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Novartis Research and Development

ABL001/Asciminib

Clinical Trial Protocol CABL001AUS04 / NCT04666259

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

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Table of contents

[redacted]

[redacted]

[redacted]

List of tables

[redacted]

List of figures

[redacted]

List of abbreviations

ABL	Abelson proto-oncogene
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute neutrophil count
AP	Accelerated phase
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATP	Adenosine triphosphate
AUC	Area under the curve
AV	block Atrioventricular block
b.i.d.	bis in die/twice a day
BC	Blast crisis
BCR	Breakpoint Cluster Region gene
BCR-ABL	BCR-ABL fusion gene (also called the Philadelphia chromosome)
BCRP	Breast Cancer Resistant Protein
BID	bis in diem/twice a day
BLRM	Bayesian Logistic Regression Model
BMA	Bone marrow aspirate
BMI	Body Mass Index
BUN	Blood urea nitrogen
CBC	Complete Blood Count
CCA	Clonal chromosome abnormalities
CCyR	Complete Cytogenetic Response
CD34	Cluster of differentiation 34
CD8	Cluster of differentiation 8
CDP	Clinical Development Plan
CDS	Core Data Sheet
CHR	Complete Hematological Response
CI	Confidence Interval
CK	Creatinine Kinase
ClinRO	Clinician Reported Outcomes
CML	Chronic Myelogenous Leukemia
CML-AP	Chronic Myelogenous Leukemia-Accelerated Phase
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
CO2	carbon dioxide
[redacted]	[redacted]

[redacted]

CP	Chronic phase
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP3A4	Cytochrome P450 3A4
DBP	Diastolic Blood Pressure
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DIN	Drug Inducted Nephrotoxicity
DLCO	Carbon monoxide diffusing capacity
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DQF	Data Query Form
DS&E	Drug Safety and Epidemiology
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
ELN	European Leukemia Network
EOI	End of Infusion
EOT	End of Treatment
ERT	Electronic Research Technology, Inc
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First In Human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GDPR	General Data Protection Regulation
GFR	Glomerular Filtration Rate
GGT	Gamma-glutamyl transferase

[redacted]

h	Hour
hADME	Human ADME study (Absorption, Distribution, Metabolism and Excretion)
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High density lipoprotein
HED	Human Equivalent Dose
HEOR	Health Economics & Outcomes Research
HIV	Human immunodeficiency virus
HNSTD	Highest Non-Severely Toxic Dose
[redacted]	[redacted]
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IN	Investigator Notification
INN	International Nonproprietary Name
INR	International normalized ratio
IWRS	Interactive Web Response System
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and
Km	Michaelis-Menten constant
K-M	Kaplan-Meyer
LDH	lactate dehydrogenase
LDL	Low density lipoprotein
LFT	Liver function test
LLN	Lower limit of normal
LLOQ	lower limit of quantification
LSC	Leukemia stem cell
MCyR	Major Cytogenetic Response
mCyR	Minor Cytogenetic Response
[redacted]	[redacted]
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMR	Major Molecular Response
MRI	Magnetic resonance imaging

[redacted]

MRSD	Maximum Recommended Starting Dose
MTD	Maximum Tolerated Dose
Nab	Neutralizing antibody
NCCN	National Comprehensive Cancer Network
NCDS	Novartis Clinical Data Standards
[redacted]	[redacted]
NOVDD	Novartis Data Dictionary
NTI	Narrow Therapeutic Index
ObsRO	Observer Reported Outcomes
OS	Overall survival
p.o.	oral(ly)
[redacted]	[redacted]
PBPK	Physiologically based pharmacokinetic
PCR	Polymerase Chain Reaction
PCyR	Partial Cytogenetic Response
PD	Pharmacodynamic(s)
PerfO	Performance Outcomes
[redacted]	[redacted]
P-gp	Permeability glycoprotein
Ph+	Philadelphia chromosome positive
PHI	Protected Health Information
PK	Pharmacokinetic(s)
PLT	Platelets
PPD	Premature Participant Discontinuation
PPS	Per-protocol set
[redacted]	[redacted]
PSD	Premature Subject Discontinuation
PT	prothrombin time
QD	Quaque die/once a day
QMS	Quality Management System
QT	Q to T interval (ECG)
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RAP	The Report and Analysis Plan
RBC	red blood cell(s)
RDC	Remote Data Capture
RDE	Recommended dose for expansion
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
RoW	Rest of World
RP2D	Recommended phase two dose

[redacted]

RQ-PCR	Real time quantitative polymerase chain reaction
[redacted]	[redacted]
s.c.	subcutaneous
SAE	Serious Adverse Event
SAP	The Statistical Analysis Plan (SAP) is a regulatory document which provides evidence of preplanned analyses
SBP	Systolic Blood Pressure
SC	Steering committee
sCR	serum creatinine
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBIL	Total bilirubin
TD	Study Treatment Discontinuation
TdP	Torsades de Pointes
TKI	Tyrosine Kinase Inhibitor
TTF	Time to treatment failure
UGT	Uridin diPhospho-glucuronosyltransferase
ULN	Upper limit of normal
ULQ	upper limit of quantification
US	United States
USPI	US prescribing information
UTI	Urinary Tract Infection
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
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
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
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 paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	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 patients 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
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/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication 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

[redacted]

Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
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.
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
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug
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.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized participant
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
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 or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, 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

[redacted]

	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 study treatment.
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.
Victim drug	The drug that is affected by the drug-drug interaction
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

[redacted]

Amendment 3 (22-Mar-2022)

At the time of this amendment 25 patient have been enrolled for the study

The primary purpose of this amendment is:

Per FDA guidance, the cohort allocation and asciminib dosage depends on T315I mutational status, and to ensure that patients with T315I negative status did not develop a detectable T315I mutation post mutation analysis and prior to receiving asciminib. Novartis recognizes that, in order to ensure patients have not acquired a new kinase domain mutation, such as T315I, before study drug treatment, eligible patients will now require having kinase domain mutation testing at Baseline.

