** all scheduled data collection time points. • *BCR::ABL1* ≤1% at and by all scheduled data collection time points. • Duration of MMR, MR4.0, MR4.5. • Time to first* MMR, first MR4.0, first MR4.5. • Time to treatment failure. • Event Free Survival (EFS) • Progression free survival. • Overall survival. *by competing risk analysis • TTD due to selected reasons (i.e. Discontinuation due to lack of efficacy/treatment failure/disease progression/suboptimal response/death) • Change from baseline in overall scores and individual scales of the EORTC QLQ-C30, EORTC QLQ-CML24.

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

Trial Design:

This is a phase IIIb, multi-center, open-label, randomized study of oral asciminib 80 mg QD versus nilotinib 300 mg BID in adult patients with newly diagnosed Ph+ CML-CP. It is planned to randomize approximately 550 patients in the study in a 1:1 randomization to asciminib or nilotinib. Randomization will be stratified based on European Treatment Outcome Study (EUTOS) long-term survival (ELTS) score (low versus intermediate versus high) to help achieve a balance between the treatment arms. The primary analysis will be performed when approximately CCI discontinuations of either study treatment due to AE occur.

Eligible participants on both arms may choose to participate in an optional CCI TFR Phase. Participants with loss of MMR during TFR Phase will enter the TRI Phase.

Brief Summary:

The primary purpose of this Phase IIIb study CABL001J12302 is to assess the tolerability of oral asciminib (80 mg QD) in comparison with that of the 2G TKI nilotinib (300 mg BID), in adult patients with newly diagnosed Ph+ CML-CP (Treatment Phase).

- Overall study duration: approximately 7.5 years.
- The approximate Treatment Phase duration for an individual participant is expected to be between CCI .
- During the Treatment Phase, visits are planned every 2 weeks for the first month of treatment and every 12 weeks until end of treatment. Additional visits may be scheduled depending on local labels.

- TFR Phase eligibility: CCI [redacted]
- During the TFR Phase, visits are monthly (every 4 weeks) for months 1-6 following treatment cessation, every two months (every 8 weeks) for months 7-12, and then every 12 weeks thereafter CCI [redacted].
- Participants who lose MMR (BCR:ABL1 >0.1% IS) CCI [redacted] assessment during the TFR Phase will have study treatment re-initiated within 4 weeks and will be monitored for BCR::ABL levels IS monthly (every 4 weeks) for months 1-6, then every 12 weeks for at least CCI [redacted] following treatment re-initiation.

Treatment of Interest

The treatment of interest is asciminib.

Number of Participants:

It is planned to randomize approximately 550 patients in the study to observe the CCI [redacted] discontinuations of study treatment due to AE. The study population will include adult patients (≥18 years of age) with newly diagnosed CML-CP. It is estimated that approximately 647 patients will be screened.

Key Inclusion Criteria

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

1. Signed informed consent must be obtained prior to participation in the study.
2. Male or female patients ≥ 18 years of age.
3. Patients with CML-CP within 3 months of diagnosis.
4. Diagnosis of CML-CP (European Leukemia Network [ELN] 2020 criteria) with cytogenetic confirmation of the Philadelphia (Ph) chromosome. A cryptic Ph chromosome should be confirmed by metaphase Fluorescence in situ Hybridization (FISH)
    - Documented chronic phase CML will meet all the below criteria (Baccarani et al 2013):
        - < 15% blasts in peripheral blood and bone marrow,
        - < 30% blasts plus promyelocytes in peripheral blood and bone marrow,
        - < 20% basophils in the peripheral blood,
        - Platelet (PLT) count ≥ 100 x 10^9/L (≥ 100,000/mm^3),
        - No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly.
5. Evidence of typical BCR::ABL1 transcript [e14a2 and/or e13a2] which is amenable to standardized RQ-PCR quantification by the central laboratory assessment. However, if a local qualitative assay, validated according to local regulation, from an accredited local

laboratory has confirmed evidence of typical BCR::ABL1 transcript [e14a2 and/or e13a2], these results can be used for eligibility if the central Real Time Quantitative Polymerase Chain Reaction (RQ-PCR) results arrived are not available at the time of randomization.

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Adequate end organ function as defined by:
   - Total bilirubin (TBL) < 3 x Upper Limit of Normal (ULN); patients with Gilbert's syndrome may only be included if TBL ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN,
   - Creatinine Clearance (CrCl) ≥ 30 milliliters per minute (mL/min) as calculated using Cockcroft-Gault formula, Serum lipase ≤ 1.5 x ULN. For serum lipase > ULN - ≤ 1.5 x ULN, value must be considered not clinically significant and not associated with risk factors for acute pancreatitis.
8. Patients must have the following laboratory values within normal limits or corrected to within normal limits with supplements prior to randomization:
   - Potassium (potassium increase of up to 6.0 mmol/L is acceptable if associated with CrCl* ≥ 90 mL/min)**,
   - Total calcium (corrected for serum albumin); (calcium increase of up to 12.5 mg/dl or 3.1 mmol/L is acceptable if associated with CrCl* ≥ 90 mL/min),
   - Magnesium (magnesium increase of up to 3.0 mg/dL or 1.23 mmol/L if associated with CrCl* ≥ 90 mL/min),
   - For patients with mild to moderate renal impairment (CrCl* ≥ 30 mL/min and <90 mL/min) - potassium, total calcium (corrected for serum albumin) and magnesium should be within normal limits or corrected to within normal limits with supplements prior to randomization.

     *CrCl as calculated using Cockcroft-Gault formula.

     ** pseudohyperkaliemia in case of thrombocytosis is not an exclusion criterion.

The Treatment Phase will continue until the participant enters the optional TFR Phase or up to a maximum of CCI of treatment. To be eligible for the optional TFR Phase, participants must meet the additional TFR inclusion criteria.

Inclusion Criteria for optional TFR Phase

- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures
- CCI
- CCI
- Separate signed informed consent must be obtained prior to participation in the TFR Phase.

Key Exclusion Criteria

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

1. Previous treatment of CML with any other anticancer agents including chemotherapy and/or biologic agents or prior stem cell transplant, with the exception of hydroxyurea and/or anagrelide.
2. Known cytopathologically confirmed central nervous system (CNS) infiltration (in absence of suspicion of CNS involvement, lumbar puncture not required).
3. Impaired cardiac function or cardiac repolarization abnormality including but not limited to any one of the following:
   - History of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG) within 6 months prior to starting study treatment.
   - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular (AV) block (e.g., bifascicular block, Mobitz type II and third degree AV block).
   - QT interval corrected by Fridericia's formula (QTcF) $\geq$ 450 ms on the average of three serial baseline ECG (using the QTcF formula). If QTcF $\geq$ 450 ms and electrolytes are not within normal ranges, electrolytes should be corrected and then the patient re-screened for QTcF.
   - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
     - Risk factors for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia.
     - Concomitant medication(s) with a "Known risk of Torsades de Pointes" per crediblemeds.org that cannot be discontinued or replaced 7 days prior to starting study treatment by safe alternative medication.
     - Inability to determine the QTcF interval.
4. Severe and/or uncontrolled concurrent medical disease that in the opinion of the Investigator could cause unacceptable safety risks or compromise compliance with the protocol (e.g. uncontrolled diabetes, active or uncontrolled infection; uncontrolled arterial or pulmonary hypertension, uncontrolled clinically significant hyperlipidemia).
5. History of significant congenital or acquired bleeding disorder unrelated to cancer.
6. Major surgery within 4 weeks prior to study entry or patients who have not recovered from prior surgery.
7. History of other active malignancy within 3 years prior to study entry with the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively.
8. History of acute pancreatitis within 1 year prior to randomization or medical history of chronic pancreatitis.
9. History of chronic liver disease leading to severe hepatic impairment, or ongoing acute liver disease.

10. Known history of chronic Hepatitis B (HBV), or chronic Hepatitis C (HCV) infection. Testing for Hepatitis B surface antigen (HBs Ag) and Hepatitis B core antibody (HBc Ab/anti HBc) will be performed at screening. If anti-HBc is positive, HBV-DNA (deoxyribonucleic acid) evaluation will be carried out at screening. A patient having positive HBV-DNA will not be enrolled in the study. Also, a patient with positive HBsAg will not be enrolled in the study. HCV Ab testing will also be performed at screening. For details on the criteria see Appendix 10.4
11. History of Human Immunodeficiency Virus (HIV) unless well-controlled on a stable dose of anti-retroviral therapy at the time of screening.
12. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study treatment (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or gastric bypass surgery).
13. Participation in a prior investigational study within 30 days prior to randomization or within 5 half-lives of the investigational product, whichever is longer.
14. Pregnant or nursing (lactating) women
15. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment and for a period of time after stopping study medication. For asciminib, this period of time is 3 days after last dose; if local regulations or locally approved prescribing information differ from the protocol required duration of contraception, the longer duration must be followed and the same requirements will be described in the Informed Consent Form (ICF). Participants taking nilotinib should be willing to follow contraception requirements in the locally-applicable prescribing information for nilotinib.

Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or total hysterectomy or bilateral salpingectomy, at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male partner's sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant
- Use of oral, (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate history of vasomotor symptoms). Women are considered not of child bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral salpingectomy at least six weeks prior to enrollment on the study. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered to be not of child bearing potential.

Sexually active males taking study treatment do not require contraception.

16. Known hypersensitivity to the study treatment.

Note: The Investigator has the discretion to include/exclude a patient in the study, who will be found to have symptoms representative of coronavirus disease of 2019 (COVID-19) or tested positive for COVID-19 during the screening phase. Such patients should be managed as per the country specific guidelines related to COVID-19. For patients who test positive for COVID-19, re-testing is recommended before initiating study treatment.

Exclusion Criteria for optional TFR Phase

- CCI [redacted]

Exclusion criteria for Treatment Re-initiation (TRI) Phase

- In case of a pregnancy during the TFR Phase, the pregnant woman must be discontinued from the study upon loss of MMR CCI [redacted] and cannot enter the TRI phase

Treatment Arms:

Participants will be assigned at Baseline/Day 1 to one of the following 2 treatment arms in a ratio of 1:1:

- Arm 1: Asciminib 80 mg QD administered under fasting conditions
- Arm 2: Nilotinib 300 mg BID administered under fasting conditions

Data Monitoring/Other Committee:

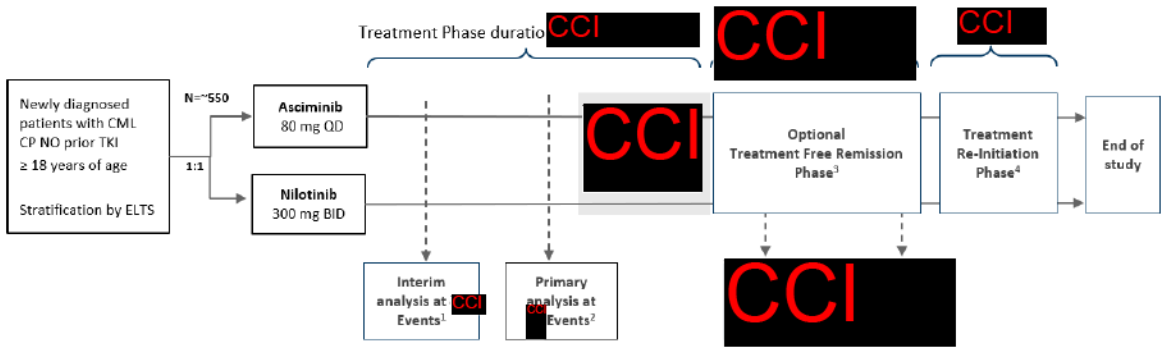
Yes (See Section 10.1.4)

Key words

Asciminib (ABL001), Abelson proto-oncogene (ABL), newly diagnosed Chronic Myelogenous Leukemia (CML), Chronic Myeloid Leukemia (CML), Chronic Myelocytic Leukemia (CML), Chronic Granulocytic Leukemia (CGL), cancer of the white blood cells, clonal bone marrow stem cell disorder proliferation of mature granulocytes, Chronic Myeloproliferative Disorders, Philadelphia chromosome, nilotinib, *BCR::ABL1*, Specifically Targeting the ABL Myristoyl Pocket (STAMP) Inhibitor, Leukemia, Phase 3, Phase 3b, tyrosine kinase inhibitor, Treatment Free Remission (TFR)

1.2 Schema

Figure 1-1 Study design



[1]A single interim analysis will take place when approximately CCI discontinuations due to AE have occurred. If statistical significance is reached, the IA will be used to allow for an early assessment of the benefits of asciminib. Refer to Section 9.8 Interim Analysis for details.

[2]Primary analysis will take place when approximately CCI discontinuations of study treatment due to AE have occurred. Refer to Section 9.9 Sample size determination

CCI .

[4]Participants with loss of MMR during the TFR Phase will enter the Treatment Re-initiation Phase until EOS and CCI .

Refer to Section 1.3 Schedule of activities (SoA) and Section 6.1.5 Treatment Duration for additional details.

Figure 1-2 Study Design (TFR Phase)

TFR = treatment free remission; MMR = Major Molecular Response; EOS = End of Study

CCI Additional Consent required prior to entry into TFR Phase

CCI whichever is the latest. For premature discontinuations in the TRI Phase, survival follow-up should also continue until the end of study (EOS).

Refer to Section 1.3 Schedule of activities (SoA), Section 4.7 End of Study Definition, and Section 6.1.5 Treatment Duration for additional details.

1.3 Schedule of activities (SoA)

SoA Table 1-1, Table 1-2 and Table 1-3 refer to the Treatment Phase, the Treatment Free Remission Phase (TFR), and the Treatment Re-initiation Phase (TRI), respectively. The SoA lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Participants should be seen for all visits/assessments as outlined in the SoA or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Eligible participants CCI [redacted], may choose to participate in an optional TFR Phase. Participants who opt to enter the TFR Phase should remain on treatment until the Treatment Phase EOT/TFR Baseline visit (Table 1-1) and until signing the ICF for the TFR Phase. Study treatment should be stopped (TFR Phase initiated) on the same day as, or 1 day after, the Treatment Phase EOT/TFR Baseline visit. Any remaining study medication will be returned to the site at the Treatment Phase EOT/TFR Baseline Visit.

Refer to Table 1-2 for the assessments during the TFR Phase.

Loss of MMR CCI [redacted] during the TFR Phase requires treatment re-initiation in the TRI Phase (Table 1-3). Participants who re-initiate treatment must complete the TFR END visit (Table 1-2) within 4 weeks of loss of MMR, on the same day as or 1 day prior to re-initiating treatment. Participants who received nilotinib in the Treatment Phase may switch to asciminib for the TRI Phase, subject to the investigator's discretion. IRT drug dispensing for TRI Phase will take place at the TFR END visit.

Participants who discontinue from the Treatment Phase, TFR Phase or TRI Phase are to complete the corresponding end of phase (EOT, TFR END, TRI END) visit as soon as possible and complete the Safety and Survival follow-up visits as indicated in the SoA, as applicable. At this final visit, all dispensed study treatment should be reconciled, and the adverse events and concomitant medications not previously reported must be recorded on the case report form (CRF).

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

All targeted Treatment Phase visit dates should be defined based on the Baseline/Day 1 visit date. Targeted TFR and TRI Phase visit dates should be defined based on the prior phase end visit date (EOT or TFR END). The 30-Day Safety Follow up and Survival Follow up visits are based on the End of Treatment (EOT)/ TFR END/TRI END visit date. Treatment Phase Screening and Baseline/ Day 1 visits must be done on site, as well as the EOT/ TFR END/TRI END Visits.

The Treatment Phase visit **"Baseline/Day 1"** is the **Day 1** of the study, (first day of study treatment administration). **"After 2 Weeks"** is performed 2 weeks after Baseline/Day 1 at **day 15** of the study (**"After 4 Weeks"** at **day 29** and so on).

The assessments (see Table 1-1) for **"Baseline/ Day 1"**, except for the ones specified as pre-dose, can be done with a window of -3 days from first dose (study day 1).

Refer to Table 1-1, Table 1-2 and Table 1-3 for visit windows. For PROs the collection window is described in Section 8.5.1.

Where multiple assessments are required to be performed at the same time point, and where the order of assessments is important for the evaluation of data, the order is based on study priorities and assessment needs.

Table 1-1 Schedule of Activities (Treatment Phase)

Period	Screening	Treatment Phase (CCI)								CCI	End of Treatment Phase	30 Day Safety follow-up[5]	Survival follow-up Phase (Every 12 weeks until EOS)[5]
Visit Name	**Screening**	**Baseline/ Day 1***	**After 2 Weeks* (Day 15)**	**After 4 Weeks* (Day 29)**	**After 12 Weeks* (Day 85)**	**After 24 Weeks* (Day 169)**	**After 36 Weeks * (Day 253)**	**After 48 Weeks * (Day 337)**	**Every 12w to 144 Weeks**	CCI	**EOT/CCI /TFR Baseline[13]**	**30 Day Safety follow-up**	**Survival follow-up**
Visit Window	**-21 to -1**	**1**	(+5 days for each visit, when applicable as per Section 1.3 and Section 8)									**+7 days**	**+/-14 days**
Obtain Informed consent	X									X (Optional TFR consent)[13]			
Interactive Response Technology (IRT) Registration	X	X[7]	X (Ongoing Basis)								X		
Randomization		X[7]											
Review Inclusion/Exclusion Criteria	X									X (for TFR)[14]	X (for TFR)[14]		
Demography	X												
Medical History/Current Medical conditions[4]	X												
Disease History	X												

Period	Screening	Treatment Phase (CCI)								CCI	End of Treatment Phase	30 Day Safety follow-up[5]	Survival follow-up Phase (Every 12 weeks until EOS)[5]
Visit Name	**Screening**	**Baseline/ Day 1***	**After 2 Weeks* (Day 15)**	**After 4 Weeks* (Day 29)**	**After 12 Weeks* (Day 85)**	**After 24 Weeks* (Day 169)**	**After 36 Weeks * (Day 253)**	**After 48 Weeks * (Day 337)**	**Every 12w to 144 Weeks**	CCI	**EOT/CCI /TFR Baseline[13]**	**30 Day Safety follow-up**	**Survival follow-up**
Visit Window	**-21 to -1**	**1**	(+5 days for each visit, when applicable as per Section 1.3 and Section 8)									**+7 days**	**+/-14 days**
Cardiovascular risk factor assessments (including Family History[2])	X										X		
Prior Antineoplastic Therapy	X												
Prior/Concomitant Medications	X	X (Ongoing Basis)										X	
Physical Examination	S	S (Ongoing Basis)											
Extramedullary involvement	X	X[7]	X	X	X	X	X	X	X	X	X		
Vital Signs	X	X[7]	X	X	X	X	X	X	X	X	X		
Body weight	X	X[7]	X	X	X	X	X	X	X	X	X		

Period	Screening	Treatment Phase (CCI)								CCI	End of Treatment Phase	30 Day Safety follow-up[5]	Survival follow-up Phase (Every 12 weeks until EOS)[5]
Visit Name	**Screening**	**Baseline/ Day 1***	**After 2 Weeks* (Day 15)**	**After 4 Weeks* (Day 29)**	**After 12 Weeks* (Day 85)**	**After 24 Weeks* (Day 169)**	**After 36 Weeks * (Day 253)**	**After 48 Weeks * (Day 337)**	**Every 12w to 144 Weeks**	CCI	**EOT/CCI /TFR Baseline[13]**	**30 Day Safety follow-up**	**Survival follow-up**
Visit Window	**-21 to -1**	**1**	(+5 days for each visit, when applicable as per Section 1.3 and Section 8)									**+7 days**	**+/-14 days**
Body Height	X												
Hematology and Clinical Chemistry[10]	X	X[7]	X	X	X	X	X	X	X	X	X		
HbA1c	X				X	X	X	X	X	X	X		
Coagulation	X	If clinically indicated											
Other Hepatic Tests for suspected Drug-Induced Liver Injury (DILI)		If clinically indicated (Refer to Section 6.5.2.1, Section 8.4.5, Section 10.4)											
Hepatitis screen[9]	X												
Blood collection for *BCR::ABL1* quantification by RQ-PCR[11]	X			X	X	X	X	X	X	X	X		

Period	Screening	Treatment Phase (CCI)							CCI	End of Treatment Phase	30 Day Safety follow-up[5]	Survival follow-up Phase (Every 12 weeks until EOS)[5]
Visit Name	Screening	Baseline/ Day 1*	After 2 Weeks* (Day 15)	After 4 Weeks* (Day 29)	After 12 Weeks* (Day 85)	After 24 Weeks* (Day 169)	After 36 Weeks* (Day 253)	After 48 Weeks* (Day 337)	Every 12w to 144 Weeks	CCI	EOTCCI /TFR Baseline[13]	30 Day Safety follow-up	Survival follow-up
Visit Window	-21 to -1	1	(+5 days for each visit, when applicable as per Section 1.3 and Section 8)									+7 days	+/-14 days
CCI													
Bone marrow assessment for cytogenetic assessment[12]	X (If no previous result < 3 months old available)	If clinically indicated											
ECOG Performance status	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Test (serum)	X	X[7]		X	X	X	X	X	X	X	X		
Pregnancy Test (urine)		S- Every 4 weeks if serum pregnancy test is not performed											
Electrocardiogram (ECG) in Triplicate	X	X	X	X	As clinically indicated								
Adverse Events/SAE		X (Ongoing basis)									X	X[1]	

Period	Screening	Treatment Phase CCI								CCI	End of Treatment Phase	30 Day Safety follow-up[5]	Survival follow-up Phase (Every 12 weeks until EOS)[5]
Visit Name	**Screening**	**Baseline/ Day 1***	**After 2 Weeks* (Day 15)**	**After 4 Weeks* (Day 29)**	**After 12 Weeks* (Day 85)**	**After 24 Weeks* (Day 169)**	**After 36 Weeks * (Day 253)**	**After 48 Weeks * (Day 337)**	**Every 12w to 144 Weeks**	CCI	**EOTCCI /TFR Baseline[13]**	**30 Day Safety follow-up**	**Survival follow-up**
Visit Window	**-21 to -1**	**1**	(+5 days for each visit, when applicable as per Section 1.3 and Section 8)									**+7 days**	**+/-14 days**
Study treatment dispensation		X		X	X	X	X	X	X	X			
Study treatment administration		X (Ongoing basis)											
EORTC QLQ-C30 plus CML24[6,8]		X		X (Every 4 weeks up until 12 Weeks)		X		X	X (Week 96 only)	X (Week 156 and Week 216 only)	At EOT and every 4 weeks until 12 weeks after EOT[8]		

CCI

Period	Screening	Treatment Phase CCI								CCI	End of Treatment Phase	30 Day Safety follow-up[5]	Survival follow-up Phase (Every 12 weeks until EOS)[5]
Visit Name	**Screening**	**Baseline/ Day 1***	**After 2 Weeks* (Day 15)**	**After 4 Weeks* (Day 29)**	**After 12 Weeks* (Day 85)**	**After 24 Weeks* (Day 169)**	**After 36 Weeks * (Day 253)**	**After 48 Weeks * (Day 337)**	**Every 12w to 144 Weeks**	CCI	**EOT/CCI /TFR Baseline[13]**	**30 Day Safety follow-up**	**Survival follow-up**
Visit Window	**-21 to -1**	**1**	(+5 days for each visit, when applicable as per Section 1.3 and Section 8)									**+7 days**	**+/-14 days**
Trial Feedback Questionnaires (TFQ)[3]		S				S					S		
Disposition	X										X		X
Survival follow-up													X
Antineoplastic therapies since discontinuation of study treatment												X	X
Stem Cell Transplant status													X
Progression Status													X

CCI

Period	Screening	Treatment Phase CCI)								CCI	End of Treatment Phase	30 Day Safety follow-up[5]	Survival follow-up Phase (Every 12 weeks until EOS)[5]
Visit Name	Screening	Baseline/ Day 1*	After 2 Weeks* (Day 15)	After 4 Weeks* (Day 29)	After 12 Weeks* (Day 85)	After 24 Weeks* (Day 169)	After 36 Weeks* (Day 253)	After 48 Weeks* (Day 337)	Every 12w to 144 Weeks	CCI	EOT CCI /TFR Baseline[13]	30 Day Safety follow-up	Survival follow-up
Visit Window	-21 to -1	1	(+5 days for each visit, when applicable as per Section 1.3 and Section 8)									+7 days	+/-14 days
CCI													

* The visit "Baseline/Day 1" is the Day 1 of the study, (first day of study treatment administration). "After 2 Weeks" is performed 2 weeks after Baseline/Day 1 at day 15 of the study ("After 4 Weeks" at day 29 and so on).

S: assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

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

[2] Refer to Section 8.4.4.

[3] The TFQ is not considered study data and will be received electronically outside of the clinical database. TFQ at EOT only applicable for participants not entering TFR phase.

[4] Including ELTS score at diagnosis prior to treatment with hydroxyurea (if applicable).

[5] 30-Day Safety Follow up and Survival Follow up visits are based on the EOT visit date. A follow up visit for AE/SAE monitoring for 30 days post the EOT visit is only required for participants who do not enter the TFR Phase. The survival follow-up Phase every 12 weeks is required for participants not entering the TFR Phase. For TFR/TRI phase participant 30 Day safety follow up and survival follow up, refer to Table 1-2 and Table 1-3.

[6] CCI

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

[8] CCI . For participants entering TFR Phase, refer to Table 1-2 for ePRO assessments after end of treatment.

[9] Refer to Appendix 4

Period	Screening	Treatment Phase CCI								CCI	End of Treatment Phase	30 Day Safety follow-up[5]	Survival follow-up Phase (Every 12 weeks until EOS)[5]
Visit Name	Screening	Baseline/ Day 1*	After 2 Weeks* (Day 15)	After 4 Weeks* (Day 29)	After 12 Weeks* (Day 85)	After 24 Weeks* (Day 169)	After 36 Weeks * (Day 253)	After 48 Weeks * (Day 337)	Every 12w to 144 Weeks	CCI	EOTCCI /TFR Baseline[13]	30 Day Safety follow-up	Survival follow-up
Visit Window	-21 to -1	1	(+5 days for each visit, when applicable as per Section 1.3 and Section 8)									+7 days	+/-14 days

[10] For both treatment arms, additional local safety laboratory testing for hematology and clinical chemistry may be performed at relevant time points to comply with the local prescribing information for asciminib and nilotinib. These laboratory results should be recorded in the participant's source documentation and do not need to be recorded in the clinical database.

[11] If the sample collected at the Treatment Phase-Screening visit is not available (e.g., damaged or lost during transit to the laboratory) or not evaluable for RQ-PCR, the Treatment Phase-Baseline sample will be prioritized for BCR::ABL1 quantification by RQ-PCR instead. Confirmed Loss of MMR is defined as a loss of MMR (i.e. BCR::ABL1 IS > 0.1% in association with a ≥ 5-fold rise in BCR::ABL1 from the lowest value achieved on study treatment and replicated by a second analysis of the same sample) and subsequently confirmed by analysis of another sample taken after an interval of not less than 4 weeks or no more than 6 weeks, unless associated with confirmed loss of CHR or loss of *BCR::ABL1* ≤ 1% or progression to AP/BC or CML related death. Refer to Section 8.3.1

[12] In case of dry tap or missing cytogenetic analysis of previous bone marrow aspiration, cytogenetics on peripheral blood is acceptable at screening.

[13] Optional TFR ICF must be signed prior to initiating TFR Phase. The Investigator should engage participant in discussion around TFR once the participant becomes eligible for TFR, or sooner as per Investigator discretion.

[14] Refer to Section 5.1.1 (Eligibility Criteria for optional TFR Phase)

CCI [redacted]

Table 1-2 Schedule of Activities (TFR Phase)

Period	Treatment-Free Remission phase (TFR) [redacted]			End of TFR phase	30 Day Safety Follow-up**	Survival Follow-up (Every 12 weeks until EOS)**
Visit Name	**TFRW4, TFRW8, TFRW12, TFRW16 TFRW20 TFRW24 (every 4 weeks)**	**TFRW32, TFRW40, TFRW48 (every 8 weeks)**	**TFRW60, TFRW72, TFRW84 (every 12 weeks)**	**TFR-END [redacted] /TRI Baseline**	**SAFETY-FUP**	**SURVIVAL FUP**
Visit Window	+5 days				**+7d**	**+/- 14d**
IRT Registration				X (dispensing if entering TRI Phase)		
Physical Examination	S (Ongoing)					
Body Weight	X	X	X	X		
Vital signs / Blood Pressure / Heart Rate	X	X	X	X		
ECOG Performance Status	X	X	X	X		
Extramedullary involvement	X	X	X	X		
Laboratory assessments						
Hematology and Clinical Chemistry[1]	X	X		X		
HbA1c[6]	X (W12 and W24)	X (W48)	X (W72)	X		
Coagulation	If clinically indicated					
Other Hepatic Tests for suspected Drug- Induced Liver Injury (DILI)	If clinically indicated (Refer to Section 6.5.2.1, Section 8.4.5, Section 10.4)					
Hepatitis screen	X (Refer to Appendix 10.4)					

Period	Treatment-Free Remission phase (TFR) CCI			End of TFR phase	30 Day Safety Follow-up**	Survival Follow-up (Every 12 weeks until EOS)**
Visit Name	**TFRW4, TFRW8, TFRW12, TFRW16 TFRW20 TFRW24 (every 4 weeks)**	**TFRW32, TFRW40, TFRW48 (every 8 weeks)**	**TFRW60, TFRW72, TFRW84 (every 12 weeks)**	**TFR-END /TRI Baseline**	**SAFETY-FUP**	**SURVIVAL FUP**
Visit Window	+5 days				**+7d**	**+/- 14d**
Blood collection for *BCR::ABL1* quantification by RQ-PCR[2]	X	X	X	X		
CCI						
Bone marrow assessment for cytogenetic assessment	whenever clinically indicated at the discretion of the investigator					
Pregnancy Test (serum)	X (at every visit)			X		
Pregnancy Test (urine)	S- Every 4 weeks if serum pregnancy test is not performed					
Electrocardiogram (ECG) in Triplicate	As clinically indicated					
Disposition				X		X
Cardiovascular risk factor assessments (including Family History)[4]				X (participants going to TRI only)		
Safety						
Adverse Events/SAE	Continuous				X	X

Period	Treatment-Free Remission phase (TFR) CCI			End of TFR phase	30 Day Safety Follow-up**	Survival Follow-up (Every 12 weeks until EOS)**
Visit Name	**TFRW4, TFRW8, TFRW12, TFRW16 TFRW20 TFRW24 (every 4 weeks)**	**TFRW32, TFRW40, TFRW48 (every 8 weeks)**	**TFRW60, TFRW72, TFRW84 (every 12 weeks)**	**TFR-END CCI TRI Baseline**	**SAFETY-FUP**	**SURVIVAL FUP**
Visit Window	+5 days				**+7d**	**+/- 14d**
Concomitant medications	Continuous				X	
Patient reported Outcomes						
EORTC QLQ-C30 plus CML24[3]	X	X	X	X		
CCI						
Trial Feedback Questionnaire				X[5]		
CCI						
Antineoplastic therapies since discontinuation of study treatment					X	X
Stem Cell Transplant status						X
Progression Status						X
Survival follow-up						X

** 30D Safety FU and Survival FUP after TFR-END are not applicable for participants entering the Treatment Re-initiation Phase

S: assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

[1] Additional local safety laboratory testing for hematology and clinical chemistry may be performed at relevant time points. These laboratory results should be recorded in the participant's source documentation and do not need to be recorded in the clinical database.

[2] Testing may be more frequent at Investigator discretion. For loss of MR4.0 but not MMR during the TFR phase, or pregnancy refer to Section 8.3.1 for more frequent testing requirements.

Period	Treatment-Free Remission phase (TFR) CCI			End of TFR phase	30 Day Safety Follow-up**	Survival Follow-up (Every 12 weeks until EOS)**
Visit Name	TFRW4, TFRW8, TFRW12, TFRW16 TFRW20 TFRW24 (every 4 weeks)	TFRW32, TFRW40, TFRW48 (every 8 weeks)	TFRW60, TFRW72, TFRW84 (every 12 weeks)	TFR-END /CCI /TRI Baseline	SAFETY-FUP	SURVIVAL FUP
Visit Window	+5 days				+7d	+/- 14d

[3] PROs to be completed before any clinical assessments when performed on-site. The PRO collection window is described in Section 8.5.1
[4] Refer to Section 8.4.4
[5] TFQ at TFR-END is only applicable for participants not entering TRI phase.
[6] HbA1C may be tested more frequently after TFR week 24 as clinically indicated (e.g. for participants with diabetes or who develop hyperglycemia)

Table 1-3 Schedule of Activities (Treatment Re-initiation phase - participants after unsuccessful TFR attempt)

Period	Treatment- Re-initiation Phase (TRI)									30 D SAFETY-FUP[4]	Survival Follow-up (Every 12 wks until EOS)[4]
Visit Name	**TRI W2**	**TRI W4**	**TRI W8**	**TRI W12**	**TRI W16**	**TRI W20**	**TRI W24[2]**	**TRI W36 and every 12 weeks until TRI-EOT[3]**	**TRI-EOT**	**30 D SAFETY-FUP**	**SURVIVAL FUP**
Visit Window	**+5 days**								**-**	**+ 7d**	**+/- 14d**
IRT Visit Registration	X (ongoing basis)								X		
Physical Examination	S (ongoing basis)										
Study Treatment Dispensation		X		X			X	X			
Body Weight	X	X	X	X	X	X	X	X	X		
Vital signs / Blood Pressure / Heart Rate	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X		
Extramedullary involvement	X	X	X	X	X	X	X	X	X		
Laboratory assessments											
Hematology and Clinical Chemistry[6]	X	X	X	X	X	X	X	X	X		
Blood collection for *BCR::ABL1* quantification by RQ-PCR		X	X	X	X	X	X	X	X		
CCI											
HbA1c				X			X	X	X		

Period	Treatment- Re-initiation Phase (TRI)									30 D SAFETY-FUP[4]	Survival Follow-up (Every 12 wks until EOS)[4]
Visit Name	**TRI W2**	**TRI W4**	**TRI W8**	**TRI W12**	**TRI W16**	**TRI W20**	**TRI W24[2]**	**TRI W36 and every 12 weeks until TRI-EOT[3]**	**TRI-EOT**	**30 D SAFETY-FUP**	**SURVIVAL FUP**
Visit Window	**+5 days**								**-**	**+ 7d**	**+/- 14d**
Pregnancy Test (serum)		X	X	X	X	X	X	X	X		
Pregnancy Test (urine)	S- Every 4 weeks if serum pregnancy test is not performed										
Coagulation	If clinically indicated										
Other Hepatic Tests for suspected Drug-Induced Liver Injury (DILI)	If clinically indicated (refer to Section 6.5.2.1, Section 8.4.5, Section 10.4)										
Hepatitis screen	Refer to Appendix 10.4										
Bone marrow assessment for cytogenetic assessment	If clinically indicated										
Electrocardiogram (ECG) in Triplicate	X	X	As clinically indicated								
Cardiovascular risk factor assessments (including Family History)[7]									X		
Safety											
Adverse Events/SAE	X (Ongoing)									X	X[1]
Concomitant medications	X (Ongoing)									X	
Patient reported Outcomes											
EORTC QLQ-C30 plus CML24[,8]		X	X	X			X	X (wk 48 only)	X		

Period	Treatment- Re-initiation Phase (TRI)									30 D SAFETY-FUP[4]	Survival Follow-up (Every 12 wks until EOS)[4]
Visit Name	TRI W2	TRI W4	TRI W8	TRI W12	TRI W16	TRI W20	TRI W24[2]	TRI W36 and every 12 weeks until TRI-EOT[3]	TRI-EOT	30 D SAFETY-FUP	SURVIVAL FUP
Visit Window	+5 days								-	+ 7d	+/- 14d
CCI [redacted]											
TFQ									X		
Antineoplastic therapies											X
Stem Cell Transplant status											X
Progression Status											X
Survival follow-up											X
Disposition									X		X

S: assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

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

[2] If MMR is not re-achieved by 24 weeks, monthly monitoring (every 4 weeks) should continue until MMR is re-achieved. Additional CCI [redacted] may be performed as clinically indicated. For Discontinuation from study treatment requirements and treatment failure criteria refer to Section 7.1

[3] After week 24, TRI visits continue every 12 wks CCI [redacted] or until all participants the Treatment Phase or TFR Phase have completed 30day Safety FUP, whichever is latest.

[4] 30-Day Safety Follow up and Survival Follow up visits are based on the TRI-END visit date.

[6] For participants on asciminib or nilotinib, additional local safety laboratory testing for hematology and clinical chemistry may be performed at relevant time points to comply with the local prescribing information for asciminib and nilotinib. These laboratory results should be recorded in the participant's source documentation and do not need to be recorded in the clinical database.

[7] Refer to Section 8.4.4

[8] PROs to be completed before any clinical assessments when performed on-site. The PRO collection window is described in Section 8.5.1.

2 Introduction

2.1 Study rationale

Considerable advancements in treatment of patients with CML-CP have increased the life expectancy of patients making it a chronic disease requiring long term medication. This emphasizes the need for treatments that combine high efficacy with a favorable safety profile as improving over the currently available options (refer to Section 2.2.2). There remains an unmet medical need for newly diagnosed patients with CML-CP requiring chronic treatment and for a specific targeted treatment option that is highly efficacious while minimizing adverse events.

To assess if asciminib may address these needs, the ongoing Phase III study CABL001J12301 sets out to evaluate primarily the efficacy of asciminib in newly diagnosed CML patients.

Asciminib has been shown to be highly selective against *BCR::ABL1*-positive cell lines when compared with imatinib, nilotinib, dasatinib, and bosutinib, which vary considerably in their degree of specificity (Wylie et al 2017, Manley et al 2020). As most AEs associated with TKIs are attributable to off-target activity, the lack of specificity to ABL kinases leads to off-target effects in a substantial proportion of patients (Steegmann et al 2012, Hantschel 2015). Asciminib is specific for ABL kinases and it is expected that this limited off-target kinase inhibition will translate into a better safety profile than currently approved Adenosine Triphosphate (ATP)-competitive TKIs, including nilotinib. The primary purpose of this Phase IIIb study CABL001J12302 is to focus on the patient relevant outcomes and to assess the tolerability of asciminib, as it translates in study treatment discontinuations due to AEs, in comparison with that of the 2G TKI nilotinib, in adult patients with newly diagnosed Ph+ CML-CP. The study also aims to assess treatment impact on quality of life. Generating such data is patient relevant as well as deemed important for Health Technology Assessment (HTA) bodies' decision making.

Treatment-free remission (TFR) is evolving into an important treatment goal for CML patients. Treatment with TKIs may be successfully stopped in select patients if the duration of treatment and sustained deep molecular response (MR4 or deeper; <0.01% BCR::ABL1 IS) is sufficient to achieve TFR (Hochhaus et al 2020). Successful TFR represents a potential operational cure for CML patients with stable disease. In view of the chronic treatment required for CML, the potential medical benefits of successful TFR include elimination of chronic side effects and reduction of long-term risks of TKI usage, minimization of drug-drug interactions, impact on quality of life, and the possibility of a pregnancy without exposure to TKIs.

Patient motivation to attempt TFR is a key factor in considering TFR as a goal of treatment in CML. Patient surveys demonstrate that up to approximately 50-80% of patients with CML would be willing to attempt TFR (Villemagne Sanchez et al 2018, Atallah, Sweet 2021).

With currently available treatment options approximately 50% of patients with newly diagnosed CML on continued TKI therapy can successfully discontinue TKIs and to not experience recurrence of the disease (Ross, Hughes 2020, Ureshino et al 2020). Therefore, to achieve a functional cure for patients with CML with TFR, there remains an unmet need for treatments

that are well tolerated and that induce DMR in a rapid manner giving the option to patients to attempt TFR.

An extension of the Treatment Phase in Phase IIIb CABL001J12302 study extends the Treatment Phase CCI [redacted] the opportunity to enter an optional TFR Phase and aims to explore CCI [redacted] characterizing TFR for all agents in CML-CP is needed for physicians and patients to make an informed decision on choice of therapy. This extension will also allow for longer median duration of treatment on study generating additional long term safety data for asciminib.

2.1.1 Clinical efficacy and safety

Asciminib is being investigated in clinical studies in CML. As of 15-Jan-2024, asciminib has been investigated in 12 completed studies and 10 ongoing studies in patients with CML- CP/ AP or CML-BC or Ph+ ALL (Asciminib Investigator's Brochure 2024) In completed studies, 388 healthy volunteers, including 24 participants with hepatic impairment and 8 participants with renal impairment, were exposed to asciminib. In addition, 200 patients with CML-CP/ AP have been treated with single agent asciminib in CABL001X2101 and the study reached its primary analysis with cut-off date on 02-Apr-2020. This completed first-in-human (FIH) phase I clinical study provided preliminary evidence of safety and efficacy of asciminib in patients with CML-CP/AP who had been previously treated with two or more TKIs over a wide range of doses (Hughes et al 2019). In addition, the safety and efficacy of asciminib in 233 patients with CML-CP who had treatment failure on or were intolerant to at least 2 prior TKIs is available from the ongoing randomized, controlled study CABL001A2301 (Réa et al 2021). The data cut-off date for the secondary analysis at Week 96 was 06-Oct-2021 (Rea et al 2022). CABL001J12301 is an ongoing phase 3, open label randomized study of asciminib versus investigator-selected TKI in patients with newly diagnosed Ph+ CML-CP. The study met its primary analysis at Week 48 with data cut-off date on 28-Nov-2023 (Hochhaus et al 2024). Asciminib as an add-on to imatinib is also being studied in patients with CML-CP who did not achieve deep molecular response after at least 1 year of treatment with imatinib (CABL001E2201) (Saglio et al 2019). The data cut-off date for the primary analysis at Week 48 was 10-Jan-2022. The cut-off date for final analysis for the randomized arms of the study at Week 96, was 06-Mar-2023. The study is ongoing for asciminib single agent cohort.

2.1.1.1 Study CABL001X2101

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

At the time of the primary analysis (cut-off date 02-Apr-2020), a total of 317 patients with Ph+ CML (chronic phase (CP), accelerated phase (AP), or blast crisis (BC)) or Ph+ ALL who have

failed or are intolerant to at least one prior TKIs, have been enrolled in the study. Patients in the study were treated with increasing doses of single agent asciminib or with asciminib in combination with nilotinib, imatinib, or dasatinib (CABL001X2101 CSR). Results from Arm 1 evaluating single agent asciminib are presented below. The results from Arm 5 (single agent asciminib for treatment of CML-BC or Ph+ ALL) and Arm 2, 3, 4 (asciminib in combination with nilotinib, imatinib or dasatinib, respectively) are not included.

As a single agent, asciminib has been studied in 200 heavily pre-treated patients with CML-CP/ AP in Arm 1 of the CABL001X2101 study. As of the data cut-off date (02-Apr-2020), 123 (61.5%) patients in Arm 1 were receiving treatment with asciminib single agent and 77 (38.5%) patients had discontinued treatment. Physician's decision was the most frequent reason for discontinuation of treatment in 32 (16.0%) patients followed by discontinuation due to AEs in 19 (9.5%) patients. The median duration of exposure was 124.6 weeks (min-max: 0 to 302 weeks).

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

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

The final study analysis was conducted with a cut-off date of 14-Mar-2023. Additional safety data from participants treated with asciminib single agent were reported. Asciminib as a single agent was well tolerated in heavily pre-treated CML-CP or CML-AP patients and presents an acceptable safety profile in clinical development. Based on the final study analysis, the most common AEs reported in at least 50 patients among the 200 with CML-CP/-AP treated with asciminib single agent when considering all doses and all grades were arthralgia and headache (32.0% each), fatigue (31.0%), lipase increase (30.5%), diarrhoea (30.0%) and nausea (28.0%, each). The most common AEs reported in at least 50 patients as suspected to be related to asciminib single agent out of 200 patients with CML-CP/ -AP were lipase increased (25.0%), fatigue (18.0%), nausea and thrombocytopenia (17.5% each) and headache and rash (15.5% each). Eighteen patients with CML-CP/-AP who were treated with asciminib single agent (9.0%) had at least one SAE assessed by the Investigator as suspected to be related to the study drug.

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

2.1.1.2 Study CABL001A2301

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

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

The study met its primary endpoint. The MMR rate at 24 weeks was 25.5% in the asciminib arm compared to 13.2% in the bosutinib arm. The estimated difference in MMR rates of asciminib compared to bosutinib at 24 weeks was clinically meaningful and statistically significant 12.2% (95% CI: 2.19, 22.30, p value: 0.029). At the 96 week cut-off, the clinical superiority of asciminib versus bosutinib increased compared to the primary analysis; the MMR rate in the asciminib arm was 37.58% (95% CI: 29.99, 45.65) compared to 15.79% (95% CI: 8.43, 25.96) in the bosutinib arm. This corresponded to a common treatment difference (after adjusting for baseline MCyR status) of 21.47% (95% CI: 10.53, 32.95) which was clinically relevant and statistically significant (p=0.001) (two-sided Cochrane-Mantel-Haenszel chi-squared test, stratified by the major cytogenetic response status at baseline). At the end of treatment analysis (data cut-off 22-Mar-2023), with additional follow up, the MMR rate was sustainably higher for the asciminib arm compared to the bosutinib arm, at each scheduled time point up to week 156. The overall MMR rate was 47.13% in the asciminib arm versus 25% in the bosutinib arm.

As of the week 96 cut-off (06-Oct-2021), 99 of the 233 patients (42.5%) were continuing the study treatment with 84 patients (53.5%) and 15 patients (19.7%) still ongoing in the asciminib and bosutinib arms, respectively. Treatment discontinuations were reported for 45.9% of patients in the asciminib arm and for 80.3% in the bosutinib arm. Lack of efficacy (defined according to the response milestones in ELN recommendations) (24.2% in the asciminib arm and 35.5% in the bosutinib arm) remained the most frequently reported reason for treatment discontinuation. The median duration of exposure to study treatment was 103.1 weeks in the asciminib arm and 30.5 weeks in the bosutinib arm (from start of treatment to last treatment as per data cut-off date).

The frequency of AEs was lower in patients on asciminib (91.0%) as compared to bosutinib (97.4%), despite the considerably longer exposure to treatment on asciminib vs bosutinib noted above. In addition, a lower percentage of patients with Grade ≥ 3 AEs (56.4% vs 68.4%) and

with AEs leading to treatment discontinuation (7.7% vs 26.3.0%) were reported in the asciminib group as compared to bosutinib group. The most common adverse events on asciminib and bosutinib (>10% in either arm), respectively, included the following: thrombocytopenia (23.1% vs. 14.5%), headache (19.9% vs. 15.8%), neutropenia (19.2% vs. 17.1%), fatigue (14.7% vs. 9.2%), hypertension (13.5% vs. 5.3%), arthralgia (12.8% vs. 3.9%), diarrhea (12.8% vs. 72.4%), nausea (11.5% vs. 46.1%), nasopharyngitis (10.9% vs. 3.9%), anemia (10.3% vs. 7.9%), abdominal pain (9.0% vs. 15.8%), rash (9.0% vs. 23.7%), vomiting (7.7% vs. 26.3%), aspartate aminotransferase increased (5.8% vs. 21.1%), and alanine aminotransferase increased (4.5% vs. 30.3%). Since the primary analysis cut-off, the incidence of arthralgia, nasopharyngitis and anemia on asciminib and abdominal pain on bosutinib increased to above 10%. Due to the considerably longer duration of exposure to treatment in patients on asciminib, leading to a higher number of patients at risk of AEs, the risk differences between treatment groups should be interpreted with caution.

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

The proportion of patients with gastrointestinal toxicity, hepatotoxicity and hypersensitivity AESIs were substantially lower in the asciminib treatment group compared to the bosutinib treatment group (both all grades and Grade ≥ 3). Comparable proportion of patients with pancreatic enzyme increase was seen without clinical events of pancreatitis in both treatment groups. Serious adverse events were reported in a lower proportion of patients in the asciminib treatment group (17.9%) compared to the bosutinib treatment group (26.3%).

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

Three on-treatment deaths occurred during the study were observed: two in the asciminib arm and one in the bosutinib arm. The 2 deaths in the asciminib arm were not considered study treatment related by the Investigators (causes of death reported as ischemic stroke and mesenteric artery embolism, respectively). The death reported in the bosutinib arm was due to septic shock and was considered related to study treatment.

At the End of Treatment cut-off (22-Mar-2023), additional safety data were reported. The median duration of exposure to study drug was approximately 5 times longer in the asciminib arm (156.00 weeks; range: 0.1 to 256.3) compared to the bosutinib treatment arm (30.50 weeks; range: 1.0 to 239.3).

Regardless of the longer duration of exposure in asciminib arm, overall, patients in the asciminib arm vs. those in the bosutinib arm experienced less AEs (91.0% vs. 97.4%), less severe AEs (grade ≥3, 59.6% vs. 68.4%), less SAEs (21.8% vs. 26.3%), less AEs leading to dose adjustment/interruptions (43.6% vs. 64.5%) and less AEs leading to treatment discontinuation (8.3% vs. 27.6%). Asciminib continued to be safe and tolerable even after the longer duration of exposure since the Week 96 cut-off. The most commonly reported AEs (occurring in ≥ 10% of patients) by preferred term (PT) included:

- Asciminib arm: thrombocytopenia, headache, neutropenia, fatigue, arthralgia, hypertension, diarrhea, nasopharyngitis, nausea, COVID-19, and anemia
- Bosutinib arm: diarrhea, nausea, ALT increased, vomiting, rash, AST increased, neutropenia, headache, abdominal pain, thrombocytopenia, and fatigue.

Please refer to the latest (Asciminib Investigator's Brochure 2024) for more details.

The main characteristics of the reported AEs were consistent with the known safety profile of asciminib in patients with CML refractory to/ intolerant of prior therapies seen in FIH study CABL001X2101, and revealed no new or worsening safety findings. For more details of this study please refer to the most current Investigators Brochure for asciminib.

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

2.1.1.3 Study CABL001E2201

Study CABL001E2201 (ASC4MORE) is an ongoing 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. The study was not designed to formally compare efficacy results between the arms. The primary analysis with data cut-off date of 10-Jan-2022, happened when all randomized subjects had completed the week 48 visit or discontinued treatment early. A follow up data analysis based on data from all subjects in arms 1-4 that had completed Week 96 visit or discontinued treatment early with the data cut-off of 06-Mar-2023 was performed. The analysis of the primary efficacy endpoint MR4.5 rate at week 48, shows a trend towards a better response to both asciminib 40 mg q.d. + imatinib and asciminib 60 mg q.d. + imatinib versus continuing imatinib or switching to nilotinib. With longer follow up at week 96, the same trend was observed. At Week 96, there were 4 subjects in both asciminib 40 mg + imatinib arm and asciminib 60 mg arm + imatinib arm achieved MR4.5 compared to 1 subject in the imatinib arm and 2 subjects in the nilotinib arm. Among subjects that achieved MR4.5 at least once before the data cut-off, the median time to MR4.5 in the asciminib 60 mg + imatinib (12.4 weeks) was approximately five times faster than in the imatinib arm (66.4 weeks) and 3 times faster than in the nilotinib arm (36.3 weeks). The median duration of exposure to study drug was longer in the asciminib 40 mg + imatinib (141.7 weeks, range 27-203) and asciminib 60 mg + imatinib (124.3 weeks, range 1-192) arms as compared to monotherapy with nilotinib (110.1 weeks, range 1-189). The median duration of exposure in the imatinib arm was 53.4 weeks (range 50-186). With data cut off of 06-Mar-2023, the most common (≥15% subjects in any of the treatment arm) AEs by preferred terms were: In asciminib 40 mg + imatinib arm: nausea (33.3%), diarrhoea (23.8%), myalgia (23.8%), pruritus (19%), rash (19.0%) and COVID-19 (19.0%); in asciminib 60 mg + imatinib arm: COVID-19 (42.9%), alopecia (19.0%) and lipase increase (19.0%); in imatinib arm: lipase increased (15%), diarrhoea (15%) and hypophospataemia (15%); in nilotinib arm: rash (38.1%), COVID-19 (28.6%) and alanine aminotransferase increased (23.8%). The study is ongoing.