To clarify and address inclusion and exclusion criteria and assessment schedule as listed below

Other administrative edits and typographical corrections are also applied throughout the protocol.

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.

- Protocol Summary: updated Key Inclusion criteria # 3
- Section 5.1: updated Key Inclusion criteria # 3
- Section 6.2.4: updated contraceptives language
- Table 6-2: updated CTCAE grade from 4.03 to 5
- Table 6-2: update Investigations (Hepatic) parameters to match CTCAE Version 5
- Table 8-1: Added footnote in Echocardiogram, Pulmonary Function test, [redacted]
- Section 8.1: removed coagulation from Screening
- Section 8.1.4: amended week 1 day 1 and week 36 for visit window
- Section 8.3.2.1: added medical monitor
- Section 8.3.2.2: updated title and language
- [redacted]
- Section 9.1.1: updated treatment failure with ELN criteria
- corrected table 9-4 to table 8-7 and table 9-5 to table 8-8

- **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.

[redacted]

Amendment 2 (27-Jan-2021)

Amendment rationale

At the time of this amendment, there has been no patient enrolled for the study.

The primary purpose of this amendment is:

To prohibit the use of strong CYP3A inhibitors for patients with Ph+ CML-CP harboring the T315I mutation receiving asciminib 200 mg BID.

To prohibit the use of strong CYP3A inducers for all patients in study CABL001AUS04.

To clarify the eligibility criteria regarding the inclusion of patients with mild and moderate hepatic impairment in the protocol as follows: Include patients with mild and moderate hepatic impairment with total bilirubin ≤ 3.0 x ULN with any AST increase.

Other minor edits and typographical corrections are also applied throughout the protocol.

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.

- Section 5.1: Amend inclusion criteria # 9: Inclusion of patients with mild and moderate hepatic impairment with total bilirubin ≤ 3.0 x ULN with any AST increase.
- Section 5.1: Amended inclusion criteria # 9: Remove the inclusion criteria “Aspartate transaminase (AST) ≤ 5.0 x ULN”, “Alanine transaminase ≤ 5.0 x ULN” and “Alkaline Phosphatase ≤ 2.5 x ULN
- Section 5.1: Remove inclusion criteria # 11
- Section 5.2: Added exclusion criteria # 10
- Section 6.2.1.1: Updated language for permitted concomitant therapy requiring caution and/or action
- Section 6.2.2: Updated language for prohibited medication
- [redacted]
- Table 8-4: Removed week 2 day 1 from Physical examination under Assessment
- Section 8.3.2.1: Replaced ERT with central ECG Reader.
- Table 16-1: added strong CYP3A inducer and CYP3A inhibitor names in the table
- Added Table 16-2 Concomitant medications to be used with caution

IRBs/IECs

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

[redacted]

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

[redacted]

Amendment 1 (08-Dec-2020)

Amendment rationale

At the time of this amendment, there has been no patient enrolled for the study.

The primary purpose of this amendment is:

[redacted]

Include patients with mild to moderate renal or hepatic impairment in the study. Based on the results from the dedicated hepatic (CABL001A2103) and renal (CABL001A2105) impairment studies that have already been completed with asciminib, no dose adjustments are needed.

Other minor edits and typographical corrections are also applied throughout the protocol.

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.

- Title page: Added AIM4CML name of the study
- Section 1.2.2.2: Added a sentence to refer to Asciminib Investigator's Brochure
- Section 2: Clarified the primary endpoint to laboratory evaluation for 24 weeks
- Section 2: Clarified the secondary endpoint to laboratory evaluation for 24 weeks
- [redacted]
- Figure 3.1: Updated study design
- Section 4.1: Added a sentence to refer to Asciminib Investigator's Brochure
- Section 5.1: Inclusion # 9 Updated renal and hepatic impairment inclusion criteria
- Section 5.1: Inclusion # 10 Added use of CYP3A with caution
- Section 5.2: Exclusion # 6 Updated renal and hepatic impairment exclusion criteria
- Section 5.2: Exclusion # 10 removed exclusion to use of CYP3A

[redacted]

- Section 6.2.1.1: Update language for using CYP3A with caution
- Section 6.2.2: Removed prohibition of CYP3A inhibitors paragraph
- Section 6.7: Updated language from Investigator staff to IRT
- [redacted]
- [redacted]
- [redacted]
- Table 8-1: Clarified progression status to be captured on EOT/Early Discontinuation
- Section 8.1: Clarified a new patient ID will be assigned to re-screening patients
- Section 8.3.3: Formatted the last paragraph
- Section 8.4.2: Clarified local hematologic responses
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Section 11.1: Updated data collection
- Section 12.4.2: Clarified supportive analyses to be done for patient (< 65 years; ≥ 65 years)
- [redacted]
- [redacted]
- Section 15: Added new reference
- Table 16.1: Updated table as per inclusion # 9

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.