2.1.1.4 Study CABL001J12301

Study CABL001J12301 (ASC4FIRST) is an ongoing phase III, multi-center, open-label, randomized study of oral asciminib versus Investigator selected Tyrosine Kinase Inhibitor (TKI) in adult patients with newly diagnosed Ph+ CML-CP. The primary purpose of this pivotal study is to compare the efficacy (MMR at Week 48) of asciminib with that of the BCR::ABL1 TKIs imatinib, nilotinib, dasatinib and bosutinib. The study completed recruitment in 20-December 2022 with 475 participants screened and 405 randomized.

A total of 405 patients were randomized in a 1:1 ratio and stratified according to a pre randomization-selected TKI and European Treatment and Outcomes Study long-term survival (ELTS) risk category to receive either asciminib at a dose of 80 mg once daily (201 patients) or an investigator-selected TKI at approved doses for frontline therapy: imatinib, 400 mg once daily; nilotinib, 300 mg twice daily; dasatinib, 100 mg once daily; or bosutinib, 400 mg once daily (204 patients). The study met both the primary endpoints. At the 48 week cut-off (28-Nov-2023), the MMR rate was 67.7% in the asciminib group compared with 49.0% in the investigator-selected TKI group (difference, 18.9 percentage points; 95% confidence interval [CI], 9.6 to 28.2; adjusted two-sided P<0.001]), and in 69.3% of patients in the asciminib group as compared with 40.2% in the imatinib group within the imatinib stratum (difference, 29.6 percentage points; 95% CI, 16.9 to 42.2; adjusted two-sided P<0.001) (Hochhaus et al 2024). Secondary endpoint MMR at 48 weeks of asciminib compared with investigator-selected TKIs in the second-generation TKI stratum was 66.0% and 57.8% (difference, 8.2 percentage points; 95% CI, −5.1 to 21.5).

The median duration of treatment was 16.1 months (range, 0.2 to 24.8) with asciminib, 12.9 months (range, 0.6 to 22.8) with imatinib, and 16.4 months (range, 0.3 to 23.7) with second-generation TKI. Adverse events of grade 3 or higher that occurred in 10% or more of patients in any cohort were hematologic in nature; they included thrombocytopenia (13.0% with asciminib, 6.1% with imatinib, and 13.7% with second-generation TKIs), neutropenia (10.0%, 17.2%, and 17.6%), and leukopenia (2.0%, 10.1%, and 4.9%). The percentage of patients with adverse events leading to treatment discontinuation was 4.5% with asciminib, 11.1% with imatinib, and 9.8% with second-generation TKIs (Hochhaus et al 2024). The study is ongoing.

2.1.2 Pharmacokinetics

The pharmacokinetic (PK) profile of asciminib has been evaluated both as single agent in CML patients at a dose range between 10 mg to 280 mg BID and 80 mg to 200 mg QD, as well as in healthy subjects. Asciminib was rapidly absorbed following single dose and repeated administration with a median time to reach maximum plasma concentration (Tmax) of 2 to 3 hours, independent of dose. Systemic exposure of asciminib, after oral administration of a single dose and multiple doses, as measured by Cmax and area under the curve (AUC), increases in a slightly more than dose proportional manner based on statistical analysis. No time-dependent PK was observed. The apparent terminal elimination half-life (T1/2) was estimated to be between 7 and 15 hours and steady-state was reached by 3 days. With once daily dosing regimen there was almost no accumulation of asciminib (1.1 to 1.4).

Generally, the variability of exposure was low to moderate with inter-subject variability (coefficient of variation (CV) %) ranging from approximately 25% to 70% for both Cmax and AUClast.

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

A 1.56 fold and 1.66 fold increase in AUCinf of asciminib was observed in subjects with severe renal impaired function and severe hepatic impaired function, respectively, compared to the normal renal function cohort [CABL001A2103, CABL001A2105]. No dose adjustment is considered necessary in participants with mild, moderate, and severe renal or hepatic impairment based on these study results.

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

CCI [redacted]

Asciminib is a substrate of both the BCRP and permeability glycoprotein (P-gp transporters). In a recently reported DDI study (CABL001A2107) coupled with a PBPK report, asciminib was shown to be negligibly affected by strong Cytochrome P450 3A4 (CYP3A4), P-gp and BCRP inhibition at 40 mg BID and 80 mg QD, while weakly affected by strong CYP3A induction at the same doses. Cautionary use is recommended with strong CYP3A4 inducers. A covariate analysis for heavy smokers from a population PK report (CABL001A2301) indicated that the potential for clinical DDIs with co-medications that inhibit a single Uridin diPhospho-glucuronosyltransferase (UGT) enzyme is low. Study (CABL001A1101) suggested that asciminib's bioavailability was not affected by the co-administration with acid-reducing agents.

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

Based on data available from 241 patients in the Study CABL001X2101, the concentration-QTcF analysis identified a positive relationship with asciminib treatment. The estimated mean and upper bound of the 90% CI QTcF increase did not exceed 10 ms (the threshold that is considered clinically significant according to the regulatory guidance) at all the therapeutic doses as well as at the estimated highest clinical relevant exposure (HCRE) (determined based on the geometric mean Cmax at 200 mg BID dose, and accounting for a 1.59-fold increase in Cmax observed in a drug-drug interaction study). The upper bound of the 90% CI ΔQTcF at

geometric mean Cmax observed at 40 mg BID, 80 mg QD and 200 mg BID were 4.32 ms, 4.57 ms, and 6.66 ms, respectively. However, it cannot be excluded that the positive slope would cross this threshold at higher exposures. At 2-fold the estimated HCRE (3.2-fold increase in exposure at 200 mg BID) the estimated mean QTcF increase was 10.41 ms (upper bound 90% CI: 14.75 ms) [QT/QTc and ECG Assessment Report].

Please refer to the latest (Asciminib Investigator's Brochure 2024)) for more details.

2.2 Background

2.2.1 Disease background

Chronic Myelogenous Leukemia (CML) is a clonal myeloproliferative disorder of transformed, primitive hematopoietic progenitor cells characterized by overproduction of immature myeloid cells and mature granulocytes in the spleen, bone marrow, and peripheral blood. The hallmark of CML is the Philadelphia (Ph) chromosome found in up to 95% of patients (Seong et al 1999). The Ph chromosome results from a reciprocal translocation t(9;22) (q34;q11) which fuses a portion of the Abelson (ABL1*) ge*ne on chromosome 9 with a portion of the breakpoint cluster region (BCR) *ge*ne on chromosome 22. The molecular consequence of the t(9;22) translocation is the creation of the fusion protein BCR::ABL1, a constitutively active cytoplasmic tyrosine kinase with increased signaling activity, that activate multiple signal-transduction cascades affecting the growth and differentiation of hematopoietic cells, allowing them to escape constraints on normal growth and to become leukemic (Sawyers 1999).

With a constant worldwide incidence of 1.8-2.0 /100,000 per year, the prevalence of CML is steadily increasing due to improved long term outcomes with tyrosine kinase inhibitor (TKI) treatment (SEER 2022). CML mainly affects adult patients with a median age at diagnosis of 67 years. In the United States (US), it is estimated that approximately 8,860 new cases of CML will be diagnosed and about 1,220 people will die of the malignancy during 2022 (Siegel et al 2022). In Europe, a similar CML incidence has been reported with 10 to 15 cases/million/year, without any major geographic or ethnic differences (Hochhaus et al 2017).

Clinically, CML can progress through three distinct phases which become increasingly refractory to therapy: chronic phase, accelerated phase, and blast crisis (Sawyers 1999). Most patients are diagnosed in the CP, characterized by anemia, splenomegaly and leukocytosis with generally few constitutional symptoms like fatigue, weight loss, malaise, easy satiety, and left upper quadrant fullness or pain. CML-AP might be insidious or present with worsening anemia, splenomegaly and organ infiltration; most patients evolve into AP prior to BC, but without treatment around 25% may transition into BC without a preceding AP (Faderl et al 1999, Savage et al 1997).

Current management recommendations and unmet medical need

In 2001, the introduction of the TKI imatinib (Glivec®), the first drug to be targeted against an oncogenic mutation, revolutionized the treatment of patients with CML. Subsequently, several second generation (2G) TKI agents, nilotinib, dasatinib, bosutinib, have been approved for the first-line treatment of CML. TKI treatment has improved the survival rates for patients with CML and patients with optimal treatment response may expect near-normal life expectancy

(García-Gutiérrez and Hernández-Boluda 2019). Increased survival rates and the requirement of chronic therapy for CML has underlined the importance of selection of first-line treatment for newly diagnosed patients. The treatment for newly diagnosed patients with CML aims to deliver early optimal responses to decrease the possibility of disease progression, maintain the quality of life for patients requiring potentially life-long treatment, and to decrease possibility of serious side effects.

Treatment guidelines recommend selection of the first-line option for the treatment of CML-CP based on individual patient and disease characteristics determining risk score (Sokal, Hasford (Euro), EUTOS or ELTS), as well as the preexisting comorbidities and concomitant medications determining the ability of the patient to tolerate therapy (Hochhaus et al 2020, NCCN CML treatment guidelines V3.2022, Saglio and Jabbour 2018). Considering the differences in safety and efficacy profiles of imatinib and 2G TKIs, i.e. nilotinib, dasatinib and bosutinib, first-line treatment recommendations vary for these agents.

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

Newly diagnosed younger patients with CML-CP and those with high risk scores are recommended to be treated with 2G TKIs, which have shown to be more potent than imatinib (Hochhaus et al 2020, NCCN CML treatment guidelines V3.2022). Studies comparing 2G TKIs to imatinib demonstrated higher rates of efficacy responses and reduced rates of progression to AP or BC; however, the safety profile of these drugs is significantly more adverse as compared to imatinib. The development of vascular side effects such as peripheral arterial occlusive disease, cerebrovascular accidents, and coronary artery disease with nilotinib, cardiopulmonary toxicities such as pleural effusions, interstitial pneumonitis and pulmonary hypertension with dasatinib and gastrointestinal and liver related events with bosutinib, warrant caution while prescribing these agents for first-line treatment of newly diagnosed patients with CML-CP (Hochhaus 2016, Cortes and Kantarjian 2016, Cortes et al 2018). Positive benefit risk balance has been noted in a 10 year follow-up of the ENESTnd trial comparing nilotinib to imatinib in respect to TFR treatment goals. At both 5 and 10 years more patients on nilotinib achieved TFR eligibility than those on imatinib as a frontline therapy (Kantarjian et al 2021).

Many adverse events associated with imatinib and 2G TKIs are attributable to off-target activities of these inhibitors as they are not specific for ABL / BCR::ABL1 inhibition (Steegmann et al 2012). For example, hypophosphatemia with imatinib has been attributed to inhibition of Platelet-Derived Growth Factor (PDGF) signaling affecting the formation and

resorption of bone (Berman 2006). Multi-kinase inhibitor-induced rash is common in patients on imatinib therapy (Grávalos 2019). For bosutinib, a higher rate of diarrhea is considered to be due to Epidermal Growth Factor Receptor (EGFR) inhibition (Rugo et al 2019). Off-target inhibition by TKIs of SRC family kinases have been implicated in occurrence of fluid retention and pleural effusion (Giles 2009).

Nilotinib is a 2G TKI that was approved for the treatment of patients with newly diagnosed Ph+ CML-CP in 2011 and became the first 2G TKI with treatment free remission (TFR) data in its label in 2017. Currently nilotinib is one of the most frequently prescribed 2G TKI in these patients in Europe and Germany, as recent Europe market data on the TKI use in CML indicates.

Current long term treatment options require an optimal benefit risk balance, and the focus for patients living with CML-CP has shifted toward quality of life (Sweet et al 2023, Held et al 2023). Despite advancements in treatments for patients living with CML-CP which have led to an increase in life expectancy close to the general population, the consequential requirement for chronic long-term medication remains a challenge.

TFR is an important new goal for CML where treatment with TKI can be successfully stopped in some patients if the duration of treatment and deep molecular response (MR4 or lower; <0.01% BCR::ABL1 IS) is sufficient for a potential operational cure (Hochhaus et al 2020). Treatment side effects, concerns about long term risks of TKI treatment, the burden of taking a medication every day, needs for pregnancy planning, and interest in reducing costs are motives for patients and physicians to pursue a stable deep molecular response (DMR) and discontinuing treatment for TFR.

The feasibility of stopping TKI treatment (including dasatinib, imatinib, and nilotinib) with close monitoring, in patients who have achieved and sustained a deep molecular response (DMR) has been evaluated in numerous clinical studies reporting TFR success rates of approximately 40-60% of patients who meet criteria and elect to discontinue treatment (Mahon et al 2010, Saussele et al 2018, Shah et al 2020, Shah et al 2023, Mahon et al 2024).

Achieving and maintaining DMR on TKI treatment is a key requirement for eligibility to attempt TFR. Extensive evidence is available about the rates of DMR and subsequent TFR attempts for the TKIs imatinib, nilotinib and dasatinib.

The German CML-Study IV, demonstrated that at 4 years 60.4% of patients achieved MR4 and 41.9% achieved MR4.5. These percentages increased over time up to MR4 in 69.8% of patients and MR4.5 in 57.1% of patients at 6 years (Hehlmann et al 2014). The Stop imatinib (STIM1) study provided the first evidence that achieving and maintaining deep molecular responses can lead to successful therapy suspension (Mahon et al 2010, Mahon et al 2011). It was performed in 100 patients in DMR for at least 2 years. The molecular recurrence free survival was 43% at 6 months and 38% at 60 months with a median follow up of 77 months (Etienne et al 2017).

The ENESTnd study demonstrated more than half of all patients in each nilotinib arm (300 mg twice daily, 54%; 400 mg twice daily, 52%) achieved MR4.5 at the 5 year update (Hochhaus et al 2016). The ENESTfreedom study was a single-arm, phase 2 trial that assessed the potential for TFR in patients who had received ≥2 years of frontline nilotinib therapy, achieved MR4.5 and underwent a 1-year nilotinib treatment consolidation phase before attempting TFR. At Week 48 of the TFR Phase 51.6% of patients were maintaining molecular

response, at Week 96 48.9% of patients remained in MMR and at the 5-year data cut-off, 42.6% of patients were still in TFR, with 40.0% in MR4.5 (Hochhaus et al 2017, Ross et al 2018, Radich et al 2021). When the TFR eligibility criteria from ENESTfreedom were applied to the ENESTnd study, the estimated TFR eligibility rates at 5 years with nilotinib 300 mg twice daily, nilotinib 400 mg twice daily and imatinib were 20.9% (95% CI: 16.2-25.7%), 20.6% (95% CI: 15.9–25.4%) and 11.0% (95% CI: 7.3-14.6%), respectively (Kantarjian et al 2021). In the ENESTop study patients who switched from imatinib to nilotinib, achieved DMR and had consolidation treatment were offered TFR. TFR was maintained in 57.9% of patients at 48 weeks and 42.9% at 5 years (Hughes et al 2021). Nilotinib is the only TKI that has amended its label to include recommendations on treatment discontinuation with TFR studies ENESTfreedom and ENESTop included in the clinical sections (Nilotinib SmPC).

The MR4.5 rate by 5 years with dasatinib 100 mg QD in the DASISION trial was 42% (Cortes et al 2016). Later on, the DASFREE study has reported a 2-year TFR rate after dasatinib discontinuation of 46%. Patients with a stable DMR after ≥2 years of dasatinib therapy discontinued treatment and were followed for 5 years and the TFR rate reported was 44% (Shah et al 2020, Shah et al 2023).

To date TFR has not been evaluated in asciminib but earlier and deeper molecular responses have been observed across studies. In the Phase 3 ASCEMBL study for patients who had failed or were intolerant to at least 2 prior TKIs, at Week 96 the DMR rates (MR4, BCR::ABL1 IS ≤0.01%; and MR4.5, BCR::ABL1 IS ≤ 0.0032%) were consistently higher with asciminib (17.2% and 10.8%, respectively) than with bosutinib (10.5% and 5.3%, respectively) (Hochhaus et al 2023).

The Phase 2 ASC4MORE study of asciminib added to imatinib, continued imatinib or switch to nilotinib in patients with CML-CP who have been previously treated with imatinib and have not achieved deep molecular response observed that 19.0%, 28.6%, 0%, and 4.8% of patients were in MR4.5 at Week 48, and with median time to MR4.5 of 12.1, 12.4, and 24.6 Weeks in the 40mg asciminib add-on, 60-mg asciminib add-on, imatinib, and nilotinib arms, respectively (Cortes et al 2022).

In the ASCEND study where asciminib was evaluated in newly diagnosed patients with CML, 11.9% patients were observed to be in MR4 by 3 months of treatment (Yeung et al 2023). More recently the Phase 3 ASC4FIRST (CABL001J12301) study in newly diagnosed CML patients reported cumulative incidence of MR4 by week 48 as 34.0% (95% CI: 27.5% to 40.6%) with asciminib and 15.9% (95% CI: 11.2% to 21.3%) with all investigator-selected TKIs; 37.0% (95% CI: 27.6% to 46.4%) with asciminib and 10.0% (95% CI: 5.1% to 16.9%) with imatinib; and 31.0% (95% CI: 22.2% to 40.2%) with asciminib and 21.8% (95% CI: 14.3% to 30.3%) with second-generation TKIs. The probability of deeper response MR4.5 by week 48 was 18.5% (95% CI: 13.5% to 24.2%) with asciminib and 11.0% (95% CI: 7.1% to 15.7%) with all investigator-selected TKIs; 19.0% (95% CI: 12.0% to 27.3%) with asciminib and 6.0% (95% CI: 2.5% to 12.0%) with imatinib; and 18.0% (95% CI: 11.2% to 26.1%) with asciminib and 15.8% (95% CI: 9.5% to 23.7%) with second-generation TKIs (Hochhaus et al 2024).

Based on DMR rates with currently available treatment options, the possibility to successfully discontinue TKIs, and to not experience recurrence of the disease, is an option for less than 25% of newly diagnosed patients with CML (Hughes 2021, Ureshino et al 2020).

Therefore, treatments that are both well tolerated and induce DMR in a rapid and sustained manner to achieve TFR eligibility and TFR success remains a high unmet need.

For patients outside of clinical studies, NCCN guidelines for CML (NCCN V2.2024) recommend TKI discontinuation only in carefully selected patients on approved TKI therapy with a minimum of 3 years treatment and who have sustained DMR (MR4: *BCR::ABL1* ≤0.01% IS) for at least 2 years. According to current ELN recommendations (Hochhaus et al 2020) treatment discontinuation may be considered in patients with durable DMR independent of the TKI, as long as a patient is on first-line therapy or second-line therapy with intolerance as the only reason for changing TKI. The recommended treatment duration per ELN is at least 5 years for imatinib, 4 years for second generation TKIs, and with duration of >3 years of DMR (with sustained MR4) or >2 years (with sustained MR4.5; BCR::ABL1 ≤0.0032% IS).

While NCCN and ELN guidelines for TFR are based on studies evaluating TFR with dasatinib, imatinib, or nilotinib, CCI [redacted]. Characterizing TFR for all agents in CML-CP is needed for physicians and patients to make an informed decision on choice of therapy.

2.2.2 Background on asciminib

Asciminib is an oral, potent inhibitor of BCR::ABL1 tyrosine kinase with a novel mechanism of action. In contrast to BCR::ABL1 TKIs, such as imatinib, nilotinib, dasatinib, bosutinib and ponatinib that directly interact with the ATP-site on the SH1 domain of the enzyme, asciminib inhibits the ABL1 kinase activity by specifically targeting the ABL myristoyl pocket (STAMP). Asciminib functionally mimics the role of the myristoylated Gly2 residue by occupying the vacant binding site and restoring the negative regulation to the kinase activity. This site has only been implicated in the autoregulation of ABL1, ABL2 and BCR::ABL1, thus explaining the specificity of asciminib towards these three enzymes (Manley et al 2020).

Asciminib has been shown to be highly selective against *BCR::ABL1*-positive cell lines when compared with imatinib, nilotinib, dasatinib, and bosutinib, which varied considerably in their degree of specificity (Wylie et al 2017, Manley et al 2020). As most AEs associated with TKIs are attributable to off-target activity, the lack of specificity to ABL kinases leads to off-target effects in a substantial proportion of patients (Steegmann et al 2012, Hantschel 2015). Asciminib is specific for ABL kinases and it is expected that this limited off-target kinase inhibition will translate into a better safety profile than currently approved ATP-competitive TKIs.

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

Asciminib was also approved by the Japan Pharmaceuticals and Medical Devices Agency (PMDA) in March 2022, for the treatment CML with resistance or intolerance to previous therapy. The posology is 40 mg BID.

2.3 Benefit/Risk assessment

Overall, asciminib (as monotherapy or in combination with other TKIs) has shown a favorable benefit-risk profile in two independent clinical studies. Results from the phase I study (CABL001X2101) showed positive responses with asciminib in a heavily pretreated population who had resistance to or unacceptable side effects from TKIs. In the ASCEMBL study (CABL001A2301) asciminib demonstrated significantly superior efficacy over bosutinib in patients treated with two or more prior TKIs (Hochhaus et al 2020). The MMR rate at 6 months with asciminib was almost two times that seen with bosutinib (Rea et al 2021). Based on the positive results of these studies, asciminib received an accelerated approval on 29-Oct-2021 by the US FDA for the use in CML-CP patients previously treated with 2 or more previous TKIs. FDA also granted approval in CML-CP patients harboring the T315I mutation based on data from a specific cohort from study CABL001X2101.

In the current protocol, asciminib will be a first-line treatment and allow for a population with a newly diagnosed condition who enter the trial to have a longer duration of treatment with less side effects and lower risk of treatment discontinuation, due to the tolerability of asciminib. In addition, these participants may potentially benefit from a better response to asciminib. Efficacy of the drug is assessed through molecular monitoring in central lab standardized to the international scale (IS). With the exception of the bone marrow assessment required as clinically indicated, the protocol does not include invasive examination. Participant visits are aligned with the safety monitoring requirements as well as with current treatment recommendations and represent a common schedule that is also required in clinical practice outside of the study. It is therefore anticipated that the protocol will take every precaution to allow for the best possible safety of the participants while at the same time carefully managing the additional burden of the trial to participants.

Management of side effects represent a significant challenge with TKIs, in particular as participants may achieve a normal life expectancy. Data from ASCEMBL (Rea et al 2021) support a more favorable safety profile of asciminib compared with bosutinib. Participants may benefit from the treatment with asciminib and the improved quality of life. The most frequently reported AEs in both the clinical studies (CABL001X2101 and CABL001A2301) are listed in Section 2.1.1.

In this trial, the risks are managed through detailed information provided in the (Asciminib Investigator's Brochure) 2024) and requirements delineated in the study protocol. Other risks to participants in this trial will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, and adherence to dose modification and interruption guidance provided in the protocol.

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

efficacy/sustained response, based on molecular response data, will permit rapid decision making, and discontinuation/re-initiation of therapy if necessary (see Section 7.1).

Women of child-bearing potential will be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and as a part of inclusion to the study will need to agree that in order to participate in the study, including TFR Phase, they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they will not enter or continue in the study.

The local labels for nilotinib characterize both efficacy and safety of the compound and provide guidance to maximize the efficacy and minimize the risks to participants.

There may be unforeseen risks with asciminib which could be serious. Refer to the latest (Asciminib Investigator's Brochure) 2024) for additional details.

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

There is no known contraindication for the use of an inactivated, viral-vector, messenger ribonucleic acid (mRNA), subunit, DNA or live-attenuated based SARS-CoV-2 vaccine in cancer patients on asciminib in this trial.

TFR is an important evolving goal in CML (Hochhaus et al 2020). Considering the chronic nature of CML, patient drivers for attempting TFR include the benefits of removing TKI-related adverse events, reducing long-term TKI exposure, allowing pregnancy planning, and removing the burden of taking medication (Villemagne Sanchez et al 2018).

TFR following discontinuation of asciminib has not been evaluated in clinical studies. TFR data from studies with nilotinib, imatinib and dasatinib report approximately 50% of patients who discontinue TKI therapy for TFR experience a molecular recurrence, with a majority occurring in the first 6 months and in some cases as early as 1 month (Mahon et al 2010, Etienne et al 2017, Saussele et al 2018, Shah et al 2020, Mahon et al 2024). A metaphase analysis across TFR trials and observational studies found the probability of recurrence in months 0-6, 6-12, 12-18 and 18-24 was 35%, 8%, 3%, and 3% respectively (Dulucq et al 2020).

Several factors have been reported with risk of molecular recurrence when attempting TFR including a higher risk score at diagnosis, female gender, rate of response to TKI, BCR::ABL1 transcript type (e14a2 or e13a2), duration of TKI therapy, and duration of DMR before TKI discontinuation (Mahon et al 2010, Rousselot et al 2014, Lee et al 2016, Saussele et al 2018, Shah et al 2020, Shanmuganathan et al 2021, Mahon et al 2024). Of these, duration of TKI therapy and duration of DMR before cessation attempt have been most consistently associated with TFR success. In the largest TFR study to date with 728 patients, EURO-SKI reported the duration of treatment with imatinib (≥6 years) and duration of DMR (MR4.0 for 3 years) were significantly associated with MMR maintenance at 6 months. In the recent final report for

EURO-SKI, multiple logistic regression models confirmed duration of treatment, in addition to % blasts at diagnosis, and BCR::ABL1 transcript type as independent factors for MMR maintenance for the entire study period of 36 months (Mahon et al 2024).