[redacted]

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.

[redacted]

Protocol summary

Protocol number	CABL001AUS04
Full Title	An open label, multi-center Phase IIIb study of asciminib (ABL001) monotherapy in previously treated patients with chronic myeloid leukemia in chronic phase (CML-CP) with and without T315I mutation
Brief title	A Phase IIIb study of asciminib in CML-CP with and without T315I mutation
Sponsor and Clinical Phase	Novartis/ Phase IIIb Study
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Asciminib (ABL001) is a potent BCR-ABL1 allosteric inhibitor currently being developed by Novartis for the treatment of CML (Chronic Myelogenous Leukemia). Unlike drugs such as imatinib, nilotinib, dasatinib, bosutinib and ponatinib, which bind to the ATP-site of the ABL kinase domain, asciminib binds to the myristoyl pocket and consequently, restores the negative regulation of the kinase activity[1]. Given this unique mechanism of action, it has been proven to have activity against BCR-ABL1 mutations that are known to confer resistance to the ATP site TKIs (tyrosine kinase inhibitors)[1]. Moreover, the selective binding of asciminib is predicted to reduce toxicities, which is an encouraging feature for patients where side effects from previous treatments were the reason for drug discontinuation. Based on phase I data, asciminib has been proven safe and effective in patients who had more than 2 lines of therapy, with 32% and 44% of those achieving MMR in 6 and 12 months, respectively[2]. The incidence of grade 3/4 treatment emergent AEs were mostly less than 10%, which implies a favorable safety profile in a heavily pre-treated CML population. The ongoing ASCEMBL study is a phase III study, which is investigating the efficacy of treatment with asciminib versus bosutinib in CML-CP patients with at least 2 prior TKI therapies. Data from this study are expected to be presented at an upcoming medical meeting and results will be shared with regulatory authorities. Despite its phase III design with randomization, questions remain such as safety and efficacy on a larger patient population including those harboring the T315I mutation and of a daily dosing schedule. A once daily regimen could be more convenient as we believe it will greatly improve patient's adherence as well as quality of life. For that dosing schedule, the dose of 80 mg was selected based on similar efficacy and safety profile when compared to 40 mg twice daily from early phase data. The study currently proposed is a phase IIIb open-label study on patients with resistant or intolerant CML-CP previously treated with at least 2 prior TKIs in the absence of T315I mutation and at least 1 prior TKI in the presence of the T315I mutation. Our goal is to gain further efficacy and safety data with asciminib monotherapy on a larger population of patients. The study will contain the following cohorts: • Cohort A asciminib 40 mg BID • Cohort B asciminib 80 mg QD • Cohort C asciminib 200 mg BID, exclusively for those harboring the T315I mutation

	As above, patients with CML-CP without the T315I mutation will be randomly assigned to either cohort A or B (both primary). Randomization into those 2 cohorts will be pursued to eliminate selection bias at the time of patient allocation. Additionally, there will be a separate cohort enrolling patients harboring the T315I mutation to strengthen the body of evidence generated in the CABL001X2101 study, which has already treated 58 patients with that mutation in the asciminib extension cohort at 200 mg BID showing encouraging antileukemic activity and well tolerated safety profile.
Primary Objective(s)	• To evaluate safety profile of monotherapy asciminib in CML-CP in 3L and beyond, for Cohorts A and B
Secondary Objectives	• To estimate the rate of patients with molecular response at specific time points for Cohort A ,B and C • To estimate time to molecular response • To evaluate the duration of hematologic and molecular response
Study design	This study will be a multicenter Phase IIIb study of randomized open-label asciminib in patients with CML without T315I mutation who have had at least 2 prior TKIs and CML-CP with T315I mutation with at least 1 prior TKI. The primary outcome is to evaluate the safety profile of asciminib with AEs, SAEs and laboratory studies' assessment at 24 weeks of therapy. The secondary endpoints will include efficacy and safety measures at 12, 24, 48, 72 weeks of therapy. For patients without T351I mutation, they will be randomly assigned to the following cohorts: •**Cohort A (45)** where patients will be given asciminib at 40 mg twice daily •**Cohort B (45)** where patients will receive asciminib at 80 mg daily Data from CABL001X2101 study showed encouraging efficacy and safety findings in 40 mg twice daily and 80 mg daily-treated patients. • **Cohort C (25)**, patients harboring the T315I mutation will be treated on the dose of 200 mg twice daily. The higher dose required for that patient population related to its required concentration to attain optimal blockade of the kinase activity[2]. Patients will continue therapy until disease progression, unacceptable toxicity or elective treatment discontinuation.
Study population	One hundred and fifteen (115) patients with CML-CP without T315I mutation who have had at least 2 prior TKIs (90 patients) and CML-CP harboring the T315I mutation (25 patients) with at least 1 prior TKI will be considered for the current study. Patients with a medical history of the T315I mutation at study entry will be included in the trial. Previous medical records should be used to confirm the patient's mutational status/history.
Key Inclusion criteria	Participants eligible for inclusion in this study must meet **all** of the following criteria: 1. Written informed consent must be obtained and signed prior to participation in the study 2. Male or female patients with a diagnosis of CML-CP ≥ 18 years of age 3. Patients must meet all of the following laboratory values at the screening visit: • < 15% blasts in peripheral blood or bone marrow • < 30% blasts plus promyelocytes in peripheral blood or bone marrow • < 20% basophils in the peripheral blood • ≥ 50 x 10^9/L (≥ 50,000/ mm^3) platelets • Transient prior therapy related thrombocytopenia (< 50,000/mm^3 for ≤ 30 days prior to screening) is acceptable

	• No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly 4. Mutation Analysis testing performed at screening 5. Prior treatment with a minimum of: • 2 prior ATP-site TKIs (i.e. imatinib, nilotinib, bosutinib, dasatinib or ponatinib) in case of absence of T315I mutation • 1 prior ATP site TKI (i.e. imatinib, nilotinib, bosutinib, dasatinib or ponatinib) in case of presence of T315I mutation 6. Failure (adapted from the 2020 ELN Recommendations) or intolerance to the most recent TKI therapy at the time of screening • Failure for CML-CP patients (CP at the time of initiation of last therapy) is defined as meeting at least one of the following criteria. • Three months after the initiation of therapy: >10% BCR-ABL1 on International Scale (IS) if confirmed within 1-3 months • Six months after the initiation of therapy: BCR-ABL1 ratio > 10% IS • Twelve months after initiation of therapy: BCR-ABL1 ratio > 1% IS • At any time after the initiation of therapy, loss of CHR, MR2 • At any time after the initiation of therapy, the development of new BCR-ABL1 mutations which potentially cause resistance to current treatment • At any time 12 months after the initiation of therapy, BCR-ABL1 ratio ≥ 1% IS or loss of MMR • At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cells: CCA/Ph+ • Intolerance is defined as: • Non-hematologic intolerance: Patients with grade 3 or 4 toxicity while on therapy, or with persistent grade 2 toxicity, unresponsive to optimal management, including dose adjustments (unless dose reduction is not considered in the best interest of the patient if response is already suboptimal) • Hematologic intolerance: Patients with grade 3 or 4 toxicity (absolute neutrophil count [ANC] or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by manufacturer 7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2 8. Evidence of typical BCR-ABL1 transcript [e14a2 and/or e13a2] at the time of screening which are amenable to standardized RQ-PCR quantification. 9. Adequate end organ function, within 12 days before the first dose of asciminib treatment. Patients with mild to moderate renal and hepatic impairment are eligible if: • Total bilirubin ≤ 3.0 x ULN with any AST increase • Serum lipase ≤ 1.5 x ULN. For serum lipase > ULN - ≤ 1.5 x ULN, value should be considered not clinically significant and not associated with risk factors for acute pancreatitis • Creatinine clearance ≥ 30 mL/min as calculated using Cockcroft-Gault formula 10. Patients must avoid consumption of grapefruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days

	before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed. 11. Patients must have the following electrolyte values (as per central laboratory tests) within normal limits or corrected to be within normal limits with supplements prior to first dose of study medication: • Potassium (potassium increase of up to 6.0 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits) • Total calcium (corrected for serum albumin); (calcium increase of up to 12.5 mg/dl or 3.1 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits) • Magnesium, with the exception of magnesium increase > ULN – 3.0 mg/dL; > ULN - 1.23 mmol/L associated with creatinine clearance (calculated using Cockcroft-Gault formula) within normal limits.
Key Exclusion criteria	1. Known second chronic phase of CML after previous progression to AP/BC 2. Previous treatment with a hematopoietic stem-cell transplantation 3. Cardiac or cardiac repolarization abnormality, including any of the following: • History within 6 months prior to starting study treatment of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG) • 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 at screening ≥450 msec (male patients), ≥460 msec (female patients) • 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 wwwcrediblemeds.org/ that cannot be discontinued or replaced 7 days prior to starting study drug 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, pulmonary hypertension) 5. History of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis 6. Known presence of significant congenital or acquired bleeding disorder unrelated to cancer 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. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or gastric bypass surgery) 9. Previous treatment with or known/ suspected hypersensitivity to asciminib or any of its excipients.

	10. Treatment with medications that meet one of the following criteria and that cannot be discontinued at least one week prior to the start of treatment with study treatment; • For Cohort A (40 mg BID) and for Cohort B (80 mg QD) patients not harboring the T315I mutation o strong inducers of CYP3A • For Cohort C (200 mg BID for patients harboring the T315I mutation) o strong inducers of CYP3A o strong inhibitors of CYP3A 11. Participation in a prior investigational study within 30 days prior to randomization or within 5 half-lives of the investigational product, whichever is longer 12. Pregnant or nursing (lactating) women 13. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception. Highly effective contraception methods include: • Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. 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) total hysterectomy or bilateral tubal ligation 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 sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject. • Use of oral, 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 and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking study medication. In the case of oophorectomy alone, women are considered post-menopausal and not of childbearing potential only when the reproductive status of the woman has been confirmed by follow up hormone level assessment. 14. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 3 days after stopping study (only for patients treated with asciminib). A condom is required for all sexually active male participants on asciminib treatment to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner.