Based on these aforementioned TFR studies, and additional studies of TFR with dasatinib, imatinib, or nilotinib, the current NCCN guidelines for CML (NCCN V2.2024) recommend outside of clinical studies a minimum of 3 years treatment and sustained MR4 for at least 2 years. ELN recommends at least 5 years for imatinib (4 years for second generation TKIs), and with duration of DMR > 3 years (with sustained MR4) or > 2 years (with sustained MR4.5) (Hochhaus et al 2020).

The ENESTfreedom Phase 2 study assessed TFR success rate in patients who had received ≥3 years of frontline nilotinib therapy with at least 1 year DMR prior to TFR entry (last 4 quarterly assessments were at least in MR4.0 and with MR4.5 in the last assessment and ≤2 assessments between MR4 and MR4.5) (Ross et al 2018). The ENESTop study included patients who switched from imatinib to nilotinib and with ≥3 years treatment and with at least 1 year DMR prior to TFR attempt (last 4 quarterly assessments with no confirmed loss of MR4.5) (Hughes et al 2021). Duration of nilotinib therapy before the start of TFR was identified as the only significant predictor of durable TFR in a pooled analysis of data from ENESTfreedom and ENESTop (Radich et al 2019). The dasatinib study DASFREE allowed a minimum 2 years treatment with at least 1year DMR (MR4.5) prior to TFR attempt. No disease progression or CML related deaths were reported by 5 year follow up in ENESTfreedom, ENESTop, or DASFREE (Radich et al 2021, Hughes et al 2021, Shah et al 2023).

Patients who lose response in TFR and resume treatment have very high success rates of re-achieving molecular response upon resuming TKI treatment after a TFR attempt (Mahon et al 2024). In the ENESTFreedom study 90/91 (98.9%) patients who entered the TRI Phase regained MMR, most (91.2%) within the first 12 weeks of re-starting nilotinib. Of those 91 patients, 84 (92.3%) regained MR4.5 (Radich et al 2021).

In this study, eligibility for TFR Phase is based on well controlled disease in chronic phase with a minimum of CCI [redacted]

Patients entering TFR Phase in this study will be monitored closely for molecular recurrence indicated by rise in BCR::ABL1 transcripts, with RQ-PCR assessments via validated central laboratory testing at a high frequency of every 4 weeks for first 24 weeks, every 8 weeks for next 24 weeks, and then every 12 weeks. Loss of MR4 in TFR Phase after 24 weeks will trigger increased monitoring frequency to every 4 weeks until a return to DMR or loss of MMR. Patients who therefore are at risk of losing MMR in TFR will be more closely monitored, enabling early identification of any subsequent loss of MMR CCI [redacted]. At this point the patient will be discontinued from the TFR Phase and study treatment resumed within one month.

CCI [redacted]

CCI

A polymyalgia-like syndrome of musculoskeletal and/or joint painoften referred to as 'TKI withdrawal', has been associated with discontinuation of TKIs as a physician reported adverse event in TFR studies (Lee et al 2016, Radich et al 2021, Hughes et al 2021). Studies estimate the proportion of physician reported increase in musculoskeletal pain ranges from 10-50% of patients after TKI discontinuation or TFR, with an overall rate of 20-30% (Kota et al 2019). A 14-site prospective, nonrandomized clinical trial reported that within 3 months of discontinuation, 35 of 172 patients (20.3%) had a physician reported pain AE while 22 of 172 (12.8%) had an increase in self-reported pain, and 18 of 154 (11.7%) initiated a pain medication; overall, 60 of 172 patients (34.9%) had increased pain (Flynn et al 2022). This phenomenon is suggested to be likely due to undefined off-target effect(s) of the TKI (Richter et al 2014).

Withdrawal symptoms of musculoskeletal pain that have been reported in TFR after discontinuation of imatinib, nilotinib, or dasatinib are mostly temporary, typically grade 1/2, and can be managed with pain medication or behavioral approaches. In studies thus far, these AEs have not been reported to cause a significant decrease in QOL, and very few cases result in TKI re-initiation or study discontinuation based solely on pain symptoms (Kota et al 2019, Flynn et al 2022).

Based on the above, the expected benefits of conducting this study of asciminib versus nilotinib in newly diagnosed CML patients, and with the option to attempt TFR for participants who meet all eligibility criteria, outweigh the potential risks.

3 Objectives, endpoints, and estimands

Table 3-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s) • The primary objective of the study is to assess the tolerability of asciminib versus nilotinib, in participants with newly diagnosed CML-CP, with respect to the time to discontinuation of study treatment due to adverse event (TTDAE).	**Endpoint(s) for primary objective(s)** • Time to discontinuation of study treatment due to adverse event (TTDAE). TTDAE is defined as the time from the date of first dose of study treatment to the date of discontinuation of study treatment due to adverse event (AE)
Secondary Objective(s) of Treatment Phase • **Secondary objective on efficacy** • To compare the efficacy of asciminib versus nilotinib at and by all scheduled data collection time points	**Endpoint(s) for secondary objective(s) of Treatment Phase** • MMR **at** all scheduled data collection time points. • MMR **by** all scheduled data collection time points. • MR4.0 and MR4.5 **at** and **by** all scheduled data collection time points. • Complete Hematological Response (CHR) **at** and **by** all scheduled data collection time points. • *BCR::ABL1* ≤1% at and by all data collection time points. • Duration of MMR, MR4.0, MR4.5. • Time to first* MMR, first MR4.0, first MR4.5. • Time to treatment failure.

Objective(s)	Endpoint(s)
	• Event Free Survival. • Progression free survival. • Overall survival. *by competing risk analysis
• Time to Treatment Discontinuation (TTD) for selected reasons of discontinuation	• TTD due to selected reasons (i.e. Discontinuation due to lack of efficacy/treatment failure/disease progression/ suboptimal response/death)
• **Secondary objectives on PRO** • To assess the effect of asciminib versus nilotinib on patient-reported disease-related symptoms, functioning, and health-related quality of life (HRQoL)	• Change from baseline in overall scores and individual scales of the EORTC QLQ-C30, EORTC QLQ-CML24.
• **Secondary objectives for safety** • To characterize the safety and tolerability profile of asciminib versus nilotinib during the course of study.	• Type, frequency and severity of adverse events, dose modification due to adverse event, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG changes, and other safety data (vital signs, physical examination).

CCI

Objective(s)	Endpoint(s)
[redacted]	

3.1 Primary estimands

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

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

Primary estimand: The primary estimand is described by the following attributes:

- **Population**: Newly diagnosed adult Ph+ CML-CP patients, as defined by Inclusion/ Exclusion criteria; that have asciminib or nilotinib as their first starting dose.
- **Endpoint**: Time to discontinuation of study treatment due to AE, where discontinuation of study treatment due to other reasons is considered as a competing risk event.
- **Intercurrent events (IE):**
  - Change of study treatment per protocol (dose reduction/interruption): *treatment policy strategy*
  - Dosing errors (e.g., missed dose): *treatment policy strategy*
  - Deviation in any intake of concomitant medications: *treatment policy strategy*
  - Intake of prohibited medications: *treatment policy strategy*
  - Handling of remaining intercurrent events (IE): no other IE foreseen.

Treatment:

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

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

3.2 Secondary estimands

Not applicable.

4 Study design

4.1 Overall design

This is a phase IIIb, multi-center, open-label, randomized study of oral asciminib 80 mg QD versus nilotinib 300 mg BID in adult patients with newly diagnosed Ph+ CML-CP.

The study is designed to compare the tolerability of asciminib with nilotinib for the treatment of newly diagnosed, previously untreated patients with Ph+ CML-CP. Refer to Section 1.2 Schema for study design figure.

This study has 3 phases: Treatment Phase, optional TFR Phase, and TRI Phase. Please see Figure 1-1 and Figure 1-2 for the study design.

Treatment Phase

It is planned to randomize approximately 550 participants in the study in a 1:1 randomization to asciminib or nilotinib. Randomization will be stratified based on EUTOS long-term survival (ELTS) score from diagnosis (low versus intermediate versus high prior to treatment with hydroxyurea (if applicable), to help achieve a balance between the treatment arms. No crossover of study treatment across arms is allowed in the Treatment Phase. For further details on study treatments, treatment arms and dose modifications refer to Section 6.

All participants will receive study treatment[redacted]. The treatment will continue until the participant enters the TFR Phase, or completes[redacted] of study treatment and is not eligible or does not consent to enter TFR Phase, or experiences unacceptable toxicity, disease progression, death, lost to follow-up and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent.

Participants who discontinue the study treatment prematurely due to any reason will return for an end of treatment (EOT) visit.

For all participants not entering the TFR Phase, a safety follow up visit/call will be performed approximately 30 days after end of treatment (EOT) visit. In addition, three PRO assessments should be performed after EOT at the time points specified in Table 1-1. Survival follow up should continue for all participants until the end of study (EOS).

At the end of the Treatment Phase, participants considered to be still deriving benefit from treatment may be eligible for post-trial access to continued treatment. For information on post-trial access please refer to Section 6.7.1.

Optional TFR Phase

To enter the optional TFR Phase, participants will have [redacted] Participants must give consent to enter the optional TFR Phase. [redacted].

Participants stop taking study treatment on the day they enter the TFR Phase (Refer to Section 1.3). The duration of the TFR Phase will be [redacted] unless there is a loss of

MMR (BCR:ABL1 IS >0.1%). During the TFR Phase, BCR::ABL1 IS levels are monitored every 4 weeks by RQ-PCR for the first 24 weeks, then every 8 weeks for the next 24 weeks, and then every 12 weeks thereafter.

For loss of MR4.0 (BCR::ABL1 IS >0.01%) but no loss of MMR after week 24 during the TFR Phase, assessment frequency will be increased to every 4 weeks until BCR::ABL1 IS levels return to a range between MR4 and MR4.5. If BCR::ABL1 IS levels remain between MMR and MR4 for 4 consecutive measurements (16 weeks from initial loss of MR4.0), assessments can reduce to prior frequency, and no less than every 12 weeks.

In case of a pregnancy during the TFR Phase, the pregnant woman can stay in the TFR Phase as long as no asciminib/nilotinib treatment is needed, but must be discontinued from the study upon loss of MMR. BCR::ABL1 IS levels should be monitored every 4 weeks for the duration of the pregnancy.

The TFR Phase lasts until CCI [redacted] or until the participant experiences disease progression, death, lost to follow-up and/or discontinuation at the discretion of the investigator or withdrawal of consent, whichever is sooner.

Participants who discontinue the TFR Phase due to any reason will return for an end of treatment (TFR END) visit. For those not entering TRI Phase, a safety follow up visit/call will be performed approximately 30 days after end of TFR (TFR END) visit, and survival follow up should continue for all participants until the end of study (EOS).

Participants who are still in TFR CCI [redacted] will be referred to their physician for continued BCR::ABL1 IS monitoring.

Concurrent participation in another clinical trial that involves investigational therapy is not permitted at any time during this study.

Treatment Re-initiation (TRI) Phase

Loss of MMR at any time during the TFR Phase (where loss of MMR in the TFR Phase is defined as CCI [redacted] at a Novartis designated laboratory) requires study treatment re-initiation in the TRI Phase within 4 weeks.

CCI [redacted]

Participants who have re-initiated treatment are monitored for BCR::ABL1 IS levels every 4 weeks for the first 24 weeks, then every 12 weeks thereafter. Participants not re-achieving MMR by 24 weeks should continue monthly (every 4 weeks) monitoring until MMR is re-achieved. Additional mutational analysis may be performed as clinically indicated. For treatment discontinuation requirements and treatment failure criteria refer to Section 7.1.

CCI [redacted] or until EOS (whichever is the latest), or until the participant experiences unacceptable toxicity, treatment failure, disease progression, death, lost to follow-up and/or treatment is discontinued

at the discretion of the investigator or withdrawal. The duration of TRI Phase for a given participant may be longer than CCI depending on when the participant entered the TRI Phase. For EOS refer to Section 4.7.

Participants who discontinue the TRI Phase due to any reason will return for an end of treatment re-initiation (TRI END) visit. A safety follow up visit/call will be performed approximately 30 days after end of re-initiation visit. Survival follow up should continue for all participants until the end of study (EOS).

At the end of the re-initiation phase, participants considered to be still deriving benefit from treatment may be eligible for post-trial access to continued treatment. For information on post-trial access please refer to Section 6.7.1.

4.2 Scientific rationale for study design

The proposed study CABL001J12302 is a phase IIIb, multi-center, open-label, randomized study of oral asciminib versus nilotinib in adult patients with CML-CP. This patient population includes adult patients ≥18 years of age with newly diagnosed CML-CP enrolled within 3 months of initial diagnosis. The study will include patients with a documented diagnosis of CML-CP as per ELN management recommendations (Baccarani et al 2013). Participants could have received treatment with hydroxyurea and/or anagrelide for disease control following initial diagnosis, but treatment with any TKIs prior to randomization is not allowed. The inclusion and exclusion criteria are expected to support enrollment of a patient population representative of adult patients with newly diagnosed CML-CP while maintaining adequate safeguards for patient safety in view of the experimental nature of the study.

In this trial, the tolerability of asciminib will be assessed versus the tolerability of nilotinib through the impact on treatment discontinuations due to AE. Randomization will be done 1:1 between asciminib and nilotinib. The estimated sample size of the study is approximately 550 participants.

The randomized active comparator design, comparing asciminib with nilotinib, a registered first line treatment for CML, minimizes the risk of operational bias and provides a rigorous tool to appropriately assess the tolerability, efficacy and safety of asciminib vs nilotinib in this patient population.

Randomization will be stratified by EUTOS long-term survival (ELTS) risk group (low versus intermediate versus high). ELTS score is a predictive and prognostic score used to estimate the progression and survival risk in newly diagnosed patients with CML-CP. Similar to the historically used Sokal score, ELTS score also uses hematologic data, spleen size, and age, but is focused on CML–specific Overall Survival (OS) by reducing the negative prognostic value of age as applicable to TKIs. The ELTS score has been validated in several studies for its ability to significantly discriminate risk groups regarding long-term survival outcome and has been shown to provide better prognostic discrimination than Sokal, Hasford (Euro) or EUTOS score in CML (Pfirrmann 2020, Geelen 2018, Castagnetti 2018). The ELN recommendations and National Comprehensive Cancer Network (NCCN) treatment guidelines recommend the use of the ELTS score as the preferred method to assess baseline CML risk and thus to inform the first-line treatment decisions for newly diagnosed patients with CML-CP (Hochhaus et al 2020, NCCN CML treatment guidelines V3.2022).

The randomization by this stratification factor will help achieve a balance across the treatment arms for the possible prognostic factors, comorbidities and baseline disease characteristics presented by patients.

As the study's purpose is to focus on patient relevant outcomes, the primary endpoint of the study is the **time to discontinuation of study treatment due to adverse event (TTDAE).**

The study will be conducted as an open label study. A double blind approach was not taken as it was not feasible to conduct this study in a double-dummy fashion. The requirements of dose administration in relation to food and frequency of dosing are distinct for the two treatments (Section 6.1.1). Blinding would be very complex and increase the likelihood of dosing errors.

CCI [redacted]

Eligible participants for the optional TFR Phase will have a CCI [redacted]

Increased frequency of BCR::ABL1 level IS monitoring is in line with international guidance during the TFR Phase (ELN and NCCN), in addition to entry into the Re-Initiation phase required within one month of loss of MMR (NCCN). CCI [redacted] (Kantarjian et al 2021).

In conclusion, the proposed study design is appropriate to address the principal scientific question.

4.3 Justification for dose

The investigational arm of study CABL001J12302 will evaluate asciminib at a continuous dose of 80 mg once-daily (QD).

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

The asciminib dose of 80 mg QD for patients with newly diagnosed CML-CP is based on the clinical experience at a wide range of doses in studies CABL001X2101 and CABL001A2301

and the subsequent PK/Pharmacodynamic (PD) modelling based exposure-response and exposure-safety analyses that showed wide therapeutic range and similarity of response and safety for asciminib 40 mg BID and 80 mg QD.

Clinical experience with asciminib single agent 80 mg total daily dose

Study CABL001X2101

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

As of the cut-off date of 02-Apr-2020, study CABL001X2101 had enrolled 200 CML-CP/AP patients treated with single agent asciminib, where 53 (26.5%) patients were treated with a total daily dose of 80 mg and 132 (66%) patients were treated with a total daily dose higher than 80 mg. Data with asciminib single agent total daily dose of 80 mg and higher than 80 mg from study CABL001X2101 was analyzed to determine the efficacy and safety profile for asciminib across dose levels. The median duration of exposure to study treatment was 124.6 weeks (min-max: 0-302) and 123 (61.5%) patients are still on treatment.

In study CABL001X2101 asciminib was well tolerated and its safety profile was similar across all doses explored; and no particular safety findings were observed for any specific dose level or regimen (QD/BID) (See Section 2.1.1.1 for further details).

Study CABL001A2301

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

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

The study met its primary objective: asciminib 40 mg BID was superior compared to bosutinib 500 mg QD, as demonstrated by the MMR rate at 24 weeks; the study showed significantly improved efficacy with favorable safety and tolerability of asciminib as compared to bosutinib in CML-CP patients treated with at least 2 prior TKIs. (See Section 2.1.1 for further details).

Exposure-safety and exposure-efficacy analyses

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

BID to 200 mg BID, 80 mg QD, 120 mg QD and 200 mg QD, and for whom PK data was available (N=353 for safety and N=303 for efficacy).

Simulated CCI [redacted] respectively. However, this difference in Cmax and Ctrough is not considered as clinically relevant given the large therapeutic window of asciminib.

The exposure-safety analyses were based on PK-safety set included 199 participants from study CABL001X2101 and 154 participants from study CABL001A2301. The exposure-safety relationship was explored using various safety endpoints such as laboratory and vital signs abnormalities and AEs. The exposure metrics were based on daily predictions of AUC, Cmax and Cmin from the population PK model and a 5-day-average prior to safety event. In all safety endpoints analyzed (except Grade 2 or Higher Aspartate Aminotransferase (AST) increase), no significant relationship was found between probability of safety events and increase in exposure within the range of dose levels and regimens investigated. For Grade 2 or higher AST increase, the increase in the probability of an event due to exposure was very small; for example, the increase was from 0.1% to 0.3% in study CABL001A2301 for a 5-fold increase in exposure. Regarding dose reduction due to an AE, it was found that the time to first such events was not associated with increasing exposure. Finally, analysis of change from baseline in serum creatinine was also found to be independent of exposure. In summary, asciminib has a similar safety profile across all dose regimens (and associated asciminib exposure) whether at 40 mg BID, 80 mg QD or 200 mg BID. The amount of safety data obtained at asciminib 80 mg QD may be considered small, however, the small sample size at the 80 mg QD dose (N=18) is more than counterbalanced by the total amount of data at 80mg QD and higher total daily doses (N=150) with records collected over several years of treatment. Despite the increase in Cmax (by about 60% based on PopPK) with the 80 mg QD compared to that of the 40 mg BID, in view of the lack of association between the chance of AEs with increasing exposure (by 5-fold), the 80 mg QD regimen was considered to have a similar safety profile to that of 40 mg BID.

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

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

Participant benefit

In the study CABL001J12302, in view of decreasing participants burden and increasing compliance in the first line setting, a once-daily (QD) dose of asciminib 80 mg will be evaluated. As presented above, the safety and efficacy of 80 mg QD is not expected to differ from the 40 mg BID dose that was tested in study CABL001A2301 in patients with CML-CP who received at least 2 prior ATP-binding site TKIs. Furthermore, this is consistent with the 80mg QD dose studied in the CABL001J12301, which is the primary efficacy study of asciminib in first line, run in parallel.

A twice-daily intake under fasting conditions poses practical challenges for many patients with regard to managing their daily meals and schedules, and it may impact treatment adherence and long-term compliance. According to Geissler et al 2017, 35.8% of patients taking their medication once-daily were highly adherent, whereas patients taking their medication twice-daily were highly adherent only in 24.9% of patients and 26.7% were in the low adherence group. Consequently, QD dosing is likely to be associated with better adherence and patient convenience.

On 29-Oct-2021, the US FDA granted approval of asciminib (Scemblix) for the use in adult patients with CML-CP previously treated with 2 or more TKIs with a recommended asciminib dosage for these patients of either 80 mg QD or 40 mg BID. Scemblix has also been approved for the treatment of CML-CP in adult patients previously treated with 2 or more TKIs in Canada, the EU, Japan, Switzerland, and the UK amongst other countries.

In conclusion, based on the current efficacy and safety data available, safety-exposure and efficacy–exposure analyses, and in line with the approved label in the US and elsewhere for ≥3rd line CML-CP, asciminib 80 mg QD has been selected as the dose and regimen to be used in this phase IIIb study. Additionally, the once daily regimen is patient-centric and is likely to support better patient adherence to treatment in this patient population.

4.4 Rationale for choice of comparator

The comparator arm for this study is nilotinib. The approved dose of nilotinib is 300 mg BID in first-line treatment of CML patients in chronic phase.

The ENESTnd trial (Hochhaus et al 2016) compared nilotinib, 300 mg BID, with imatinib, 400 mg QD, now with a minimum follow-up of 10 year (Hughes et al 2021) Following nilotinib treatment, the 5- and 10-year cumulative probabilities for achieving MMR were 77% and 82.6%, MR4 (66% and 73%) and MR4.5 (54% and 64%), respectively (Kantarjian et al 2021). Although these results were significantly better than with imatinib, nevertheless 5- and 10-year overall survival (OS) were similar (94% vs. 92% and 87.6% vs. 88.3%, respectively). The rates of changing primary treatment were 40% for nilotinib and 50% for imatinib. Similar results have been reported in other company sponsored (Hochhaus et al 2016) and academic studies.

Nilotinib is registered as treatment of newly diagnosed CML patients in many countries in Europe, Asia, North and South America and it is mentioned as one of the first line CML therapy options in the ELN recommendations (Hochhaus et al 2020). With its high utilization in newly diagnosed CML patients, as recent Europe market data on the TKI use in CML indicates, nilotinib is deemed a suitable comparator for asciminib in this study.

4.5 Purpose and timing of interim analyses

One formal interim analysis is planned when approximately CCI discontinuation of study treatment due to AE events have occurred. The purpose of this interim analysis is to allow for an early assessment of the tolerability of asciminib. The study will continue regardless of the outcome of the interim analysis, and the results of the interim analysis will not lead to any change in the design or conduct of the study. If the interim analysis results are significant such that the p-value of cause-specific hazard testing between asciminib and nilotinib arm is less than the pre-specified alpha level 0.004, an interim CSR will be produced. Following the interim analysis, the study will continue as planned to the primary analysis (approximately CCI events) and a CSR will be produced at the end of study. Additional information is presented in Section 9.8.

4.6 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster), mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis and permitted/approved by local or regional health authorities and ethics committees (as appropriate) prior to implementation of mitigation procedures.

At the Investigator's discretion and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial assessment/procedures according to Table 1-1 Schedule of Activities performed at a remote location in the event of a public health emergency.

Assessment/procedures will be performed remotely under the oversight of the Investigator, who retains accountability for the oversight. The Investigator retains accountability for all efficacy and safety decisions with delegation of tasks to an off-site healthcare professional.

The remote procedures may be utilized in certain countries and sites based on national and local/site regulations.

Off-site healthcare professionals may be provided by a third-party vendor sourced by Novartis. Where a site wishes to use off-site healthcare professionals that are not provided by Novartis this must be agreed with Novartis before use.

In addition to procedures performed by the off-site healthcare professional, the on-site staff might perform certain procedures remotely (i.e. a phone call or tele-visits). For details on dispatch of study treatment during a public health emergency please refer to Section 6-2.

4.7 End of study definition

End of study (EOS, global LPLV) is defined as when the latest of the following events has occurred:

- The participants in the Treatment Phase who did not enter the optional TFR Phase have either completed CCI of treatment or discontinued prematurely, and completed 30 day post-treatment Safety Follow Up.

- The participants who entered the TFR Phase have either completed CCI of TFR Phase or discontinued prematurely and completed 30 day Safety Follow Up, or re-initiated treatment in the TRI Phase
- The last participant in the TRI Phase has either completed CCI of treatment or discontinued prematurely, and completed 30 day post-treatment Safety Follow Up.

Any repeat assessments associated with the EOT/TFR END/TRI END visit must be documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

For information on post-trial access please refer to Section 6.7.1.

Refer to Section 4 for additional details about the study design.

5 Study population

This study will randomize approximately 550 adult participants (≥18 years of age) with newly diagnosed CML-CP (diagnosed within 3 months prior to enrollment) in a 1:1 fashion to receive either asciminib or nilotinib.

The definition of CML-CP will be according to the ELN criteria (Baccarani et al 2013) and is outlined below in the inclusion criteria.

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

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study.
2. Male or female patients ≥ 18 years of age.
3. Patients with CML-CP within 3 months of diagnosis.
4. Diagnosis of CML-CP (ELN 2020 criteria) with cytogenetic confirmation of the Philadelphia (Ph) chromosome. A cryptic Ph chromosome should be confirmed by metaphase Fluorescence In Situ Hybridization (FISH).
    - Documented chronic phase CML will meet all the below criteria (Baccarani et al 2013):
        - < 15% blasts in peripheral blood and bone marrow,
        - < 30% blasts plus promyelocytes in peripheral blood and bone marrow,
        - < 20% basophils in the peripheral blood,
        - PLT count ≥ 100 x 10^9/L (≥ 100,000/mm3),
        - No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly.
5. Evidence of typical *BCR::ABL1* transcript [e14a2 and/or e13a2] which is amenable to standardized RQ-PCR quantification by the central laboratory assessment. However, if a local qualitative assay, validated according to local regulation, from an accredited local laboratory has confirmed evidence of typical *BCR::ABL1* transcript [e14a2 and/or e13a2],

these results can be used for eligibility if the central RQ-PCR are not available at the time of randomization.

6. ECOG performance status of 0 or 1.
7. Adequate end organ function as defined by:
   - Total bilirubin (TBL) < 3 x ULN; patients with Gilbert's syndrome may only be included if TBL ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN,
   - CrCl ≥ 30 mL/min as calculated using Cockcroft-Gault formula, Serum lipase ≤ 1.5 x ULN. For serum lipase > ULN - ≤ 1.5 x ULN, value must be considered not clinically significant and not associated with risk factors for acute pancreatitis.
8. Patients must have the following laboratory values within normal limits or corrected to within normal limits with supplements prior to randomization:
   - Potassium (potassium increase of up to 6.0 mmol/L is acceptable if associated with CrCl* ≥ 90 mL/min),**
   - Total calcium (corrected for serum albumin); (calcium increase of up to 12.5 mg/dl or 3.1 mmol/L is acceptable if associated with CrCl* ≥ 90 mL/min),
   - Magnesium (magnesium increase of up to 3.0 mg/dL or 1.23 mmol/L if associated with CrCl* ≥ 90 mL/min),
   - For patients with mild to moderate renal impairment (CrCl* ≥ 30 mL/min and <90 mL/min) - potassium, total calcium (corrected for serum albumin) and magnesium should be within normal limits or corrected to within normal limits with supplements prior to randomization.

     *CrCl as calculated using Cockcroft-Gault formula.

     ** Pseudohyperkaliemia in case of thrombocytosis is not an exclusion criterion.

5.1.1 Inclusion criteria for optional TFR Phase

Participants eligible for inclusion in this optional TFR Phase must additionally meet **all** of the following criteria at TFR baseline:

1. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures
2. 

3.
4. Separate signed informed consent must be obtained prior to participation in the TFR Phase.

5.2 Exclusion criteria

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

1. Previous treatment of CML with any other anticancer agents including chemotherapy and/or biologic agents or prior stem cell transplant, with the exception of hydroxyurea and/or anagrelide.
2. Known cytopathologically confirmed CNS infiltration (in absence of suspicion of CNS involvement, lumbar puncture not required).
3. Impaired cardiac function or cardiac repolarization abnormality including but not limited to any one of the following:
   - History of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG) within 6 months prior to starting study treatment.
   - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block).
   - QTcF $\geq$ 450 ms on the average of three serial baseline ECG (using the QTcF formula). If QTcF $\geq$ 450 ms and electrolytes are not within normal ranges, electrolytes should be corrected and then the patient re-screened for QTcF.
   - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
     - Risk factors for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia.
     - Concomitant medication(s) with a "Known risk of Torsades de Pointes" per crediblemeds.org that cannot be discontinued or replaced 7 days prior to starting study treatment by safe alternative medication.
     - Inability to determine the QTcF interval.
4. Severe and/or uncontrolled concurrent medical disease that in the opinion of the Investigator could cause unacceptable safety risks or compromise compliance with the protocol (e.g. uncontrolled diabetes, active or uncontrolled infection; uncontrolled arterial or pulmonary hypertension, uncontrolled clinically significant hyperlipidemia).
5. History of significant congenital or acquired bleeding disorder unrelated to cancer.
6. Major surgery within 4 weeks prior to study entry or patients who have not recovered from prior surgery.
7. History of other active malignancy within 3 years prior to study entry with the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively.
8. History of acute pancreatitis within 1 year prior to randomization or medical history of chronic pancreatitis.
9. History of chronic liver disease leading to severe hepatic impairment, or ongoing acute liver disease.

10. Known history of chronic Hepatitis B (HBV), or chronic Hepatitis C (HCV) infection. Testing for Hepatitis B surface antigen (HBs Ag) and Hepatitis B core antibody (HBc Ab/anti HBc) will be performed at screening. If anti-HBc is positive, HBV-DNA evaluation will be carried out at screening. A patient having positive HBV-DNA will not be enrolled in the study. Also, a patient with positive HBsAg will not be enrolled in the study. HCV Ab testing will also be performed at screening. For details on the criteria see Appendix 4.
11. History of Human Immunodeficiency Virus (HIV) unless well-controlled on a stable dose of anti-retroviral therapy at the time of screening.
12. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study treatment (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or gastric bypass surgery).
13. Participation in a prior investigational study within 30 days prior to randomization or within 5 half-lives of the investigational product, whichever is longer.
14. Pregnant or nursing (lactating) women
15. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment and for a period of time after stopping study medication. For asciminib, this period of time is 3 days after last dose; if local regulations or locally approved prescribing information differ from the protocol required duration of contraception, the longer duration must be followed and the same requirements will be described in the ICF. Participants taking nilotinib should be willing to follow contraception requirements in the locally-applicable prescribing information for nilotinib.

Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or total hysterectomy or bilateral salpingectomy, at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male partner's sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant
- Use of oral, (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate history of vasomotor symptoms). Women are considered not of child bearing potential if they are post-menopausal

or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral salpingectomy at least six weeks prior to enrollment on the study. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered to be not of child bearing potential.

Sexually active males taking study treatment do not require contraception.

16. Known hypersensitivity to the study treatment.

Note: The Investigator has the discretion to include/exclude a patient in the study, who will be found to have symptoms representative of COVID-19 or tested positive for COVID-19 during the screening phase. Such patients should be managed as per the country specific guidelines related to COVID-19. For patients who test positive for COVID-19, re-testing is recommended before initiating study treatment.

5.2.1 Exclusion criteria for TFR Phase

Participants meeting any of the following additional criteria are not eligible for inclusion in optional TFR Phase:

1. CCI [redacted]

5.2.2 Exclusion criteria for Treatment Re-initiation (TRI) Phase

Participants meeting any of the following additional criteria are not eligible to enter the TRI Phase:

1. In case of a pregnancy during the TFR Phase, the pregnant woman **must** be discontinued from the study upon loss of MMR CCI [redacted] and cannot enter the TRI Phase

5.3 Screen failures

Participants who sign an informed consent form and are subsequently found to be ineligible prior to randomization will be considered as screen failures. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening period (see SAE section for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized. Data and samples collected from participants prior to screen failure may still be analyzed. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

Re-screening is allowed once for participants that were initially screen failures for reasons which are amenable to correction, such as abnormal laboratory values and/ or concurrent medical conditions after reaching an adequate level of control. All eligibility criteria must be re-checked and met prior to enrollment of the participant into the study. A new ICF will need

to be signed if the Investigator chooses to re-screen the participant, and the participant will be assigned a new subject number.

5.4 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned within the Electronic Data Capture (EDC) system when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent screening if the participant is rescreened. The Participant No. consists of the Site Number (Site No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

Once assigned, the subject No. must not be reused for any other participant**.**

6 Study treatment(s) and concomitant therapy

6.1 Study treatment(s) (Treatment Phase and TRI Phase)

The study treatment is either asciminib (80 mg QD) or nilotinib (300 mg BID).

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

Nilotinib could be considered as Investigational Medicinal Product (IMP) depending on local regulations.

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

6.1.1 Investigational and comparator drugs

Table 6-1 Investigational and comparator drugs

Treatment Title	Asciminib (ABL001)	Nilotinib (AMN107)
80 mg tablet QD administered under fasting conditions		300 mg capsule BID (total daily dose of 600 mg) administered under fasting conditions
Type	Drug	Drug
Dose Formulation	Tablet	Capsule
Unit Dose Strength(s)	40mg	50 mg, 150 mg, 200 mg
Dosage Level(s)	80 mg QD	300 mg BID (total daily dose of 600 mg)
Route of Administration	Oral	Oral
Use	Experimental	Active comparator
IMP	Yes	Yes
Sourcing	Global	Global or Local
Packaging and Labeling	Study treatment will be provided in bottles. Each bottle will be labeled as	Study treatment will be provided in bottles. Each bottle will be labeled as

Treatment Title	Asciminib (ABL001)	Nilotinib (AMN107)
	required per country requirement. Open-label packs.	required per country requirement. Open-label packs

6.1.2 Additional study treatments

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

6.1.3 Treatment arms

Participants will be assigned at Baseline/ Day 1 to one of the following 2 treatment arms in a ratio of 1:1:

- Arm 1: Asciminib 80 mg QD administered under fasting conditions
- Arm 2: Nilotinib 300 mg BID (total daily dose of 600 mg) administered under fasting conditions

6.1.4 Guidelines for continuation of treatment

Please refer to Section 6.5.2 for follow-up for toxicities.

6.1.5 Treatment duration

During the Treatment Phase, all participants will receive treatment for CCI [redacted]. The treatment will continue until the participant CCI [redacted], or experiences unacceptable toxicity, disease progression, death, lost to follow-up and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent.

Participants with loss of MMR during the TFR Phase will re-initiate asciminib/nilotinib treatment in the Re-initiation Phase within 4 weeks. CCI [redacted] or until EOS (whichever is latest) or until unacceptable toxicity, disease progression, death, lost to follow-up and/or the treatment is discontinued at the discretion of the investigator or withdrawal of consent.

CCI [redacted]

Upon Treatment reinitiation, refer to Section 6.5 for guidance on dose reduction/escalation.

See Section 6.7 for information on continued access to study treatment after the end of the study.

6.1.5.1 Treatment beyond disease progression

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

6.2 Preparation, handling, storage, and accountability

Asciminib (investigational drug):

The Investigator or responsible site personnel must instruct the participant or caregiver to take the investigational drug as per protocol.

Investigational drug will be dispensed to the participant by authorized site personnel only. All dosages prescribed to the participant and all dose changes during the study must be recorded on the appropriate eCRF.

Each study site will be supplied with asciminib in packaging as described under Table 6-1 investigational and comparator drugs section. The investigational drug, asciminib, will be provided as global clinical open-label supply and will be packed and labeled under the responsibility of Novartis Global Clinical Supply (GCS).

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

Nilotinib:

Nilotinib will be provided by Novartis. Sourcing of nilotinib by Novartis can be either through clinical supply or local commercial supply. Clinical supply will be provided globally through Global Clinical Supply and labeled as per local regulations. Local commercial supply will be sourced in the country where appropriate and as per local regulations. If nilotinib is sourced through local commercial supply, drug will be labeled in-country and the locally approved form and packaging of nilotinib will be used.

All participants:

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of study treatment directly to a participant's home may be permitted (if allowed by local or regional health authorities and ethics committees, as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of study treatment from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be dispensed according to the Schedule of Assessments (Table 1-1, Table 1-3). In this case, regular phone calls or virtual contacts (every 4 weeks until 12 weeks, then every 12 weeks or more frequently if needed) as needed will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

6.2.1 Handling of study treatment

Investigational drug and comparator must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, all investigational drug and comparator must be stored according to the instructions specified in the Asciminib Investigator's Brochure or label for nilotinib.

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

In the event of a public health emergency, the treatment for remote administration will be shipped from the pharmacy to the participants' home in accordance with the local practice.

Asciminib

Investigational drug is to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance. Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The Investigator or designated site staff must maintain an accurate record of the shipment and dispensing of investigational drug in a drug accountability log. Monitoring of investigational drug accountability will be performed by monitors during site visits and at the completion of the trial.

The site may destroy and document destruction of unused investigational drug, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the Investigator will return all unused investigational drug, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

Nilotinib

The handling of nilotinib should follow the current applicable local label.

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

6.2.2 Instruction for prescribing and taking study treatment

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

Investigational drug labels will comply with the legal requirements of each country and will include storage conditions and a unique medication number (corresponding to investigational drug and strength).

Dose and treatment schedule are described in Table 6-1 and all the information about the administration of the investigational drug are described in the Section 6.1.3 and Section 6.2. Dose reductions can be performed as described in Section 6.5.

At the Baseline/Day 1 visit the participants will be randomized into one of the 2 treatment arms (stratified by ELTS score at diagnosis, prior to treatment with hydroxyurea (if applicable)), and the responsible site personnel will identify the investigational drug package(s) to dispense by the medication number(s) assigned by IRT to the participant if the participant is randomized to asciminib.

Asciminib arm:

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

- Participants should take asciminib daily at approximately the same time each day in the morning.
- Participants should take asciminib on an empty stomach. No food should be consumed for two hours before and at least one hour after the dose is taken. Each dose may be taken with a glass of water, approximately 240 mL (8 ounces) of water.
- Participants should be instructed to swallow whole tablets and not to chew or to break them.
- If vomiting occurs during the first hour after taking the drug, re-dosing is allowed before the next scheduled dose.
- If the participant does not take asciminib within 12 hours after the usual dosing time, that dose should be skipped and treatment should continue with the next daily dose at the prescribed level.

All kits of investigational drug will be recorded in the IRT system.

Nilotinib arm:

Nilotinib should be taken twice daily approximately 12 hours apart and must not be taken with food. The hard capsules should be swallowed whole with water. No food should be consumed for 2 hours before the dose is taken and no food should be consumed for at least one hour after the dose is taken.

For participants who are unable to swallow hard capsules, the content of each hard capsule may be dispersed in one teaspoon of apple sauce (puréed apple) and should be taken immediately. No more than one teaspoon of apple sauce and no food other than apple sauce must be used (Nilotinib SmPC).

Dosages for nilotinib prescribed and dispensed to the participants and all dose changes during the study must be recorded on the appropriate eCRF. Nilotinib batch number and expiry should be captured in IRT.

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Treatment assignment, randomization

In this randomized, open label trial, participants will be randomized in a 1:1 ratio to one of the two treatment arms. Randomization will be stratified based on the participant's ELTS score (low versus intermediate versus high). The score assessed at diagnosis prior to treatment with hydroxyurea (if applicable) will be recorded at screening. The score will be calculated using the European LeukemiaNet calculator available at //.leukemia net.org/leukemias/cml/elts_score/

Prior to dosing all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The Investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm. Where applicable, IRT will specify a unique medication number for the package of asciminib and nilotinib to be dispensed to the participant. The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and Investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers for asciminib. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing only the asciminib and nilotinib packaged and labelled by global sponsor.

6.3.2 Treatment blinding

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

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

6.4 Study treatment compliance

The Investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the Investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the Investigator and/or study personnel at each visit using tablet/capsule counts (if applicable) and information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log. Total daily dose of

study treatment administered with start and end date will be collected on the dedicated eCRF page.

Remote treatment administration compliance will be assessed by the off-site healthcare professional, and information provided to the Investigator and/or study personnel (as per Section 4.5).

6.5 Dose modification

Asciminib: The investigational arm of study CABL001J12302 will evaluate asciminib at a dose of 80 mg once-daily (QD). Dose escalation beyond 80 mg QD for asciminib is ***not permitted***.

Nilotinib: The prescribed dose for nilotinib is 300 mg BID (total daily dose of 600 mg). Dose escalation beyond 300 mg BID for nilotinib is ***not permitted***.

No crossover of study treatment across arms is allowed during the Treatment Phase.

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

Dose modifications are summarized in Table 6-2. The dose reduction indicated as "recommendations" are provided to assist Investigators in the event the participant experiences toxicity. However, deviations from "mandatory" dose interruptions and/or reductions are not allowed and mandatory interruptions or reductions must be strictly followed. Participants in the nilotinib arm who require a dose reduction may require a new capsule strength in order to appropriately reduce their dose and this should be done at the earliest opportunity. Re-escalation to asciminib 80 mg QD and/or nilotinib 300 mg BID respectively is permitted if a change in the participant's individual benefit/risk assessment at the lower dose level is seen. Re-escalation will be allowed only once for any specific event for any participant per protocol. Further re-escalation to a maximum of 80 mg QD (asciminib) or 300 mg BID (nilotinib) may be allowed in case the event is considered to be significantly different than the one(s) experienced previously and must be based on discussion with and approval by the Novartis medical monitor. Input from the study steering committee, may be sought if required Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-2.

These dose changes must be recorded on the appropriate eCRF.

A participant must discontinue treatment with study treatment if, after treatment is resumed at a lower dose level, the toxicity recurs with the same or worse severity, except for recurrence of cytopenias (Table 6-2). If a participant requires a dose interruption more than 28 days for a non-hematologic toxicity, then the participant must be discontinued from study treatment. If a hematologic toxicity (cytopenia Grade 3 or 4) lasts for more than 42 days without recovery to at least a Grade 2, despite the dose interruption and adequate management (including hematopoietic growth factors), then the participant must be discontinued from the study treatment. Permanent discontinuation will indicate an event that will be counted for the primary endpoint TTDAE.

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

Dose modifications for asciminib and nilotinib	
Worst toxicity CTCAE Grade (version 5)[a]	**Required action**
Investigations (Hematologic) **If a hematologic toxicity (cytopenia Grade 3 or 4) lasts for more than 42 days without recovery to at least a Grade 2, despite the study treatment interruption and adequate management (including hematopoietic growth factors), then the participant must be discontinued from the study treatment.**	
Neutropenia (ANC)	
Grade 1 (ANC < LLN – 1.5 x 10^9/L)	**Recommendation**: Maintain dose level
Grade 2 (ANC < 1.5 – 1.0 x 10^9/L)	**Recommendation**: Maintain dose level
Grade 3 (ANC < 1.0 – 0.5 x 10^9/L)	**Mandatory**: Omit dose until resolved to ≤ Grade 2, (recheck Complete Blood Count (CBC) 2x/week), then: if resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, then reduce dose ↓1 dose level
Grade 4 (ANC < 0.5 x 10^9/L)	**Mandatory**: Omit dose until resolved to ≤ Grade 2, (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, then reduce dose ↓1 dose level
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	**Mandatory**: Omit dose until resolved, then ↓ 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN – 75 x 10^9/L)	**Recommendation**: maintain dose level
Grade 2 (PLT < 75- 50 x 10^9/L)	**Recommendation**: maintain dose level
Grade 3 (PLT < 50 – 25 x 10^9/L)	**Mandatory**: Omit dose until resolved to ≤ Grade 2, (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, then reduce dose ↓1 dose level
Grade 4 (PLT < 25 x 10^9/L)	**Mandatory**: Omit dose until resolved to ≤ Grade 2, (recheck CBC 2x/week), then: if resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, then reduce dose ↓1 dose level
Recurrence of all cytopenias	**Recommendation**: Omit dose until resolved to ≤ Grade 2, then maintain current dose level.
Non-hematologic adverse reactions except where further specified in individual sections	
Grade 1	**Recommendation:** Maintain dose level
Grade 2	**Recommendation:** Omit dose until resolved to ≤ Grade 1, then maintain dose level
Grade 3	**Mandatory:** Omit dose until resolved to ≤ Grade 1, then reduce dose ↓ 1 dose level
Grade 4	**Mandatory:** Permanently discontinue participant from study treatment
Investigations (Renal)	
Serum creatinine	
>ULN – 1.5 x ULN	**Recommendation**: maintain dose level
>1.5 – 3.0 x baseline; > 1.5 – 3.0 x ULN	**Recommendation**: Omit dose until resolved to ≤ 1.5 x ULN or baseline, then maintain dose level
>3.0 x baseline; > 3.0 – 6.0 x ULN	**Mandatory**: Permanently discontinue participant from study treatment

Dose modifications for asciminib and nilotinib	
> 6.0 x ULN	**Mandatory**: Permanently discontinue participant from study treatment
Investigations (Hepatic)	
Isolated TBL elevation	
> ULN – 1.5 x ULN irrespective of baseline levels	**Recommendation**: Maintain dose level
> 1.5 – 3.0 x ULN irrespective of baseline levels	**Recommendation:** Omit dose. Repeat liver tests[b] within 48-72 hours, then monitor weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN or baseline: if resolved in ≤ 14 days, then maintain dose level if resolved in > 14 days, then reduce dose ↓1 dose level
> 3.0 – 10.0 x ULN irrespective of baseline levels	**Mandatory:** Omit dose. Repeat liver tests within 48-72 hrs then monitor weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN or baseline; if resolved in ≤ 14 days, then reduce dose ↓1 dose level; if resolved in > 14 days, then discontinue participant from study treatment. The participant should be monitored weekly (including liver tests[b]), or more frequently if clinically indicated, until TBL have resolved to baseline or stabilization over 4 weeks
> 10.0 x ULN irrespective of baseline levels	**Mandatory:** Permanently discontinue participant from study treatment. The participant should be monitored weekly (including liver tests[b]), or more frequently if clinically indicated, until TBL have resolved to baseline or stabilization over 4 weeks

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

Dose modifications for asciminib and nilotinib	
AND >2.0 x ULN **Note: For participants with Gilbert's syndrome, at least 2-fold increase in direct bilirubin.	
Investigation (metabolic)	
Asymptomatic amylase and/or lipase elevation	
> ULN – 1.5 x ULN	**Recommendation**: Maintain dose level, measure 2x per week
> 1.5 – 2.0 x ULN	**Recommendation**: Maintain dose level, measure 2x per week
> 2.0 – 5.0 x ULN	**Mandatory:** Omit dose until resolved < 1.5 x ULN If resolved: resume study treatment at reduced dose. If events reoccur at reduced dose, permanently discontinue study treatment. If not resolved: Permanently discontinue study treatment. Perform diagnostic tests to exclude pancreatitis.
>5.0 x ULN	**Mandatory:** Omit dose until resolved to ≤ 1.5 x ULN or baseline, then: If resolved in ≤ 7 days, then reduce dose ↓1 dose level. If resolved in > 7 days, then discontinue treatment and obtain appropriate imaging (i.e., Magnetic resonance imaging (MRI), CT scan or ultrasound).
> 5.0 x ULN and with signs or symptoms	**Mandatory**: Permanently discontinue participant from study treatment. Obtain appropriate imaging (i.e., MRI, Computed tomography (CT) scan or ultrasound).
Vascular disorders	
Hypertension	
Systolic BP 140-159 mm Hg or Diastolic BP 90-99 mm Hg	**Recommendation**: Maintain dose level. Initiate antihypertensive drug/ increase the dose of existing antihypertensive drug or change treatment plan as per Investigator's assessment
Systolic BP ≥160 mm Hg or Diastolic BP ≥100 mm Hg	**Mandatory**: Omit dose until resolved ≤ Grade 1/baseline, then reduce dose ↓ 1 dose level. Initiate anti-hypertensive drug/ increase the dose of existing anti-hypertensive drug or change treatment plan as per Investigator's assessment
CTCAE Grade 4	**Mandatory**: Permanently discontinue participant from study treatment
Cardiac	
LVEF < 45% as determined by locally read ECHOs	**Recommended:** For Grade 2 (asymptomatic, resting LVEF < 50 – 40%), close monitoring with a follow-up ECHO within 4 weeks is recommended. **Mandatory:** For Grade 3 events (symptomatic CHF responsive to intervention; LVEF < 40 – 20%) follow guidance for cardiac "other" described below. For Grade 4 (refractory CHF or poorly controlled; LVEF < 20%) Permanently discontinue participant from study drug treatment
Cardiac "other" (such as unstable angina)	
Grade 2	**Recommended:** Omit dose until resolved ≤ Grade 1/baseline, then reduce dose ↓ 1 dose level. If another recurrence is seen, discontinue. If recovery to ≤ Grade 1 is greater than 28 days, the participant must be discontinued from study treatment
Grade 3 and Grade 4	**Mandatory:** Permanently discontinue participant from study treatment
Gastro-intestinal	
Pancreatitis	
Grade 2 (enzyme elevations with radiologic findings for pancreatitis as	**Mandatory**: If radiologic findings, hold treatment until resolved to ≤ Grade 1 or baseline. If treatment delay is ≤ 21 days, then reduce dose ↓ 1 dose level.

Dose modifications for asciminib and nilotinib	
per CTCAE v5.0. For isolated increased enzymes please see table for asymptomatic amylase and/or lipase elevation)	If treatment delay > 21 days, discontinue treatment and keep monitoring with appropriate imaging (i.e., MRI, CT scan or ultrasound)**.
Grade ≥ 3	**Mandatory**: Permanently discontinue participant from study treatment. Obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).
Diarrhea* **	
Grade 1	**Recommendation**: Maintain dose level but, initiate anti-diarrhea treatment
Grade 2	**Recommendation:** Omit dose until resolved (initiate anti-diarrhea treatment) to ≤ grade 1, then maintain dose level. If diarrhea returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then reduce dose ↓ 1 dose level
Grade 3	**Recommendation**: Omit dose, initiate anti-diarrhea treatment and discontinue participant from study treatment
Grade 4	**Mandatory:** Initiate anti- diarrhea treatment and permanently discontinue participant from study treatment
Nausea/vomiting	
Grade 1	**Recommendation**: Maintain dose level but, may initiate anti-nausea treatment
Grade 2	**Recommendation**: Omit dose until resolved (initiate anti-nausea and other supportive treatment) to ≤ grade 1, then maintain dose level. If nausea/vomiting returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then reduce dose ↓ 1 dose level
Grade 3	**Mandatory**: Omit dose until resolved (initiate anti-nausea and other supportive treatment) to ≤ grade 1, then reduce dose ↓ 1 dose level. Recommendation: Omit dose for ≥ grade 3 vomiting or grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic (as per local practice)
Grade 4	**Mandatory**: Permanently discontinue participant from study treatment.
Skin and subcutaneous tissue disorders	
Rash/photosensitivity	
Grade 1	**Recommendation**: Maintain dose level. Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
Grade 2	**Recommendation**: Maintain dose level, but initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
Grade 3, despite skin toxicity therapy	**Recommendation**: Omit dose until resolved to Grade ≤ 1, then: If resolved in ≤ 7 days, reduce dose ↓ 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then discontinue participant from study treatment
Grade 4, despite skin toxicity therapy	**Mandatory**: Permanently discontinue participant from study treatment
General disorders and administration site conditions	
Fatigue/ Asthenia (General disorders and administration site conditions)	
Grade 1 or 2	**Recommendation**: Maintain dose level
Grade 3	**Recommendation**: Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then reduce dose ↓ 1 dose level
All dose modifications should be based on the worst preceding toxicity. [a] Common Toxicity Criteria for AEs (CTCAE Version 5.0).	