	In addition, these male participants must not donate sperm for the time period specified above. 15. If a patient is presenting with symptoms suggestive of possible COVID-19 infection, we advise ruling it out by appropriate testing recommended by health authorities. • Nucleic acid amplification tests for viral RNA (polymerase chain reaction), in order to measure current infection with SARS-CoV-2 • Antigen tests for rapid detection of SARS-CoV-2 • Antibody (serology) tests to detect the presence of antibodies to SARS-CoV-2
Study treatment	Asciminib 40 mg BID, 80 mg QD or 200 mg BID (T315I mutation only)
Efficacy assessments	• Molecular response (RQ-PCR, mutational analysis) • Hematologic Response
Key safety assessments	• Physical examination • Vital Sign • Height and weight • ECOG performance status • Laboratory chemistry and hematology • Serology • Electrocardiogram (ECG) • Echocardiogram • Pulmonary function tests with DLCO
Data analysis	Primary objective of the study is to assess safety profile of asciminib during 24 weeks for all patients within each cohort, Approximately total 115 (45+45+25=115) patients will be enrolled for Cohort A (n1=45), Cohort B (n2=45) and for Cohort C (n3=25) for the study. For all primary safety analyses, the Safety Set will be used, unless stated otherwise. All AEs and SAEs will be summarized. No inferential tests for safety analyses will be performed. All primary, secondary [redacted] variables will be summarized descriptively. Categorical data will be presented in frequencies and percentages. For continuous data descriptive statistics (mean, standard deviation, median 25th and 75th percentiles, min and max) will be provided. As appropriate, 95% confidence intervals will also be reported. Kaplan Meier's estimates will be reported for the time to event variables. As the primary time point is by 24 weeks, the primary analysis will be an interim analysis where formal primary DBL will be complete and all analyses will be performed. As appropriate, annual interim analyses will be planned for publication or any regulatory purpose. No formal interim analysis will be performed.
Key words	Phase IIIb, open-label trial, asciminib, CML-CP, previous treatment with TKIs, T315I mutation

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1 Introduction

1.1 Background

1.1.1 Overview of disease pathogenesis, epidemiology and current treatment

Chronic myeloid leukemia (CML) is a hematological stem cell disorder characterized by a specific chromosomal translocation leading to the Philadelphia (Ph) chromosome which is detected in 95% of patients (Nowell and Hungerford 1960; Rowley 1973]). The molecular consequence of the translocation is the fusion of the *ABL1* proto-oncogene to the *BCR* gene resulting in the production of an activated form of the ABL1 protein tyrosine kinase (TK) (Bartram et al 1983; Heisterkamp et al 1983). BCR-ABL1 drives the growth factor independence, increased proliferation, genomic instability, suppression of apoptosis and alteration of the adhesive properties of CML cells (Hochhaus 2009) and the expression of BCR-ABL1 in mice results in the development of a CML-like disease (Daley et al 1990; Kelliher et al 1990). This evidence that BCR-ABL1 is a genetic driver of CML was subsequently confirmed by the clinical efficacy of imatinib in patients (IRIS Study STI571A0106).

Clinically, CML is characterized by overproduction of immature myeloid cells and mature granulocytes in the spleen, bone marrow and peripheral blood. Most patients, however, present in the CP, characterized by splenomegaly and leukocytosis with generally few symptoms. CML progresses through three distinct phases of increasing refractoriness to therapy: chronic phase (CP), accelerated phase (AP), and blast crisis (BC). With conventional chemotherapy, such as busulfan or hydroxyurea, the median survival time commonly reported for CML was about 4 years, but progression to AP and BP was only slightly delayed. Interferon-alfa delayed progression significantly, with a median survival of approximately 6 years. Allogeneic hematopoietic stem cell transplantation provided CML patients the highest chance for cure and long term control of the disease. However, during the last decade, TK inhibitor (TKI) therapy became the standard treatment for most patients with CML, with complete cytogenetic response rates of 70% to 90% and 5-year progression-free survival and overall survival of 80% to 95% commonly reported (Vardiman 2009).

The National Comprehensive Cancer Network (NCCN) guideline on CML (NCCN guideline v 1.2014) and the European Leukemia Net (ELN) (Baccarani et al 2013) recommend continuing TKI treatment indefinitely in all responding patients. The first TKI, imatinib mesylate (imatinib, STI571, Gleevec™/Glivec™), an adenosine triphosphate (ATP)-competitive TKI with selectivity towards BCR-ABL1, revolutionized treatment of CML and significantly improved the prognosis of patients since its approval in 2001. It is effective in most patients with CML at well-tolerated doses, and is indicated as frontline therapy for Ph+ CML-CP and in patients with Ph+ CML in blast crisis (BC), accelerated phase (AP), or in CP after failure of interferon-alpha therapy. However, despite the remarkable efficacy of imatinib, some patients are either intolerant to the drug or can develop resistance (O'Hare 2006). Imatinib resistance is primarily due to nucleotide substitutions in BCR-ABL1, which encode mutant forms of protein's tyrosine kinase domain that impair imatinib binding. Over-expression of the BCR-ABL1 protein may also cause resistance. Rates of resistance increase with each stage of progression of CML (CP < AP < BC) (Branford 2003).

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Multiple agents, including nilotinib, dasatinib, ponatinib, bosutinib, radotinib (Korea) and omacetaxine (USA, Canada) are able to treat various forms of imatinib-resistant CML and are currently approved for patients with CML-CP previously treated with prior therapy. With the exception of omacetaxine, which is a cytotoxic chemotherapeutic agent, all of these drugs are ATP-competitive TKIs. Like imatinib, nilotinib, dasatinib and most recently bosutinib are also indicated for the treatment of patients with newly diagnosed CML. The activity of nilotinib or dasatinib in patients previously treated with a second generation TKI is not known. In contrast to the ATP-competitive TKIs, asciminib inhibits the enzymatic activity of BCR-ABL1 through an allosteric mechanism.