Dose modifications for asciminib and nilotinib
[b] Core liver tests consist of ALT, AST, TBL (fractionated [direct and indirect], if TBL > 2.0 x ULN), and alkaline phosphatase [c] "Combined" defined as TBL increase to the defined threshold concurrently with ALT/AST increase to the defined threshold. If combined elevations of AST or ALT and TBL do not meet the defined thresholds, please follow the instructions for isolated elevation of TBL and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omitted dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction. [d] "Cholestasis" defined as Alkaline Phosphatase (ALP) elevation (>2.0 xULN and R value <2) in participants without bone metastasis. Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury. * Note: If TBL > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g. review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the Investigator. ** Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, participants will be discontinued permanently from study treatment. *** Note: Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools, or overt diarrhea.

Table 6-3 Dose reduction steps for asciminib and nilotinib

Dose reduction*	Starting dose level – 0	Dose level – 1
Asciminib	Two 40 mg tablets QD (once daily) (total daily dose 80 mg)	One 40 mg tablet QD (total daily dose 40 mg)
Nilotinib	Two 150 mg capsules BID (twice daily) (total daily dose 600 mg)	Two 200 mg capsules QD (total daily dose 400 mg)

*Dose reduction should be based on the worst toxicity demonstrated at the last dose.

Asciminib dose reduction below a total daily dose of 40 mg is not allowed.

Nilotinib dose reduction below a total daily dose of 400 mg is not allowed.

6.5.1 Dose adjustments for QTcF prolongation

For participants treated with either asciminib or nilotinib:

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

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

- Assess the quality of the ECG recording and the QT value and repeat if needed.
- Interrupt study treatment until confirmed resolution of QTcF and as per dose reduction guidelines for non-hematological AEs.
- Determine serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study treatment.
- Review concomitant medication associated with QT prolongation, including drugs with a "Known," "Possible," or "Conditional risk of Torsades de Pointes" (refer to Table 10-1),

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

- Check the dosing schedule and treatment compliance.

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

- Interrupt study treatment
- Repeat ECG and confirm ECG diagnosis by a cardiologist
- If QTcF confirmed > 500 ms:
  - Correct electrolytes, eliminate culprit concomitant treatments, and identify and address clinical conditions that could potentially prolong the QT as per the ECG and QTc Clinical Safety Standards Guidelines.
  - Consult with a cardiologist (or qualified specialist)
  - Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 ms.

After resolution to ≤ 480 ms, consider re-introducing treatment with study treatment at reduced dose, and increase ECG monitoring for the next treatment(s), (e.g. pre-dose and 2 hours post dose after one week and two weeks of study treatment re-introduction):

- If QTcF remains ≤ 500 ms after dose reduction, continue planned ECG monitoring during subsequent treatment
- If QTcF recurs > 500 ms after dose reduction, discontinue participant from trial.

6.5.2 Follow-up for toxicities

Participants whose treatment is interrupted or permanently discontinued due to a study treatment related adverse event or clinically significant laboratory value should be followed up at least once a week for 4 weeks, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary. All participants must be followed up for AEs and SAEs for 30 days following the last dose of study treatment.

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

Participants with transaminase increase combined with total bilirubin increase may be indicative of potentially severe DILI and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

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

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

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

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

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

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

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

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

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

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

Disease	Assessment
Hepatitis A, B, C, E (HAV, HBV, HCV, HEV)	• IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Epstein-Barr Virus (EBV) infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total Immunoglobulin M (IgM), Immunoglobulin G (IgG), IgE, IgA
Alcoholic hepatitis	• Ethanol history, Gamma-glutamyl transferase (GGT), Mean Corpuscular Volume (MCV), CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.

Disease	Assessment
Wilson disease (if <40 yrs old)	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

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

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

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

6.6 Concomitant and other therapy

For participants treated with asciminib:

Anti-emetics

Use of anti-emetics is allowed. Prophylactic anti-emetics should be started only once the participant experiences nausea or vomiting, at the discretion of the Investigator. It is recommended that participants use drugs that do not cause QT prolongation. Please note that some anti-emetics have a known risk for Torsade de Pointes and should be used with caution (refer to Section 6.6.1.1 and Table 10-1).

Contraceptives

Hormonal contraceptives are allowed as contraception methods.

Anticoagulation agents

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

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

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

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

Drugs that affect gastric pH

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

6.6.1 Concomitant therapy

For all participants in the study:

The participant must notify the investigational site about any new medications he/she takes after Day 1. All medications, procedures, and significant non-drug therapies (including physical therapy, blood transfusions and vaccines) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms. All prior concomitant medications, antineoplastic surgery, chemotherapy, biologic, immunologic and radiation therapy must also be recorded in the appropriate eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the Investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

Chronic medication (as permitted by protocol and in accordance with the local label for nilotinib) should be maintained at the same dose and schedule throughout the study period, as medically feasible.

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

For participants in TFR Phase:

A polymyalgia-like syndrome of musculoskeletal and/or joint pain beginning the first weeks or months after TKI discontinuation has been reported in about 20–30% of patients (Radich et al 2021). In most patients the symptoms are mild and self-limited, but some patients may require temporary treatment with acetaminophen or nonsteroidal anti-inflammatory drugs. In some instances a short course of oral corticosteroids may be required. All adverse events, medications,

procedures, and significant non-drug therapies must continue to be recorded on the appropriate Case Report Forms during the TFR Phase.

6.6.1.1 Permitted concomitant therapy requiring caution and/or action

For participants treated with asciminib:

The following drugs should be used with caution (see Table 10-1 for examples):

Substrates of CYP2C9 and CYP3A4/5 with narrow therapeutic index (NTI)

In vitro, asciminib has shown to be a reversible inhibitor of CYP3A4/5, CYP2C8, CYP2C9, CYP2B6, CYP2C19, with weak to no inhibition of CYP2D6, CYP1A2, CYP2A6, and CYP2E1. Under therapeutic conditions, clinical interactions of asciminib with CYP2B6 and CYP2C19 substrates are unlikely to occur. Based on the results from a dedicated clinical DDI study [CABL001A2106], asciminib is shown to be a weak inhibitor of CYP3A and CYP2C9, and does not affect CYP2C8. Therefore, the substrates of CYP2C9 and CYP3A4/5 with narrow therapeutic index (NTI) should be used with caution, refer to Table 10.1.

Substrates of OATP1B, of BCRP or of both transporters

Caution should be exercised during concomitant administration of asciminib with substrates of OATP1B, of BCRP or of both transporters, including, but not limited to sulfasalazine, methotrexate, pravastatin, atorvastatin, pitavastatin, rosuvastatin and simvastatin, refer to Table 10-1. Refer to OATP1B and BCRP substrates' dose reductions, as recommended in their prescribing information. As far as possible avoid co-administering rosuvastatin and consider alternative statins. If during the study co-administration of rosuvastatin is required, then the dose of rosuvastatin should be reduced, as recommended in its prescribing information.

Substrates of P-gp with narrow therapeutic index (NTI)

PBPK models predict that co-administration of asciminib at 80 mg q.d. with a P-gp substrate (digoxin) would increase digoxin Cmax by 30% and 38% and AUCinf by 20% and 22%, respectively. Caution should be exercised during concomitant administration of asciminib with P-gp substrates known to have a narrow therapeutic index, including but not limited to digoxin, dabigatran, and colchicine, refer to Table 10-1.

Strong CYP3A4 inducers

Strong inducers of CYP3A4 have the potential to reduce asciminib concentration. According to the DDI study (CABL001A2107), asciminib is weakly affected by co-mediation of strong CYP3A4 inducer.

Therefore, strong CYP3A4 inducers should be used with caution, refer to Table 10-1.

Known Possible or Conditional risk of Torsades de Pointes/QT prolongation

As far as possible avoid co-administering drugs with a "Known", "Possible" or "Conditional" risk of Torsades de Pointes during the course of the study.

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

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

For participants treated with nilotinib (nilotinib SmPC):

- CYP3A4 inhibitors: The administration of nilotinib with agents that are strong CYP3A4 inhibitors should be avoided. Should treatment with any of these agents be required, it is recommended that nilotinib therapy be interrupted if possible. If transient interruption of treatment is not possible, close monitoring of the individual for prolongation of the QT interval is indicated.
- Inducers of CYP3A4: Concomitant use of nilotinib with medicinal products that are potent inducers of CYP3A4 is likely to reduce exposure to nilotinib to a clinically relevant extent. Therefore, in participants receiving nilotinib, co-administration of alternative therapeutic agents with less potential for CYP3A4 induction should be selected.
- Warfarin: control of warfarin pharmacodynamic markers (INR or PT) following initiation of nilotinib therapy (at least during the first 2 weeks) is recommended.
- CYP3A4 substrates and have a narrow therapeutic index: Appropriate monitoring and dose adjustment may be necessary for medicinal products that are when co-administered with nilotinib.
- Nilotinib should be used with caution in participants taking anti-arrhythmic medicinal products or other substances that lead to QT prolongation. A list of drugs associated with QT prolongation is available online at crediblemeds.org.
- If necessary, an antacid may be administered approximately 2 hours before or approximately 2 hours after the dose of nilotinib.

6.6.1.2 Use of bone modifying agents

For all participants in the study:

The use of bone modifying agents regardless of indication is allowed.

6.6.2 Prohibited medication

For all participants in the study:

Other anticancer agents

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

Continuation of hydroxyurea which had been administered for urgent control of high cell counts prior to randomization is allowed during the first two weeks of study, and should be tapered.

6.7 Continued access to study treatment after the end of the study

6.7.1 Post trial access

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

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

Mechanisms for provision of PTA may include a rollover protocol (CABL001A2001B), provision of the Novartis/Sponsor investigational product in a non-trial setting (known as post-study drug supply [PSDS] when no further safety or efficacy data are required, or any other mechanism appropriate for the country.

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

6.8 Treatment of overdose

There is limited experience of asciminib overdose. In clinical studies, asciminib has been administered at doses up to 280 mg twice daily with no evidence of increased toxicity. General supportive measures and symptomatic treatment should be initiated in cases of suspected overdose (asciminib SmPC).

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of study treatment or TFR Phase

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

The Investigator must discontinue study treatment for a given participant if he/she believes that continuation would negatively impact the participant's well-being.

The Investigator must discontinue TFR Phase for a given participant if he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment or TFR Phase is required under the following circumstances:

- Participant/guardian decision
- Major Protocol Deviation, or any other protocol deviation that results in a significant risk to the participant's safety
- Pregnancy
    1. In the event of a pregnancy during study, if a participant wants to pursue the pregnancy then participant **must** be discontinued from the study treatment. However, in the event of a spontaneous miscarriage or in the event of elective abortion, the participant is permitted to continue study treatment.
    2. In case of a pregnancy during the TFR Phase, the pregnant woman can stay in the TFR Phase as long as no asciminib/nilotinib treatment is needed, but **must** be discontinued from the study upon loss of MMR [redacted] and are not eligible to enter the TRI Phase.
- Use of prohibited treatment as per recommendations in the prohibited treatment Section 6.6.2
- Any situation in which continued study participation might result in a safety risk to the participant

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

- In the event of detection of T315I mutation or mutation with known resistance to study treatment (NCCN V2.2024) at any point during the study associated with treatment failure or loss of response (as per ELN criteria, Hochhaus et al 2020), the participant **must** be discontinued from the study treatment.
- In the event of confirmed loss of MMR (in 2 consecutive tests, Section 8.3.1) at any time during the study treatment the participant **must** be discontinued from the study treatment.
- In the event of treatment failure (as per ELN criteria, Hochhaus et al 2020) the participant **must** be discontinued from the study treatment.

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

- In the event of detection of T315I mutation or mutation with known resistance to study treatment (NCCN 2024) at any point during the study associated with treatment failure or loss of response (as per ELN criteria, Hochhaus et al 2020), the participant **must** be discontinued from the study treatment.
- In the event of confirmed loss of MMR (in 2 consecutive tests, Section 8.3.1) at any time during the study treatment, subsequent to the initial confirmed re-achievement of MMR response in the TRI Phase, the participant **must** be discontinued from the study treatment.
- In the event of treatment failure (as per ELN criteria, Hochhaus et al 2020) the participant must be discontinued from the study treatment.

Treatment Failure Criteria:

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

- *BCR::ABL1 transcript level* > 10% IS at 3 months if confirmed within the next 1–3 months
- *BCR::ABL1 transcript level* > 10% IS at 6 months
- *BCR::ABL1 transcript level* > 1% IS at or after 12 months
- This may be assessed at the Week 48 or Week 60 visit, as per investigators discretion.
- If the participant meets the ELN treatment failure criteria, the participant should be discontinued either at an unscheduled visit or by the latest at the subsequent scheduled visit.
- Detection of a BCR::ABL1 mutation which can potentially cause resistance to study treatment (asciminib or nilotinib) or high-risk additional chromosome abnormalities in Ph+ cells at any time after initiation of study treatment. [Per ELN treatment recommendations for known mutations resistant to specific TKI and high-risk additional chromosome abnormalities (Hochhaus et al 2020)].

In the event of disease progression the participant must be discontinued from the study treatment or TFR Phase.

- The following events are considered disease progression.
  - CML-related death (any death during treatment or follow-up if the principal cause of death is marked as "study indication" in the eCRF by the Investigator, or if the death occurred subsequent to documented progression to AP/BC and the cause of death is reported as "unknown" or not reported by the Investigator)
  - Accelerated phase (AP) as defined by any of the following:
    - ≥ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate
    - ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate

- ≥ 20% basophils in the peripheral blood (unless within the first 3 months of study treatment).
- Thrombocytopenia (< 100 x 10^9/L) that is unrelated to therapy

- *As thrombocytopenia is a known adverse reaction to CML therapy, platelets <100 x 10^9/L are only considered as CML-AP if the subject had these values within 30 days of treatment discontinuation, where treatment discontinuation is due to disease progression. based on the additional criteria listed in this section. Additionally, isolated thrombocytopenia at baseline which is deemed by the investigator as not CML-AP, does not fulfill the criteria of progression to CML-AP.
- Blast crisis (BC) as defined by any of the following:
  - ≥ 30% blasts in peripheral blood or bone marrow aspirate
  - Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma).

- In the event that the results from the central RQ-PCR test at screening do not confirm presence of typical BCR::ABL1 transcript amenable to RQ-PCR quantification the participant must be discontinued from study treatment.

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

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

All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the SoA (Table 1-1, Table 1-2, Table 1-3).

Participants who discontinue from study treatment phase, TFR or TRI Phase agree to return for the EOT/ TFR END/TRI END and follow-up visits and assessments as indicated in the schedule of activities (refer to Table 1-1, Table 1-2, Table 1-3). Otherwise every effort should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

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

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

- New / concomitant treatments
- AEs / SAEs

The Investigator must also contact the IRT to register the participant's discontinuation from study Treatment Phase, TFR Phase or TRI Phase.

Participants who discontinue from study Treatment Phase, TFR Phase or TRI Phase for reasons other than documented disease progression, death, lost to follow-up, or WoC/opposition to use data/biological samples, must continue to be followed up for disease progression and survival until EOS as outlined within the schedule of assessments (Table 1-1, Table 1-2, Table 1-3).

7.2 Participant discontinuation from the study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in Section 1.3 Schedule of Activities.

7.3 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

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

This request should be as per local regulations (e.g., in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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

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

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made as detailed in Section 1.3 Schedule of Activities.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

7.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

7.5 Early study termination by the Sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination are (but not limited to):

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

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or Novartis depending on local regulation will be responsible for informing Institutional Review Boards/ Independent Ethics Committees (IRBs/IECs) of the early termination of the trial.

8 Study Assessments and Procedures

Study procedures and their timing are summarized in Section 1.3 Schedule of Activities. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with Novartis upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in Section 1.3 Schedule of Activities, is essential and required for study conduct.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Additional unscheduled visits may be performed at the discretion of the Investigator at any time during the study as clinically indicated.

8.1 Screening

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

All screening assessments should occur within 21 days before randomization.

Screening assessments include: demography, ELTS score (from diagnosis), physical examination, extramedullary involvement, vital signs, body height and weight, ECG, ECOG performance status, laboratory (hematology, clinical chemistry, coagulation, hemoglobin A1c (HbA1c), Hepatitis screen, serum pregnancy test, peripheral blood collection for *BCR::ABL1* RQ-PCR for evidence of typical transcripts, evaluation of all relevant medical history including smoking history and other cardiovascular risk factors and other comorbidities, CML disease history, antineoplastic medication, prior and concomitant medication and must be performed prior to randomization. ELTS score should be based on the variables recorded at the time of initial diagnosis of CML. For details of assessments required during screening please refer to Table 1-1.

During the screening visit, inclusion and exclusion criteria will be assessed. Screening assessments to confirm eligibility must be performed prior to randomization.

If results from a recent bone marrow analysis, done in the past 3 months, are available, these results may be used for eligibility purposes. If results are not available, local bone marrow aspirate must be performed and results available prior to randomization.

The screening ECGs as well as the results of the central *BCR::ABL1* RQ-PCR (or local *BCR::ABL1* qualitative assessment), central hematology, chemistry and hepatitis screen must be available prior to randomization to evaluate eligibility.

Evidence of typical *BCR::ABL1* transcript [e14a2 and/or e13a2] which is amenable to standardized RQ-PCR quantification by the central laboratory assessment is required. However, if a local qualitative assay, validated according to local regulation, from an accredited local laboratory has confirmed evidence of typical *BCR::ABL1* transcript [e14a2 and/or e13a2], these results can be used for eligibility if the central RQ-PCR results have not arrived.

Participants with potassium, and/or magnesium and/or total calcium levels that are < LLN at screening, must have their potassium, and/or magnesium, and/or calcium replenished through supplementation and the levels must be within normal limits prior to randomization. In case of hyperkalemia with thrombocytosis, pseudohyperkalemia should be excluded.

A participant who has a laboratory test (peripheral blood test) or ECG results that do not satisfy the entrance criteria may have the tests repeated. These tests may be repeated as soon as the Investigator believes the re-test results are likely to be within the acceptable range to satisfy the entrance criteria, but should be completed within the 21 day screening period. In this case, the participant will not be required to sign another ICF, and the original participant identification (ID) number assigned by the Investigator will be used.

In the event that the laboratory tests cannot be performed within the screening visit window, or the re-tests do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the participant is considered a screen failure, and must be discontinued from the study. A new ICF will need to be signed if the Investigator chooses to re-screen the

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

8.1.1 Eligibility screening for Treatment Phase

Following registering in the IRT for screening, participant eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

8.1.2 Eligibility screening for optional TFR Phase

Participant eligibility criteria for the optional TFR Phase will be assessed beginning at every scheduled visit from CCI .

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

Participant demographics: age, sex, race/predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) including risk group, CML disease history, and prior and concomitant medication including antineoplastic medication should also be recorded on the appropriate eCRF.

Participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by health authorities. The collection of race and ethnicity is performed to enable the Sponsor to evaluate the potential influence of baseline factors such as age, race/ethnicity, or influence of risk group (e.g., ELTS), on the effect of asciminib with respect to the study endpoints.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the protocol Section 6.8 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

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

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever, in their judgment, the test abnormality occurred prior to the informed consent signature. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the participant's eCRF.

8.3 Efficacy assessments

Planned time points for all efficacy assessments are provided in Section 1.3 Schedule of Activities.

If a Public Health emergency limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented as described in Section 4.5 and Section 1.3.

8.3.1 Molecular Response

Molecular response (MR) will be assessed in all participants.

During the Treatment Phase peripheral blood samples for analysis of *BCR::ABL1* levels will be collected from all participants at screening, Week 4, Week 12 and then every 12 weeks until end of study treatment, treatment failure or early discontinuation. Levels of *BCR-ABL1* transcripts will be determined by RQ-PCR testing of peripheral blood by a Novartis designated central laboratory.

During the TFR Phase peripheral blood samples will be collected from all participants at Day 1 (Treatment Phase EOT/TFR Baseline), every 4 weeks for the first 24 weeks, every 8 weeks for the following 24 weeks, and then every 12 weeks CCI , until loss of MMR, or early discontinuation, whichever is earlier.

Loss of MR4.0 but not MMR, after Week 24 during the TFR Phase triggers a return to more frequent monitoring of BCR::ABL1 IS levels every 4 weeks via central RQ-PCR to identify potential loss of MMR. Four week frequency of monitoring will end at one of the following time points:

- When the BCR::ABL1 IS levels return to a range between MR4.0 and MR4.5. At this point, the participant can return to prior frequency of RQ-PCR BCR::ABL1 IS monitoring.
- When the BCR::ABL1 IS levels remain lower than MMR for four consecutive measurements (16 weeks from initial loss of MR4.0). At this point, the participant can return to prior frequency of RQ-PCR BCR::ABL1 IS monitoring.

Loss of MMR (CCI requires re-initiation of treatment in the TRI Phase within 4 weeks.

During the TRI Phase peripheral blood samples will be collected from all participants at Day 1 (TFR END Visit/TRI Baseline), every 4 weeks for the first 24 weeks, and then every 12 weeks to EOS or to CCI whichever is the latest, or until treatment failure or early discontinuation. Where MMR is not re-achieved by 24 weeks, every 4 weeks assessment should be continued until MMR is re-achieved.

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

MMR and related variables are defined as the following:

- MMR criteria is defined as a ≥ 3.0 log reduction in *BCR::ABL1* transcripts compared to the standardized baseline equivalent to ≤ 0.1 % *BCR::ABL1* % by international scale as measured by RQ-PCR, confirmed by duplicate analysis of the same sample
- Confirmed MMR during TRI Phase is defined as *BCR-ABL1* IS levels $\leq 0.1\%$ confirmed by analysis of sample at next scheduled visit.

- MR4.0 criteria is defined as *BCR::ABL1* IS levels ≤ 0.01%
- MR4.5 criteria is defined as *BCR::ABL1* IS levels ≤ 0.0032%
- Confirmed MR4.5 during TRI Phase is defined as *BCR-ABL1* IS levels ≤ 0.0032% confirmed by analysis of sample at next scheduled visit.
- Unconfirmed Loss of MMR is defined as *BCR::ABL1* IS > 0.1% in association with a ≥ 5-fold rise in *BCR::ABL1* from the lowest value achieved on study treatment and replicated by a second analysis of the same sample.
- Confirmed Loss of MMR is defined as a loss of MMR (i.e. *BCR::ABL1* IS > 0.1% in association with a ≥ 5-fold rise in BCR::ABL1 from the lowest value achieved on study treatment and replicated by a second analysis of the same sample) confirmed by analysis of another sample taken after an interval of not less than 4 weeks and not more than 6 weeks unless associated with confirmed loss of CHR or loss of *BCR::ABL1* IS ≤ 1% or progression to AP/BC or CML related death.
- Loss of MR4.0 is defined as *BCR-ABL1* IS > 0.01% confirmed by subsequent sample analysis within 12 weeks showing loss of MR4 associated with a ≥ 5-fold rise in BCR-ABL1 from the lowest value achieved on study treatment, unless it is associated with confirmed loss of CHR, loss of *BCR::ABL1* IS ≤ 1% or progression to AP/BC or CML-related death.
- Loss of MR4.5 is defined as *BCR-ABL1* IS > 0.0032% confirmed by subsequent sample analysis within 12 weeks showing loss of MR4.5 associated with a ≥ 5-fold rise in BCR-ABL1 from the lowest value achieved on study treatment, unless it is associated with confirmed loss of CHR, loss of *BCR::ABL1* IS ≤ 1%, or progression to AP/BC or CML-related death.

TFR Phase MMR and related variables are defined as the following:

- Loss of MMR during the TFR Phase is defined as CCI [redacted] re-initiation of treatment within 4 weeks in the TRI Phase.
- Loss of MR4.0 during the TFR Phase is defined as *BCR-ABL1* IS > 0.01%, confirmed by duplicate analysis of the same sample; loss of MR 4.0 at a single assessment during TFR Phase after Week 24 requires increased BCR::ABL1 monitoring frequency.

Details on scheduling and blood sample collection are described in Section 1.3.

For participants who discontinue study treatment/TFR/TRI for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent (WoC)/opposition to use data/biological samples, survival status must continue to be monitored until EOS as in Table 1-1, Table 1-2 and Table 1-3.

If at one visit the result is missing due to problem during transit to the central PCR laboratory, or the PCR result is difficult to interpret or sample not analyzable, or if the PCR sample was not collected, a subsequent unscheduled visit sample must be collected within 4 weeks as an unscheduled visit.

Table 8-1 Blood samples (Molecular response for Treatment Phase)

Sample Type	Volume	Visit	Time Point
Peripheral Blood for *BCR::ABL1* RQ-PCR	10 milliliters (mL)	Screening	Anytime
		After 4 Weeks	Anytime
		After 12 Weeks	Anytime
		After 24 Weeks	Anytime
		After 36 Weeks	Anytime
		After 48 Weeks	Anytime
		Every 12 weeks up to EOT	Anytime
		EOT	Anytime
		Confirmed Loss of MMR	Within 4-6 weeks from detection of loss of MMR

During visits in which MR is assessed, the visit should occur within +5 days.

Table 8-2 Blood samples (Molecular response for optional TFR Phase)

Sample Type	Volume	Visit	Time Point
Peripheral Blood for *BCR::ABL1* RQ-PCR	10 milliliters (mL)	TFR Baseline (same visit as EOT	Anytime
		Every 4 Weeks: Week 4 - 24	Anytime
		Every 8 weeks: Week 24 - 48	Anytime
		Every 12 weeks CCI [redacted]	Anytime
		TFR END	Anytime

During visits in which MR is assessed, the visit should occur within +5 days.

For loss of MR4.0 (BCR::ABL1 IS >0.01%) but no loss of MMR (BCR::ABL1 IS ≤0.1%) after week 24 during the TFR Phase, assessment frequency will be increased to every 4 weeks until BCR::ABL1 IS levels return to MR4 or better (BCR::ABL1 IS ≤ 0.01%), or BCR::ABL1 IS levels remain between MMR and MR4 (BCR::ABL1 IS <0.1% and >0.01%) for 4 consecutive measurements (16 weeks from initial loss of MR4.0), assessments can reduce to prior frequency. Loss of MMR CCI [redacted] requires re-initiation of treatment within one month in the TRI Phase.

In case of a pregnancy during the TFR Phase, BCR::ABL1 IS levels should be monitored every 4 weeks for the duration of the pregnancy.

Table 8-3 Blood samples (Molecular response for TRI Phase)

Sample Type	Volume	Visit	Time Point
Peripheral Blood for *BCR::ABL1* RQ-PCR	10 milliliters (mL)	TRI Baseline (same visit as TFR END)	Anytime
		Every 4 Weeks: Week 4 - 24	Anytime
		Every 12 weeks thereafter	Anytime
		TRI END	Anytime

During visits in which MR is assessed, the visit should occur within +5 days.

If MMR (BCR::ABL1 IS ≤0.1%) is not re-achieved by Week 24, monthly (every 4 weeks) assessment should be continued until MMR is re-achieved.

8.3.2 Hematological Response

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

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

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

8.3.3 Appropriateness of efficacy assessments

Assessment of hematologic response with RQ-PCR is a standard measure of assessing the return of blood counts to normal values, in response to treatment for CML (Cortes et al 2011). Regular assessment of hematologic response as well as assessing molecular response with RQ-PCR is considered as standard in CML therapy and recommended in treatment guidelines and expert panel recommendations (Hochhaus et al 2020, NCCN CML treatment guidelines V3.2022). It is acknowledged that response can be assessed using only standardized results via International Scale (IS) as *BCR::ABL1%.* Mutational testing for treatment decisions will be done at the timepoints indicated in Table 1-1, Table 1-2 and Table 1-3 and can be done at any time point as clinically indicated in case of treatment failure and at EOT.

8.4 Safety assessments

Safety assessments are specified below with Section 1.3 Schedule of Activities detailing when each assessment is to be performed.

NOTE: Additional local safety laboratory testing for hematology and chemistry may be performed at relevant time points to comply with the local prescribing information for asciminib and nilotinib.

For details on AE collection and reporting, refer to Section 8.6.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur if needed for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

8.4.1 Physical examinations

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological.

Information for all physical examinations must be included in the source documentation at the study site as unique source data, this information will not be captured in the CRF. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after first administration of study treatment which meet the definition of an Adverse Event must be recorded on the Adverse Event

CRF. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Physical examination will be evaluated as described in Table 1-1, Table 1-2 and Table 1-3.

Presence of extramedullary leukemic involvement will be checked with each physical examination as outlined above. Findings on physical examination consistent with extra-medullary leukemic involvement will be recorded (e.g. any organ involvement). With regards to lymph nodes, only those palpable lymph nodes should be considered to be CML related if leukemic blast infiltration has been confirmed via biopsy/histology or by technically adequate aspiration cytology. When extramedullary involvement other than of the spleen or liver is the only evidence of blast crisis, this finding must be confirmed by technically adequate (not contaminated with peripheral blood) aspiration cytology and/or biopsy (especially for isolated lymph nodes) and data entered into the extramedullary involvement eCRF.

Extramedullary involvement will be evaluated as described in Table 1-1, Table 1-2 and Table 1-3.

Height in centimeters (cm) and body weight (to the nearest 0.01 kilogram (kg)) will be measured as specified in Table 1-1, Table 1-2 and Table 1-3.

ECOG Performance status scale will be used as described in Table 1-1, Table 1-2 and Table 1-3.

8.4.2 Vital signs

Vital signs include systolic and diastolic blood pressure (supine position preferred when ECG is collected), pulse rate measurement, and body temperature and will be performed as described in Table 1-1, Table 1-2 and Table 1-3.

8.4.3 Electrocardiograms

ECGs will be locally collected and evaluated. ECGs should be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of data collection during study visits is ECG collection, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions e.g., at screening to assess eligibility. The Investigator or qualified personnel must calculate QTcF if it is not auto-calculated by the ECG machine. Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate CRF. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

After the participant has rested approximately 10 minutes in a supine position, three sequential standard 12-lead ECGs (triplicate) must be obtained with a recommended minimal interval of 5 minutes between each ECG at the time points specified in Section 1.3. After obtaining the triplicate ECG recordings, the mean (average) value of each parameter (e.g. Heart rate, PR

interval, QRS duration, QT interval) must be manually calculated by the site staff and documented in study source documents and the eCRF.

QTc prolongation will be based on the average time seen in the scans for each time point. The enrollment of participants will be based on locally assessed QTcF time. The participant may not be dosed if the average of the 3 ECGs confirm a QTcF ≥ 450 ms.

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

Additional unscheduled ECGs may be performed at the discretion of the Investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. For any ECGs with participant safety concerns, triplicate ECGs should be collected. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study.

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

A standard 12 lead ECG will be performed as described in Table 1-1, Table 1-2 and Table 1-3.

Local ECG results will be reported on the appropriate eCRF.

Dose adjustments in case of QT prolongation should be performed per Section 6.5.1.

The original ECGs, appropriately signed, must be archived at the study site.

8.4.4 Estimation of cardiac risk factors

Personal and family history (consisting of father, mother and siblings) of the following medical conditions is to be taken at the screening visit: coronary artery disease, hyperlipidemia, Type 1 diabetes mellitus, Type 2 diabetes mellitus, arterial hypertension, medication taken or not for hypertension for personal history, myocardial infarction or cerebrovascular accident. In addition, history of smoking, low physical activity and unhealthy diet must be recorded at the screening/baseline and at the end of the treatment.

8.4.5 Clinical safety laboratory tests

Central laboratory will be used for analysis of hematology, coagulation, HbA1C, biochemistry, serum pregnancy and hepatitis marker specimens collected (safety monitoring as per Section 1.3, Section 6.5.2.1, and Section 10.4). Details on the collections, shipment of the samples and reporting of results by the central laboratory are provided to Investigators in the [CABL001J12302 laboratory manual]. The time windows granted for laboratory evaluations are identical with the corresponding visit time windows for each visit (see Section 1.3). As per Table 8-4, each sample for the analysis of Glucose and Triglycerides needs to be collected under fasting condition: [ideally] 8 hours fasting is required with only water being allowed to be consumed.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria: 1) they induce clinical signs or symptoms, 2) they are considered clinically significant, or 3) they require concomitant therapy or procedures. Clinically significant

abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from screening or the previous visit.

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

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

Table 8-4 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Volume (MCV), PLTs, Erythrocytes, Leukocytes, Erythrocyte Cell Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Blasts, Promyelocytes, Myelocytes, Metamyelocytes)
Coagulation	International normalized ratio (INR) and Activated Partial Thromboplastin Time (APTT)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Total Calcium, Magnesium, Phosphate, Chloride Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin (TBL), Total Cholesterol, Low Density Lipoprotein (LDL Cholesterol), High Density Lipoprotein (HDL Cholesterol), Total Protein, Triglycerides (fasting), Urea Nitrogen or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting), Hemoglobin A1c
Hepatitis markers	Hepatitis B Virus Surface Antigen, Hepatitis B Virus Core Antibody, Hepatitis B DNA (if only Hepatis B core antibody is positive) Hepatitis C (HCV) Antibody, Hepatitis C RNA (if Hepatis C Antibody is positive)
Liver assessments for DILI (See Section 6.5.2.1)	ALT, AST, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase. If available, testing of Glutamate Dehydrogenase (GLDH) is additionally recommended.
Pregnancy Test*	Serum / Urine pregnancy test

* For details on pregnancy testing, please refer to Section 8.4.6

As per Section 4.5, during a public health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, if participants cannot visit the site for protocol specified safety lab assessments conducted through central labs, an alternative lab (local) collection site may be used.

8.4.6 Pregnancy testing

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

All women of childbearing potential have to complete a serum ß-human chorionic gonadotrophin pregnancy test (Serum ß-HCG) at every regularly scheduled site visit as

indicated in Section 1.3 and Table 8-3. Pregnancy testing is not required for participants who are determined to be post-menopausal. The time windows granted for pregnancy testing are identical with the corresponding visit time windows for each visit.

Serum pregnancy assessments have to be analyzed by a central laboratory.

Urine pregnancy tests have to be performed at home every 4 weeks if a serum pregnancy test is not performed (i.e., when site visits are less frequent than monthly). This also includes the time points at EOT and 30-day safety follow up where required. Information for urine pregnancy test must be included in the source documentation at the study site at the next participant visit as unique source data, this information will not be captured in the CRF. If a test result indicates a pregnancy, the participant must contact the Investigator immediately to stop the study treatment.

All pregnancies of study participants should be recorded on a Clinical Trial Pregnancy Form and reported by the Investigator to the Oncology Novartis Drug Safety and Epidemiology Department (DS&E).

During the study, including Treatment Phase, TFR Phase and TRI Phase, women of childbearing potential should employ the use of highly effective contraception as defined in Section 5.2.

As per Section 4.5, during a public health emergency as declared by local or regional authorities' i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results (e.g. following country specific measures).

Assessments of fertility

A woman is considered of childbearing potential from menarche and until becoming post menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or bilateral salpingectomy must be retained as source documents.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the Investigator should use his/her medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

8.4.7 Appropriateness of safety measurements

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

8.5 Additional assessments

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

- Patient Reported Outcomes (Section 8.5.1)
- TFQ (Section 8.5.2)
- Biomarkers (Section 8.8)
- CCI [redacted] (Section 8.11)
- Cytogenetic bone marrow assessment (for screening (as applicable) and if clinically indicated) (Section 8.1 and Section 8.9)

8.5.1 Clinical outcome assessments (COAs)

8.5.1.1 Patient Reported Outcomes (PRO)

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

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

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

8.5.1.1.1 Collection of ePRO

PRO data will be collected using an electronic device. The device utilized for ePRO will be programmed for PRO collection as described in Tables 1-1, Table 1-2 and Table 1-3.

CCI [redacted]: The EORTC QLQ-C30, EORTC CML 24, CCI [redacted] will initially be assessed at CCI [redacted].

Subsequent ePRO collections:

The EORTC QLQ-C30, EORTC CML 24, CCI [redacted] should be completed at the timepoints indicated in Tables 1-1, Table 1-2 and Table 1-3.

- PRO collection timepoints are based off of the CCI [redacted].
- On days where the PRO collection overlaps with the onsite/virtual visit, the participant should complete their PROs prior to their onsite/virtual visit. The PRO should be completed within a two day window before the study visit.

- Questionnaires should be completed within a two-day window by the participant at home, independent of site study visits.

Provision of ePRO devices (or application download in case of Bring Your Own Device [BYOD]) will occur at the CCI The site will ensure set up of ePRO device is completed according to ePRO vendor training. Participants will be trained by the site on how to use the ePRO device. Participants will have an option to use either provisioned ePRO devices or of using "Bring Your Own Device (BYOD)" approach in which participants may select to use their own smartphone or internet-enabled device to complete the PRO assessments. BYOD participants will be required to download a specific PRO application onto their personal mobile device. In case of technical or ePRO device failures, back-up solutions are available as per ePRO vendor specifications. In cases of device malfunction or syncing issues or in case the device can't be located and when a participant is unable to obtain an immediate device replacement, a web version of the participant's questionnaires is available during a participant's participation for use. In order for a participant to take advantage of this functionality, the participant will need access to a computer with internet access and a web browser. Backup should only be used until a replacement device can be provided to the participant. Details on the requirements to set up the back-up process and additional guidance are available in the ePRO vendor specification guidance document.

Completion of PRO on paper copies as back-up solution or any other reason is not allowed for the study.

The CCI Participants will also be provided instructions to continue PRO assessments at home after baseline assessment at the Baseline/ CCI .

Study participants should be given sufficient space and time to complete all PRO questionnaires at the CCI . In addition, sites will be provided further instructions to support participants if technical problems should arise with ePRO devices. PRO measures should be provided in the participant's language. In case any PRO questionnaire is not available in a language the participant is familiar with, the PRO questionnaire must be omitted. If additional information or further instructions are needed, participants can receive additional technical support when they bring the ePRO device to the site during all scheduled visits.

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

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

The PRO measure(s) should be completed in the following order: EORTC QLQ-C30, and EORTC QLQ-CML24, CCI , and CCI .

8.5.1.1.2 EORTC QLQ-C30 and QLQ-CML24

The European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC-QLQ-C30) and the CML specific module, the QLQ-CML24 will be

used to evaluate patient-reported outcome measures of health-related quality-of-life, functioning, colorectal cancer symptoms, treatment-related side effects, and global health status (Anderson et al 1993).

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients and used frequently in cancer clinical trials. The questionnaire contains 30 items and is composed of both multi-item scales and single-item measures based on the participant's experience over the past week. These include five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/QoL scale (Anderson et al 1993). All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning; a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology/problems. All scoring will follow the procedures defined by the EORTC Scoring Manual (Fayers 2001).

The EORTC QLQ-CML24 assesses specific concepts relevant to the experience of patients with CML. The QLQ-CML24 has 24 items which assess symptom burden, impact on daily life and on worry/mood, body image problems, and satisfaction with care and with social life based on the participant's experience over the past week (Efficace et al 2021). The QLQ-CML24 items are scored on a 4 point Likert scale, with a range of ‘not at all’ to ‘very much’.

8.5.1.1.3 CCI

CCI

[redacted]

CCI [redacted]

8.5.1.1.4 CCI [redacted]

CCI [redacted]

8.5.2 Trial Feedback Questionnaire

By participating in the clinical trial, participants may be contacted for feedback about the trial experience at three different timepoints, as appropriate and in adherence to local regulations and guidelines. Individual trial participant responses will not be reviewed by Investigators. Responses may be used by Novartis to understand where improvements can be made in the clinical trial process. This feedback asks questions about trial experience. It does not ask questions about the trial participant's disease, symptoms, treatment effect, or adverse events, and, therefore is not considered as trial data.

The TFQ is not considered study data and will be received electronically outside of the clinical database.

8.6 Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 8.6.1 and Section 8.6.2.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 8.6.3.

During any pandemic such as COVID-19 that limits or prevents on-site study visits regular phone calls will occur for safety monitoring and discussion of the participant's health status until the participant can again visit the site. This telephone contact should preferably be done according to the study visit schedule or more frequently if needed. Please refer to Section 4.5 for further information.

8.6.1 Adverse events

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

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments. PRO measures are not reviewed for AEs by the investigator/ study personnel.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 8.6.2):

1. The Common Toxicity Criteria (CTC) AE grade (version 5). Grade 1 to 5 will be used to characterize the severity of the Adverse Event. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used.
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be ‘Not suspected.’ The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the study treatment, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant.
    a. TFR Phase: AEs reported after TKI cessation should be considered by Investigator for causality assessment with study treatment.
3. Its duration (start and end dates or ongoing) and the outcome must be reported.
4. Whether it constitutes a SAE (see Section 8.6.2 for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

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

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

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

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment (Treatment Phase or TRI Phase) or the last day of the TFR Phase (for participants not re-initiating treatment).

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method, should not be reported as a serious adverse event, except if the Investigator considers that progression of malignancy is related to study treatment.

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

For participants who enroll in the Extension study (CABL001A2001B), AEs experienced up to 30 days after the last dose of study drug in CABL001J12302 should be recorded in the CABL001J12302 study CRFs.

Information about adverse drug reactions for the investigational drug can be found in the (Asciminib Investigator's Brochure 2024) (IB) and the local label for nilotinib [Nilotinib Reference Safety Information].

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease.

8.6.2 Serious adverse events

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

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect, fetal death or a congenital abnormality or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

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

All reports of intentional misuse and abuse of the product are also considered serious adverse events irrespective of whether a clinical event has occurred.

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

8.6.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Treatment-emergent elevations in AST or ALT (>3x ULN) in combination with total bilirubin >2x ULN or jaundice in the absence of cholestasis (defined as ALP < 2 ULN) or other causes of hyperbilirubinemia can be an indicator of severe drug induced liver injury (Hy's Law). For this reason, a potential Hy's Law case requires expedited reporting, and will be handled as a serious unexpected adverse event (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the Sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded). Reporting should include all available information, especially that needed for evaluating the diagnosis, severity, and likelihood that the study treatment caused the reaction. For participant monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data. Please refer to Section 6.5.2 Follow up on potential DILI cases.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational drug, a Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Clinical Trial

Regulation 536/2014, EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30-day period after the last study visit should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

8.6.4 Pregnancy

Details of all pregnancies in female participants will be collected after the start of study treatment until EOT, TFR END, or TRI END, and 30-day safety follow up.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

Any post study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to Novartis as described in Section 8.6.3. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

If a female trial participant becomes pregnant in the Treatment Phase or TRI Phase, the study treatment must be stopped, and the pregnancy consent form should be presented to the trial participant.

If a female trial participant becomes pregnant in the TFR Phase they can stay in the TFR Phase as long as no asciminib/nilotinib treatment is needed but **must** be discontinued from the study upon loss of MMR CCI [redacted] and cannot enter the TRI Phase. The pregnancy consent form should be presented to the trial participant.

The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy.

To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications

Pregnancy should be recorded and reported by the Investigator to Novartis. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

8.6.5 Adverse events of special interest

AEs of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. AEs of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the (Asciminib Investigator's Brochure 2024).

8.6.6 Reporting of study treatment errors including misuse/abuse

Study treatment errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (definition from European Medicines Agency).

Study treatment misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Study treatment abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and (until transition to the EU CTR) reported to Safety only if associated with an SAE. Misuse or abuse (and upon transition to the EU CTR, also study treatment errors and uses outside of what is foreseen in the protocol) will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

8.7 Pharmacokinetics

PK parameters are not evaluated in this study.

8.8 Biomarkers

CCI [redacted]

Biomarkers for TFR

CCI [redacted]

CCI [redacted]

CCI

Cellular Markers:

CCI

CCI

Mutation status in CCI will be summarized using frequency counts and percentages CCI

.

Table 8-5 CCI

CCI

Optional Additional Research

If the participant agrees, by signing the optional consent for Additional Research, biological samples and coded data that remain after analysis is completed may be used for additional research to help better understand how the investigational drug works, learn more about the disease, improve the way clinical studies are conducted, or to help develop ways to detect, monitor or treat human diseases. A decision to perform such exploratory research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as assay availability.

8.9 Bone Marrow Aspirate

Bone marrow analysis may be performed locally if clinically indicated during the study.

8.10 Immunogenicity assessments

Immunogenicity is not evaluated in this study.

8.11 CCI

CCI

[redacted]

9 Statistical considerations

The primary analysis cut-off date will be when approximately CCI discontinuations of either study treatment due to AE (the event of interest) occur.

The formal interim analysis cut-off date will be when approximately CCI discontinuations of either study treatment due to AE (the event of interest) occur.

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

9.1 Analysis sets

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

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

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

The primary estimands are based on the treatment policy strategy and will analyze participants according to the treatment and stratum they have actually received.

The **TFR Eligible Set (TFRE)** comprises all participants who satisfy the TFR eligibility criteria.

The **TFR Analysis Set (TFRS)** comprises all participants who are eligible to the TFR Phase and have entered the TFR Phase.

The **Treatment Re-initiation Analysis set (TRIS)** comprises all participants who have entered the TRI Phase.

9.2 Statistical analyses

9.2.1 General considerations

The data will be analyzed by Novartis. The data from all participating centers in this protocol will be combined, so that an adequate number of participants will be available for analyses. Study data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements. Considering the competing risk event of time-to-discontinuation of study treatment due to other reasons not due to AE, the primary analysis for TTDAE will be analyzed by the cause-specific hazard model. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum, and maximum as well as 25th and 75th percentiles will be presented. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.2.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment arm for the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

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

9.2.3 Treatments

The Safety set will be used for the analyses below.

Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, 25th and 75th percentiles, minimum, and maximum will be presented. The duration of exposure in days to asciminib and nilotinib, as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics.

The number of participants with dose adjustments (reductions, interruption, or permanent discontinuation, dosing errors) and the reasons will be summarized by study treatment. All dosing data will be listed.

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

9.3 Primary endpoint(s)/estimand(s) analysis

9.3.1 Definition of primary endpoint(s)

The primary objective of the study is to assess the tolerability of asciminib versus nilotinib, in participants with newly diagnosed CML-CP, with respect to the time to discontinuation of study treatment due to adverse event (TTDAE) in the Treatment Phase. TTDAE, defined as the time from the date of first dose of study treatment to the date of discontinuation of study treatment due to adverse event (AE).

The primary estimand corresponding to the primary objective will address the following clinical questions of interest:

What is the safety/tolerability of asciminib (80 mg QD) compared to nilotinib (300 mg BID); with respect to the time to discontinuation of study treatment due to AE (TTDAE), where discontinuation of study treatment due to other reasons is considered as a competing risk event, in newly diagnosed CML-CP patients; regardless of dose interruptions/reductions; regardless of dosing errors, or intake of concomitant medication.

Refer to Section 3.1 for the primary estimand strategy, their attributes, and handling of intercurrent events.

9.3.2 Statistical model, hypothesis, and method of analysis

The analyses of the primary endpoint of TTDAE will be performed using the safety set for the comparison of asciminib versus nilotinib.

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

- **H_0**: the cause-specific hazard for the event of discontinuation of study treatment due to AE, for participants that received asciminib is *greater than or equal to* that for participants that received nilotinib.
- **H_a**: the cause-specific hazard for the event of discontinuation of study treatment due to AE, for participants that received asciminib is *less than* that for participants that received nilotinib.

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

The formal comparison of TTDAE, for asciminib versus nilotinib will be implemented via the cause-specific hazard model. The overall type I error rate will be controlled at 2.5% level.

The cumulative incidence curve will be plotted. The estimated cumulative incidence rates and 95% confidence intervals (CIs) at specified time points will be presented for each treatment arm

(asciminib and nilotinib). The cumulative incidence rate at a specified time point provides an estimate of the probability of experiencing discontinuation of study treatment due to AE at/before the specified time point and also before the occurrence of non-AE related discontinuation of study treatment.

Supplementary analysis

The cause-specific hazard ratio for the competing risk event along with the 95% CI will also be estimated from the cause-specific hazard Cox regression model. In addition, the analysis via the sub-distribution hazard regression approach will also be implemented. These supplementary analyses will be provided for information purposes only.

9.3.3 Handling of intercurrent events of primary estimand

The approaches for accounting for Intercurrent events (IE) are summarized as follows:

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

9.3.4 Handling of missing values not related to intercurrent event

For participants ongoing without study treatment discontinuation (due to AE or due to other reasons), on or prior to the analysis cut-off date, the TTDAE time will be censored at the analysis cut-off date.

9.3.5 Sensitivity analyses

In the primary analysis, death due to other reasons is considered as a competing risk, similar to other reasons of discontinuation of study treatment (except death due to AE, which are considered as events of interest). To explore the robustness of the analysis, sensitivity analysis considering death as an intercurrent event with composite strategy, will be performed. The details will be provided in the Statistical Analysis Plan (SAP). Other sensitivity analyses for the primary endpoint may be done as needed.

9.3.6 Supplementary analysis

The cause-specific hazard ratio for the competing risk event (discontinuation from study treatment due to other reasons that are not due to AEs) along with the 95% CI will be estimated

from the cause-specific hazard Cox regression model. In addition, the analysis via the sub-distribution hazard regression approach will also be implemented. These supplementary analyses will be provided for information purposes only.

9.4 Secondary endpoint(s)/estimand(s) analysis

The study has multiple secondary objectives for efficacy, PRO and safety, including:

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

9.4.1 Efficacy and/or pharmacodynamic endpoint(s)

9.4.1.1 Secondary Efficacy Endpoints

The secondary efficacy endpoints are,

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

Definitions of MMR/ MR4.0/MR4.5/CHR/*BCR::ABL1* ≤1% at and by a scheduled visit:

The **rates "at"** a scheduled visit are defined as the proportion of participants who meet the criteria for the end-point (MMR/MR4.0/MR4.5/CHR/*BCR::ABL1* ≤1%) at the specified visit. Participants discontinuing the randomized treatment due to any reason or participants meeting

failure criteria, prior to the specific visit will be considered as non-responder for the end-point at the specified visit, i.e. if a participant achieves the end-point earlier, but then loses it at the visit, he/she will be classified as a non-responder for the end-point at that visit.

For the end-point of MMR and *BCR::ABL1* ≤1%, an exception to the rule is if the evaluation at the specified visit is missing, but both evaluations from the preceding and following scheduled visits meet the criteria for the end-point, the assessment at the specified visit is imputed as a responder for the end-point.

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

The **rates "by"** scheduled visits are defined as the proportion of participants who meet the criteria for having achieved the end-point (MMR/MR4.0/MR4.5/CHR/*BCR::ABL1* ≤1%) at or before the specified visit, i.e. if a participant achieves the end-point, but then loses it before or at the visit, he/she will still be classified as achieving the end-point by that specified visit. Participants discontinuing the randomized treatment prior to the specific time point due to any reason or participants meeting failure criteria, without having achieved the end-point at or before that visit will be considered as not achieving the end-point by the specified visit.

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

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

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

In case of duration of MMR, loss of MMR must be a confirmed loss as per the definition in Section 8.3.1.

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

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

In the time-to-event analysis, time will be censored at the last molecular assessment (RQ-PCR) date while on treatment, or the EOT (whichever comes first) for participants who have not experienced the event (i.e. not achieved the end-point) or a competing risk event (as described in Section 9.4.1.2).

Definitions of Time to Treatment Failure (TTF):

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

- Treatment failure as defined in Section 7.1 based on ELN criteria (Hochhaus et al 2020),
- Confirmed loss of MMR (in 2 consecutive tests, Section 8.3.1)at any time while on study treatment,
- Progression to AP/BC while on treatment,
- Death from any cause while on treatment,
- Discontinuation of study treatment due to any reason (e.g. discontinuation of study treatment due to AE, investigator/participant decision, lack of efficacy, progression to AP/BC, death due to any cause etc.).