1.1.2 Introduction to investigational treatment

Overview of asciminib (ABL001)

Asciminib is a potent orally bioavailable BCR-ABL1 tyrosine kinase inhibitor that specifically binds to the allosteric site on the kinase SH1 domain normally occupied by the myristoylated Gly2 residue on the N-terminus of ABL1 SH3 domain (Schoepfer et al 2018). The agent inhibits the proliferation of CML and ALL cells that are dependent on BCR-ABL1. This mechanism of action contrast to that of drugs such as bosutinib (Bosulif®), dasatinib (Sprycel®), imatinib (Gleevec®), nilotinib (Tasigna®) and ponatinib (Iclusig®) that bind to the adenosine triphosphate(ATP)-site of the kinase SH1 domain.

1.1.2.1 Non-clinical experience

In vitro and in vivo pharmacology data

Asciminib displays potent anti-tumor activity *in vivo* with a clear pharmacokinetic (PK)/pharmacodynamic (PD)/Efficacy relationship [RD-2013-50145]. In a KCL-22 CML blast crisis (CML-BC) cell line mouse subcutaneous xenograft model, tumor regression was observed at doses of 7.5 mg/kg BID and above when asciminib was administered alone. Efficacy in the KCL-22 xenograft model correlated with stable inhibition of the downstream PD marker phospho-STAT5, consistent with finding that ABL1 inhibits STAT5 phosphorylation in KCL22 cells with an IC_{90} value of approximately 20 nM.

The KCL-22 xenograft model was also used to assess the activity of asciminib and nilotinib as single agents and in combination (Figure 1-1). In these experiments, when each agent was administered as monotherapy in sequence, initial sensitivity of the tumor was observed to each agent, but relapse occurred in each case. The mutations observed were as expected based on clinical experience (T315I for nilotinib) or modeling (A337V) for asciminib. In contrast, animals treated upfront with the combination of asciminib and nilotinib achieved sustained tumor regression with no evidence of disease relapse during the 70 days of treatment or for 80 days following discontinuation of treatment. Note that in this KCL-22 model, the cells (derived from a blast crisis CML patient) were grown as a solid tumor rather than as disseminated disease. Also, this model is much more aggressive than chronic phase CML in patients.

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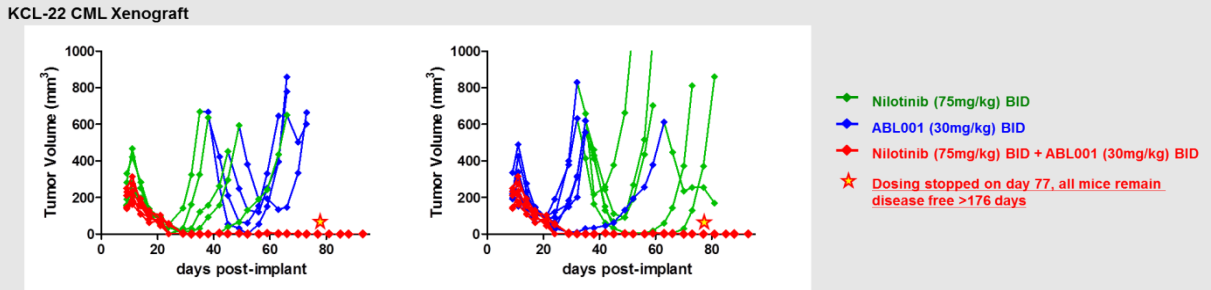
Figure 1-1 KCL-22 CML Xenograft



These data are consistent with asciminib being active against nilotinib-resistant mutations and nilotinib being active against asciminib-resistant mutations. Consequently, the findings support development of asciminib both as single agent as well as in combination with TKIs as initial therapy of CML as well as therapy after progression on nilotinib.

In addition, due to asciminib specifically targeting the ABL kinase family (ABL1, ABL2, BCR-ABL1), asciminib offers the potential for improved safety and tolerability when administered as monotherapy when compared to TKIs binding to the ATP site of BCR-ABL1, which are less specific towards ABL. Thus, there is the potential for an improved safety profile of asciminib in comparison to other TKIs.

Safety pharmacology and toxicology

An extensive toxicology safety evaluation program (subchronic, chronic, reproductive toxicology, phototoxicity and genotoxicity studies) was conducted.

Safety pharmacology studies indicate that asciminib is not expected to cause effects on the vital functions of the CNS, and the respiratory systems. The IC50 for asciminib in the hERG patch clamp is 11.4 µM (4498 ng/mL). No cardiovascular effects were observed in a single dose jacketed telemetry study in dogs at doses up to 600 mg/kg or the invasive telemetry cardiovascular safety study up to 60 mg/kg. Furthermore, no changes in cardiovascular parameters related to QTc prolongation were observed using standard electrocardiography in the 4-week dog toxicity study and in cynomolgus monkey toxicity studies (up to 39 weeks of treatment).

Asciminib does not show mutagenic, clastogenic, or aneugenic potential in the *in vitro* assays or the MNT assessment *in vivo*; therefore, no potential risk for human is perceived.

As determined by the results of the phototoxicity assessment (*in vitro* and *in vivo*), phototoxic potential was identified in the mouse UV-LLNA assay. Given these data, patients should be advised to avoid prolonged exposure to sunlight (sunbathing), to avoid sunbed and to use sunscreen.