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

Definitions of Event Free Survival (EFS):

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

- Treatment failure as defined in Section 7.1 based on ELN criteria (Hochhaus et al 2020),
- Confirmed loss of MMR (in 2 consecutive tests, Section 8.3.1) at any time while on study treatment,
- Discontinuation of study treatment due to AE,
- Progression to AP/BC (including progressions observed during the survival follow-up period),
- Death from any cause (including deaths observed during the survival follow-up period).

For participants that have not experienced an event prior to or at the analysis cut-off date, the time will be censored at the date of last on-treatment assessment or last post-treatment follow-up.

Definitions of Progression Free Survival (PFS):

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

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

For participants that have not experienced an event prior to or at the analysis cut-off date, the time will be censored at the date of last on-treatment assessment or last post-treatment follow-up.

Definition of Overall Survival (OS):

OS is defined as the time from the date of randomization to the date of death from any cause (including deaths observed during the survival follow-up period). For participants that have not

experienced an event prior to or at the analysis cut-off date, the time will be censored at the date of last contact before the analysis cut-off date.

9.4.1.2 Statistical hypothesis, models and methods of analyses of secondary efficacy endpoints

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

Analyses for (MMR/MR4.0/MR4.5/CHR/*BCR::ABL1* ≤1%) rates at and by scheduled time points:

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

Comparisons of proportion of participants achieving the end-points (at and by scheduled visits) for asciminib versus nilotinib, will be performed using a one-sided stratified Mantel-Haenszel test, stratified by the randomization stratification factor (ELTS risk score) from IRT.

The stratified Mantel-Haenszel estimate of the common risk difference will be provided (for the proportion of participants achieving the end-point) between asciminib and nilotinib, stratified by the randomization stratification factor of the ELTS risk score from IRT.

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

Duration of MMR/MR4.0/MR4.5 will be analyzed by Kaplan-Meier (KM) method and presented by KM plots. The estimated median duration along with the 95% Cis (Brookmeyer and Crowley 1982), along with the proportion of participants who are still responders at specified scheduled visits and the associated 95% CIs, will be presented for each treatment arm.

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

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

Analyses for Event Free Survival (EFS)

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

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

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

For each endpoint the time-to-event distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% CIs (Brookmeyer and Crowley 1982) of the medians, along with the proportion of participants who have not experienced the respective events at selected scheduled visits and the associated 95% CIs, will be presented for each treatment arm. The hazard ratio between the two treatments arms will be calculated, along with its 95% CI, using a stratified Cox model. The descriptive p-value obtained using a stratified log-rank test will be also presented. The stratification factor is treatment arm.

Analyses for TTD due to selected reasons

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

9.4.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment arm. The secondary safety endpoints include,

- Type, frequency and severity of adverse events, dose modification due to adverse events, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG changes, and other safety data (vital signs, physical examination).

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

- Pre-treatment period: from day of participant's first informed consent to the day before first dose of study treatment.
- On-treatment period: from day of first dose of study treatment to 30 days after last actual dose of the same study treatment (asciminib or nilotinib).
- Post-treatment period: starting at day 31 after last dose of any study treatment (asciminib or nilotinib).

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

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 deaths including on treatment and

post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, which occur during the on-treatment period (treatment-emergent AEs). Comparative analysis will be performed only for the on-treatment period. Listings of safety data will include pre-treatment, on-treatment, and post-treatment periods, with a flag to indicate data collected before, on or after the on-treatment period.

Adverse events

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

The number (and percentage) of participants with treatment-emergent adverse events (events started after the first dose of study treatment or events present prior to start of study treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

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

The number (and proportion) of participants with AESI will be summarized by treatment arm.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Summary tables for adverse events (AEs) will include only AEs that started during the on-treatment period. The incidence of on-treatment adverse events will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Serious adverse events, non-serious adverse events and AESI during the on-treatment period will be tabulated.

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

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

Vital signs

All vital signs data will be summarized by treatment arm and visit/time. Notable values will be flagged.

12-lead ECG

QT, QTcF, and Heart Rate (HR) intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted locally. Categorical analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. All ECG data will be summarized by treatment arm and visit/time.

Clinical laboratory evaluations/abnormalities

Graphical summary for each lab parameter will be provided. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) *version 5.0.* The calculation of CTCAE grades will be based on the observed laboratory values only, and clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

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

For laboratory tests where grades are defined by CTCAE *version 5.0*:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only once for the worst grade observed post-baseline in the on-treatment period.
- Shift tables using CTCAE *version 5.0* grades to compare baseline to the worst on-treatment value.

For laboratory tests where grades are not defined by CTCAE *version 5.0*:

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

Tolerability

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

9.4.3 Patient reported outcomes

The full analysis set (FAS) will be used for analyzing patient reported outcomes (PRO) data unless specified differently.

The EORTC QLQ-C30 (version 3.0) and the EORTC QLQ-CML24 will be used to assess general health related quality of life and impairment related to the patient's CML (respectively).

Change from baseline in overall scores and individual domains for each PRO instrument will be graphically indicated for each treatment arm. Participants with an evaluable baseline score and at least one evaluable post-baseline score during the Treatment Phase will be included in the change from baseline analyses.

All PRO measures require participants' direct completion and will be administered utilizing electronic device for data collection at scheduled time points from baseline to 3 months post EOT. Missing data items in a scale will be handled according to the manual for each instrument. No imputation will be applied if the total or subscale scores are missing at a visit. All measures will assess differences between the treatment arms.

Additional analyses may be performed if deemed necessary. Such analyses will be defined in the SAP. Additional details for the analyses, models and missing data handling will be specified in the SAP.

9.5 Exploratory endpoint(s)/estimand(s) analysis

9.5.1 CCI

CCI [redacted]

9.5.2 CCI

CCI [redacted]

9.5.3 CCI

CCI [redacted]

CCI [redacted]

9.5.4 CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

CCI [redacted]

9.6 (Other) Safety analyses

Not applicable.

9.7 Other analyses

Not applicable.

9.8 Interim analysis

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

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

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

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

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

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

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

9.9 Sample size determination

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

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

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

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

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

- One-sided level of significance with $\alpha =$ CCI ;
- Power= CCI
- CCI vs. CCI cumulative probability to not discontinue due to AE at week 96, for asciminib and nilotinib, respectively with the difference of $\delta =$ CCI ;
- CCI vs. CCI dropout rates at week 96, for asciminib and nilotinib, respectively;
- Accrual period of approximately 96 weeks at a uniform rate. The treatment duration is 96 weeks;
- 1:1 randomization for asciminib and nilotinib.
- One formal interim analysis using "Gamma Family" alpha spending function with parameter $\gamma =$ CCI (equivalent to $\alpha =$ CCI) for boundary, performed when around CCI discontinuations due to AE will occur;

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

9.9.1 Primary endpoint(s)

The sample size calculation is based on the primary endpoint TTDAE. The hypotheses to be tested and details of the testing strategy are described in Section 9.3.

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

$$H_0: HR = 1$$

$$H_\alpha: HR < 1$$

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

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

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

Signing a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required.

Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.

Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority.

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable

local regulations (including European Directive 2001/20/EC or European Clinical Trial Regulation 536/2014, US CFR 21 (as applicable)), and with the ethical principles laid down in the Declaration of Helsinki.

10.1.2 Informed consent process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.

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

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

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

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

Participants who are rescreened are required to sign a new ICF.

Participants who choose to enter the optional TFR Phase are required to sign an additional ICF.

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

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

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

The following informed consents are included in this study:

- Main study consent, which also included:

  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
  - Optional consent for activities that may be done outside of the study site
- Optional TFR Phase ICF
- As applicable, Pregnancy Outcomes Reporting Consent for female participants

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional additional research. The Investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for additional research. Participants who decline to participate in this optional additional research will document this.

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

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local health authority.

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

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience (Section 8.5.2).

10.1.3 Data protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

10.1.4 Committees structure

10.1.4.1 Data monitoring committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site Investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to Novartis whether to continue, modify, or terminate a trial.

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

10.1.4.2 Steering committee

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

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will consider patient cases where further discussions on patient management are required. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

10.1.5 Data quality assurance

Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

10.1.5.1 Data collection

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated Investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs

check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the Investigator staff.

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

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

Data collected by third parties (i.e. biomarkers, and PROs) will be sent electronically to Novartis.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

10.1.5.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

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

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated Contract Research Organization [CRO]) at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

10.1.6 Source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

Definition of what constitutes source data and its origin can be found in the monitoring guidelines.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters and provide reports to Novartis clinical teams to assist with trial oversight.

10.1.7 Publication policy

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT or Clinical Trials Information System (CTIS) public website (as applicable). In addition, after study completion (defined as last participant last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required health authority websites (e.g. Clinicaltrials.gov, CTIS etc.)

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial Investigator meetings.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

10.1.8 Protocol adherence and protocol amendments

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the Investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by

Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

10.1.8.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

10.2 Appendix 2: Abbreviations and definitions

10.2.1 List of abbreviations

2G	Second Generation
ABL	Abelson proto-oncogene
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALL	Acute Lymphoblastic Leukemia
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Accelerated Phase
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
AUC	Area Under the Curve
AV block	Atrioventricular Block
BC	Blast Crisis
BCR	Breakpoint Cluster Region
BCR::ABL1	*BCR::ABL1* fusion gene
BCR::ABL1	Protein BCR::ABL1
BCRP	Breast Cancer Resistant Protein
BID	Bis In Diem/twice a day
BP	Blood Pressure
BYOD	Bring Your Own Device
CABG	Coronary Artery Bypass Graft
CBC	Complete Blood Count
CCyR	Complete Cytogenetic Response
CFR	Code of Federal Regulations
CHF	Chronic Heart Failure
CHR	Complete Hematological Response
CIF	Cumulative Incidence Function
CML	Chronic Myelogenous Leukemia
CML-AP	Chronic Myelogenous Leukemia-Accelerated Phase
CML-BC	Chronic Myelogenous Leukemia- Blast Crisis
CML-CP	Chronic Myelogenous Leukemia-Chronic Phase
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	Central Nervous System
COA	Clinical Outcome Assessment
COVID-19	Coronavirus Disease of 2019
CP	Chronic Phase
CRA	Clinical Research Associate
CrCl	Creatinine Clearance
CRF	Case Report/Record Form (electronic)
CRO	Contract Research Organization

CSR	Clinical Study Report
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trials Information System
CTT	Clinical Trial Team
CV	Coefficient of Variation
CYP3A4	Cytochrome P450 3A4
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DMR	Deep Molecular Response
DNA	Deoxyribonucleic Acid
DS&E	Drug Safety and Epidemiology
DTI	Direct Thrombin Inhibitors
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EFS	Event Free Survival
EGFR	Epidermal Growth Factor Receptor
ELN	European Leukemia Network
ELTS	EUTOS Long-Term Survival
EMA	European Medicines Agency
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of life Questionnaire
EOT	End of Treatment
ER	Emergency Room
ERCP	Endoscopic Retrograde Cholangio Pancreatography
eSAE	electronic Serious Adverse Event
EU	European Union
EU CTR	European Union Clinical Trial Regulation
EURO-SKI	European Stop Tyrosine Kinase Inhibitor Trial
EUTOS	European Treatment Outcome Study
CCI	[redacted]
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First In Human
FISH	Fluorescence In Situ Hybridization
FSH	Follicle Stimulating Hormone
FU	Follow Up
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase

GI	Gastrointestinal
GLDH	Glutamate Dehydrogenase
GP	General Practitioner
h	Hour
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCG	human chorionic gonadotropin
CCI	[redacted]
HCV	Hepatitis C Virus
HDL	High density lipoprotein
HEV	Hepatitis E Virus
HIV	Human immunodeficiency virus
HR	Heart Rate
HRQoL	Health-Related Quality of Life
HSV	Herpes Simplex Virus
HTA	Health Technology Assessment
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IE	Intercurrent Events
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IMA	Imatinib
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IS	International Scale
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LDL	Low density lipoprotein
LFT	Liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
LPFT	Last Participant First Treatment
LVEF	Left Ventricular Ejection Fraction
LPLV	Last Participant Last Visit
MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)

MI	Myocardial Infarction
mL	milliliter(s)
mL/min	milliliters per minute
MMR	Major Molecular Response
MR	Molecular Response
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum Tolerated Dose
MCyR	Major Cytogenetic Response
NCCN	National Comprehensive Cancer Network
NGS	Next-Generation Sequencing
NTI	Narrow Therapeutic Index
OATP	Organic Anion Transporting Polypeptide
OS	Overall survival
PBPK	Physiologically Based Pharmacokinetic
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PFS	Progression-Free Survival
Ph+	Philadelphia Chromosome Positive
PK	Pharmacokinetic(s)
PLT	Platelets
CCI	[redacted]
CCI	[redacted]
PT	Prothrombin Time
PTA	Post Trial Access
QD	quaque die/once a day
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RD	Recommended Dose
RDE	Recommended Dose for Expansion
RNA	Ribonucleic Acid
RQ-PCR	Real Time Quantitative Polymerase Chain Reaction
CCI	[redacted]
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Steering Committee
SD	Standard Deviation
SoA	Schedule of Activities
SOP	Standard Operating Procedure
Sp	Specialist
STAMP	Specifically Targeting the ABL Myristoyl Pocket (STAMP) Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin

TdP	Torsades de Pointes
TFQ	Trial Feedback Questionnaires
TFR	Treatment Free Remission
TFRE	TFR Eligible Set
TFRS	TFR Analysis Set
TKI	Tyrosine Kinase Inhibitor
TRI	Treatment Re-initiation
TRIS	Treatment Re-initiation Analysis set
TSH	Thyroid Stimulation Hormone
TTD	Time to Treatment Discontinuation
TTDAE	Time To Discontinuation of study treatment due to AE
TTF	Time to Treatment Failure
UC	Urgent Care
UGT	Uridin diPhospho-glucuronosyltransferase
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell(s)
WHO	World Health Organization

10.2.2 Definitions

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Comparator drug	A drug used as a comparator to reduce assessment bias, assess internal study validity, and/or evaluate comparative effects of the investigational drug. In this study, the comparator drug is nilotinib
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study treatment administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. asciminib (80 mg QD) or nilotinib (300 mg BID)).
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case

	Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of study	End of study (EOS) is defined as when the latest of the following events has occurred: The participants in the Treatment Phase who did not enter the optional TFR Phase have either completed CCI of treatment or discontinued prematurely, and completed 30 day post-treatment Safety Follow Up. The participants who entered the TFR Phase have either completed CCI of TFR Phase or discontinued prematurely and completed 30 day Safety Follow Up, or re-initiated treatment in the TRI Phase. The last participant entering in the TRI phase has either completed CCI or discontinued prematurely study, and completed 30 day post-treatment Safety Follow Up.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Health Technology Assessment (HTA)	The systematic evaluation of properties, effects, and/or impacts of health care technology. An assessment report gives information about how the technology can be adapted to current available technologies and the added value of the reviewed technology to the current technologies. This final assessment contains evidence-based conclusions with the outcomes of the use of the technology supporting the decision-making process of health policy-makers. Health technologies include pharmaceuticals, equipment and machines, as well as procedures and physical techniques for health prevention and promotion (PAHO).
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug	The drug whose properties are being tested in the study
Investigational Product/ Investigational Medicinal product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference (such as an active comparator) in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medication number	A unique identifier on the label of investigational drug kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else

Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Remote	Describes any trial activities performed at a location that is not the investigative site.
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (asciminib), or nilotinib
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial.
Treatment arm/group	A treatment arm defines the dose and regimen and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the investigational drug.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

10.3 Appendix 3: Concomitant Medications: Prohibited medication and medication to be used with caution

In general, the use of any concomitant medication deemed necessary for the care of the participant is permitted in this study, except as specifically prohibited in Section 6.6.2 for participants.

The following lists are based on the internal [Pharmacokinetic Sciences memorandum on Drug-Drug Interaction] (release date: Jan-2018), which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling (2017), and the University of Washington's Drug Interaction Database (2017). These lists are not comprehensive and are only meant to be used as a guide. Please contact the medical monitor with any questions.

Table 10-1 Concomitant medications to be used with caution

Category	Drug Names
Torsade de pointe (TdP) TdP/QT risk : Known	aclarubicin, amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, cesium chloride, chloroquine, chlorpromazine, chlorprothixene, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin, gepirone, grepafloxacin, halofantrine, haloperidol, hydroquinidine (dihydroquinidine), hydroxychloroquine, ibogaine, ibutilide, levofloxacin, levomepromazine (methotrimeprazine), levomethadyl acetate, levosulpiride, meglumine antimoniate, mesoridazine, methadone, mobocertinib, moxifloxacin, nifekalant, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, probucol, procainamide, propofol, quinidine, quizartinib, roxithromycin, sertindole, sevoflurane, sotalol, sparfloxacin, sulpiride, sultopride, terfenadine, terlipressin, terodiline, thioridazine, vandetanib
TdP/QT risk: Possible[1]	abarelix, adagrasib, alfuzosin, alimenazine (trimeprazine), apalutamide, apomorphine, aripiprazole, artemether/lumefantrine, artenimol/piperaquine, asenapine, atomoxetine, bedaquiline, bendamustine, bedaquiline, betrixaban, bicalutamide, bortezomib, bosutinib, buprenorphine, cabozantinib, capecitabine, carbetocin, ceritinib, clotiapine, clozapine, cobimetinib, crizotinib,cyamemazine (cyamepromazine), dabrafenib, dasatinib, degarilix, delamanid, desipramine, dexmedetomidine, dextrometorphan/quinidine, dolasetron, efavirenz, eliglustat, encorafinib, entrectinib, epirubicin, eribulin mesylate, ezogabine (retigabine), felbamate, fexinidazole, fingolimod, fluorouracil (5-FU) , flupentixol, gemifloxacin, gilteritinib, glasdegib, granisetron, hydrocodone-ER, iloperidone, imatinib, imipramine (melipramine), inotuzumab ozogamicin, isradipine, ivosidenib, ketanserin, lacidipine, lapatinib, lefamulin, lenvatinib, leuprolide (leuprorelin), levetiracetam, levoketoconazole, levomethadone (levamethadone), lithium, lofexidine, lopinavir/ritonavir, lumateperone, lurasidone, macimorelin, maprotiline, melperone, mianserin, midostaurin, mifepristone, mirabegron, mirtazapine, necitumumab, nicardipine, nilotinib, norfloxacin, nortriptyline, nusinersen, ofloxacin, oliceridine, osilodrostat, osimertinib, oxytocin, ozanimod, pacritinib, paliperidone, palonosetron, panobinostat, pasireotide, pazopanib, perflutren lipid microspheres, perphenazine, pilsicainide, pimavanserin, pipamperone, pitolisant (tiprolisant), ponesimod, pralsetinib, pretomanib, primaquine phosphate, promethazine, prothipendyl, relugolix, remdesvir, remimazolam, ribociclib, rilpivirine, romidepsin, rucaparib, saquinavir, selpercatinib, siponimod, sorafenib, sunitinib, tacrolimus, tamoxifen, tazemetostat, tebentafusp, telavancin, telithromycin, tetrabenazine , tiapride, tipiracil/trifluridine, tizanidine, tolterodine, toremifene, tramadol, triclabendazole,

Category	Drug Names
	trimipramine, tropisetron, valbenazine, vardenafil, vemurafenib, venlafaxine, vernakalant, voclosporin, vorinostat, zotepine, zuclopenthixol (zuclopentixol)
TdP/QT risk: Conditional[1]	abiraterone, amantadine, amisulpride, amitriptyline, amphotericin B, amsacrine (acridinyl anisidide), atazanavir, bendroflumethiazide (bendrofluazide), chloral hydrate, cimetidine, clofazimine, clomipramine, diltiazem, diphenhydramine, doxepin, eperisone, esomeprazole, famotidine, fluoxetine, fluvoxamine, furosemide (frusemide), galantamine, garenoxacin, hydrochlorothiazide, hydroxyzine, indapamide, itraconazole, ivabradine, ketoconazole, lansoprazole, loperamide, metoclopramide, metolazone, metronidazole, nelfinavir, olanzapine, omeprazole, pantoprazole, paroxetine, piperacillin/tazobactam, posaconazole, propafenone, quetiapine, quinine sulfate, ranolazine, risperidone, sertraline, solifenacin, telaprevir, torsemide (torasemide), trazodone, voriconazole, ziprasidone
Strong inducers of CYP3A4	apalutamide, avasimibe, carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin, rifapentine, St. John's wort (Hypericum perforatum)
Narrow Therapeutic index substrates of CYP2C9	erdafitinib, phenytoin, quinidine, tamoxifen, warfarin (also sensitive)
Narrow Therapeutic index substrates of CYP3A4	alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus, terfanadine,
OATP (OATP1B1, OATP1B3 and OATP2B1) substrates:	aliskiren, ambrisentan, anacetrapib, atenolol, asunaprevir, atogepant, atorvastatin, bosentan, bromocriptine, caspofungin, celiprolol, danoprevir, digoxin, docetaxel, eliglustat, empangliflozin, ezetimibe, fimasartan, fexofenadine, fluvastatin, glyburide, ibrexafungerp, maraviroc, methotrexate, montelukast, nateglinide, olmesartan, paclitaxel, pirataprevir, pitavastatin, pravastatin, repaglinide, revefenacin, rifampicin, rosuvastatin, saquinavir, simvastatin, telmisartan, tezacaftor, ticlopidine, valsartan
Narrow Therapeutic index substrates of OATP1B	daunorubicin, docetaxel, doxorubicin, paclitaxel
BCRP substrates	alpelisib, atorvastatin, baricitinib, daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, ozanimod, paritaprevir, pitavastatin, rimegepant, rosuvastatin, irinotecan, ethinyl estradiol, simvastatin, sofosbuvir, sulfasalazine, tenofovir, tezacaftor, topotecan, ubrogepant, venetoclax
Narrow Therapeutic Index substrates of P-gp	baricitinib, cyclosporine, dabigatran, digoxin, docetaxel, doxepin, doxorubicin, eribulin, everolimus, fentanyl, idelalisib, ivosidenib, paclitaxel, pazopanib, phenytoin, quinidine, sirolimus, sorafenib, tacrolimus, talazoparib, tolvaptan, topotecan, vincristine

10.4 Appendix 4: Eligibility based on serologic markers for hepatitis B and C

Table 10-2 Eligibility based on serologic marker for hepatitis B

Test	Result				
HBsAg	+	-	-	-	-
HBcAb	Any	+	-	+	-
HBsAb	Any	-	+	+	-
Eligibility	Not Eligible	Indeterminate	Eligible	Eligible	Eligible

Table 10-3 Eligibility based on serologic marker for hepatitis C

Test	Result	
HCV Ab	+	+
HCV RNA	+	-
Eligibility	Not Eligible	Eligible

If indeterminate results are obtained, viral DNA (hepatitis B) or Ribonucleic Acid (RNA) (hepatitis C) should be measured to confirm negative viral status.

HBsAg positive: Indicates active infection and risk for reactivation with fulminant hepatitis. These patients are not eligible for the trial.

HBcAb positive: As a standalone marker it can indicate four possibilities: Resolved infection (Immune due to natural infection), false-positive anti-HBc (susceptible for infection), low level chronic infection and resolving acute infection.

HBV-DNA should be performed if only HBcAb is positive at screening and if positive then the patients are not eligible for the trial. Even if HBV-DNA is negative suggesting resolved infection, there is still a risk for HBV reactivation. In these cases, HBV-DNA should be monitored on a monthly basis to detect HBV reactivation.

Both HBcAb and HBsAg are positive: Indicates active infection and risk for reactivation with fulminant hepatitis. These patients are not eligible for the trial. Hence HBV-DNA testing is not necessary.

HBsAb positive: As a standalone marker, it indicates successful vaccination or previous infection that has been successfully resolved if the only positive finding. These patients are eligible for the trial.

HBsAg negative, HBcAb positive, HBsAb positive: Resolved or latent infection. These

patients are eligible for this trial; however, they are at risk for viral reactivation.

HCV Ab positive: Indicates past infection.

HCV-RNA should be assessed if only HCV Ab is positive at screening and if HCV-RNA is positive then these patients are not eligible for the trial.

All markers negative: No prior exposure or vaccination to hepatitis B and no prior exposure to Hepatitis C. Patients are eligible for the trial.

10.5 Appendix 5: Participant Engagement

The following participant engagement initiatives are included but not limited in this study and will be provided, as available, for distribution to study participants at the timepoints indicated.

If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter
- Trial Feedback Questionnaires (TFQ)
- Plain language trial summary-after CSR publication

10.6 Appendix 6: Liver safety monitoring

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

The following two categories of abnormalities/AEs have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter.
- Liver events, which will require close observation, follow-up monitoring. Please refer to Table 10-3 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 10-3 should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 10-4. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats should be performed using a central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unplanned local laboratory CRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on Investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.6.1 Liver event and laboratory trigger definitions & follow-up requirements

Table 10-4 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5

	Definition/ threshold
	• Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity
If ALT or AST abnormal at baseline:	• ALT or AST > 3x baseline or > 300 U/L (whichever occurs first)

Table 10-5 Follow up requirements for liver laboratory triggers - Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	• Maintain treatment • Repeat liver tests within 48-72 hours	Monitor liver tests weekly until resolution to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	• Interrupt treatment • Repeat liver tests within 48-72 hours • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Monitor liver tests weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, TBL, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors(e.g., conmeds, med hx, lab) in the appropriate CRF	Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

10.7 Appendix 6: Renal safety monitoring

Table 10-6 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50%[+] compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider participant hospitalization /specialized treatment
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor participant regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline , or Event stabilization: sCr level with ±10% variability over last 6 months	
[+] Corresponds to KDIGO criteria for Acute Kidney Injury	

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