Toxicity studies performed in rats, dogs and cynomolgus monkeys (up to 26, 4 and 39 weeks of treatment, respectively) identified the pancreas, liver, hematopoietic system, adrenal and gastro-intestinal tract as potential target tissues.

Fetal malformations and increased visceral and skeletal variants were observed in the rat embryo-fetal development study. There was no evidence of effects on reproductive function in the fertility study; however there was a slight effect on male sperm motility and/or sperm count

in individual animals. Phototoxic potential was identified in the phototoxicity (*in vitro* and *in vivo*) assessment.

Please refer to the latest [Asciminib Investigator's Brochure] for more details.

Non-clinical pharmacokinetics and metabolism

The preclinical pharmacokinetic profile of asciminib has been investigated in three species: mouse, rat and dog. In these species, asciminib exhibited low to moderate clearance, a moderate volume of distribution and a short apparent terminal half-life. Bioavailability was found to be low in rodents and moderate to high in dog.

Asciminib displayed high plasma protein binding across all tested species (2-6% free fraction).

The metabolite profile of asciminib has been examined in vitro using rat, dog, monkey and human hepatocytes. Interspecies differences were observed in the *in vitro* metabolism of asciminib in hepatocytes, with direct glucuronidation occurred more readily in human, to a lesser extent in dog and monkey, and was noticeably absent in rat. However, no unique, major metabolites were identified in human hepatocytes. The overall metabolic turnover was low.

The metabolite profile of asciminib has also been examined *in vivo* in rats. Following intravenous and oral administration of [^{14}C-asciminib] to intact rats, asciminib was found to be the predominant component of plasma, accounting for ~86 - 91% of radioactivity from 0 - 8 h. Asciminib was excreted primarily in the feces, with ~90% of radioactivity detected in the feces from 0 - 48 h. Renal elimination represented a minor route, with ~2.4% of radioactivity detected in the urine from 0 - 72 h. In the feces, ~58% (intravenous) and ~71% (oral) of the dose was associated with unchanged asciminib, with several oxidative metabolites accounting for the remaining radioactivity. The metabolites formed *in vivo* were consistent with those observed *in vitro*. Similar observations were noted in bile-duct cannulated rats.

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

In human liver microsomes, the major metabolic route of asciminib was found to be glucuronidation, followed by oxidative metabolism, consistent with findings from human hepatocytes. Several Uridin diPhospho-glucuronosyltransferase (UGT) enzymes were found to be capable of asciminib glucuronidation (UGT1A3, UGT1A4, UGT2B7, and UGT2B17). The oxidative metabolism of asciminib was also catalyzed by several CYP enzymes. CYP3A4/5 appears to contribute the most, followed by CYP2C8, CYP4F12, and potentially CYP2D6. Though the DDI risk with inhibitors of these enzymes is likely to be minimal, inhibitors of CYP3A4/5 still have the potential to increase asciminib concentration.

In recombinant cellular expression systems, asciminib was identified as a substrate of Breast Cancer Resistant Protein (BCRP) (Michaelis-Menten constant (Km) ≈ 4 µM) and permeability glycoprotein (P-gp) (Km could not be estimated due to insufficient saturation of efflux activity). Late fecal metabolite analysis in the human Absorption, Distribution, Metabolism, and Excretion (ADME) study [CABL001A2102] and estimated contributions of different enzyme pathways (CYP vs. UGT) by use of in vitro enzyme phenotyping methods, do suggests that at least 24% of the parent drug in the feces is due to conversion of a glucuronide (M30.5) metabolite back to parent drug (absorption then being maximally 57%). However, this late fecal

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metabolite analysis could also suggest that the 24% could be active secretion by P-gp (Drug Metabolism and Pharmacokinetics [DMPK R1700912]. This is a small percentage (< 25% of the clearance by this pathway) with a weak expected impact on asciminib concentrations. Overall, inhibitors of BCRP and P-gp may increase asciminib concentration. Therefore, BCRP and P-gp inhibitors should be administered with caution.

Based on *in vitro* phenotyping studies and human ADME study outcome, the physiologically based pharmacokinetic (PBPK) model was updated and predicted minimal to no DDI for sensitive substrates of CYP3A4, CYP2C8 and CYP2C9 (Drug Metabolism and Pharmacokinetics [DMPK-DDI-R1700912]. Indeed, the effect of asciminib 40 mg BID is expected to result in increased area under the curve (AUC) of CYP3A4, CYP2C8 and CYP2C9 probe substrate by 1.21, 1.09 and 1.07. Therefore, the effect of asciminib is expected to be weak and hence substrates of CYP2C8, CYP2C9 and CYP3A4 with narrow therapeutic index (NTI) would be used with caution.

Please refer to the latest [Asciminib Investigator's Brochure] version for more details.

1.1.2.2 Clinical experience

Asciminib is undergoing evaluation in a first-in-human (FIH) phase I clinical study, study [CABL001X2101].

This study evaluates patients with 1) CML who have been treated with at least 2 prior TKIs, or 2) who have the T315I mutation and have been treated with at least 1 prior TKI, or 3) who have Acute Lymphoblastic Leukemia (ALL) and have been treated with at least 1 prior TKI. The study evaluates administration of asciminib in a BID single agent dosing schedule, as well as in a QD single agent schedule, and in combination with nilotinib, imatinib, and dasatinib. In the present document, discussion will focus on data from CML patients treated with asciminib BID single agent only.

As of March 2020, a total of 305 CML or Ph+ ALL patients have been treated with either single agent oral asciminib or in combination cohorts. 150 CML patients have been treated with asciminib monotherapy. Based on the preliminary efficacy, safety and tolerability in patients with CML-CP or CML-AP treated with asciminib as a single agent on a BID schedule in study [CABL001X2101] and the results of a population PK/PD exposure-response model, the dose of 40 mg BID has been selected as the recommended dose to be used in future studies in patients with CML-CP who do not harbor T315I mutations.

Efficacy:

Preliminary data from the ongoing Phase I FIH study [CABL001X2101] indicate that asciminib exhibits single-agent activity in patients with CML who have failed at least two prior TKIs or are intolerant to TKIs, as demonstrated by hematologic, cytogenetic and major molecular responses (Hughes, 2019). Asciminib has demonstrated anti-tumor activity at doses greater or equal to 10 mg BID as well as higher daily doses.

To date, efficacy data in 141 patients with chronic-phase CML treated with single agent asciminib therapy (10-200 mg BID and 80-200 mg QD) are available (113 patients without T315I mutation and 28 with T315I mutation). Among 113 patients with CP-CML without T315I mutation, 92% and 54% of patients achieved complete hematologic response (CHR) and

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complete cytogenetic response (CCyR), respectively; a major molecular response (MMR) was achieved or maintained in 37% and 48% of patients by 6 months and 12 months, respectively. Among 28 patients with CP-CML carrying T315I mutation, 88% and 41% of those achieved CHR and CCyR, respectively; MMR was achieved in 25% and 28% by 6 months and 12 months, respectively.

Please refer to (Hughes, 2019) and the latest [Asciminib Investigator's Brochure] for more details.

Safety:

Asciminib was generally well tolerated in heavily pre-treated CML patients resistant to or intolerant of prior TKIs. As of March 2020, 239 patients were evaluable for safety. Seventy six study discontinuations have been reported; the most frequent reason for discontinuation was progressive disease, reported in 38 patients (15.9%). Adverse events leading to treatment discontinuation were reported in 15 patients (6.3%). Death leading to treatment discontinuation was reported in 3 patients (1.3%) (one patient in asciminib 20 mg BID due to aspiration pneumonia after bypass procedure and two patients with ALL with 80 mg and 160 mg BID due to progressive disease).

Among the 150 patients treated with asciminib monotherapy, almost all (94.7%) patients reported at least one AE, including 49.3% reported grade 3/4 AEs. The most common AEs (> 10%) among patients treated with 40 mg BID (n=35), regardless of study drug-relationship, were increased lipase, fatigue, diarrhea, thrombocytopenia, neutropenia, arthralgia, rash, headache, increased amylase, nausea, vomiting, abdominal pain, pyrexia, upper respiratory tract infection, back pain, hypertension, cough, pruritus, pain in extremity, dyspnea, bone pain, peripheral oedema, non-cardiac chest pain and insomnia. The most common reported grade 3/4 event was increased lipase (17.1%).

Forty-seven of 150 patients with CML-CP or CML-AP treated with asciminib single agent (31.3%) were reported with serious adverse events (SAE).

Electrocardiogram (ECG) data shows no reported QT prolongation (increase > 60 msec or new > 500 msec) in 40 mg BID asciminib monotherapy group. There were no reports of QT prolongation (increase > 60 msec) and two reports of new >500 msec (one each in 80 mg QD and 120 mg QD) among all asciminib monotherapy group.

Please refer to the latest [Asciminib Investigator's Brochure] for more details.

Pharmacokinetics:

PK data from 190 patients were available from the [CABL001X2101] study, as of 01-Sep-2017. When given as a single agent on a twice daily schedule, patients received escalating doses of asciminib ranging from 10 to 200 mg.

Based on the available PK data, asciminib, administered orally is rapidly absorbed with a median time to maximum plasma concentration (Tmax) of 2 to 3 hours, independent of dose. Systemic exposure of asciminib, following oral administration of single and multiple doses, as measured by Cmax and AUC, increased in an approximately dose proportional manner. The variability of exposure is low to moderate with inter-patient variability (geometric mean CV %)

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ranging from approximately 25 to 70% for both Cmax and AUClast. With the twice daily dosing regimen, median plasma asciminib accumulation ratios ranged from 1.3 to 2.5. The median accumulation half-life was estimated to be 7 to 15 hours.

The data of the hADME study [CABL001A2102] show that the relative contribution of the glucuronidation pathway to the total clearance of asciminib via metabolism is estimated to range from 30% to 61%, whereas the relative contribution of the oxidative pathway is estimated to range from 35% to 63%. CYP3A4 was the main contributor for the clearance of asciminib via the oxidative pathway while UGT2B7 and UGT2B17 were responsible for the clearance of asciminib via the glucuronidation pathway. There was no metabolite detected with mean contribution to plasma radioactivity AUC0-24hours ≥ 10%. Asciminib was the predominant drug-related component in plasma at all time points analyzed, ranging from 91.9 to 94.2% of the total radioactivity AUC0-24 hours AUC, with an average value of 92.7%.

Please refer to the latest [Asciminib Investigator's Brochure] for more details.

Exposure-response relationship:

Exposure-efficacy

A preliminary population PKPD model has been developed using data from the [CABL001X2101] study (cut-off 02-May-2016). The time course of molecular response (change in BCR-ABL1 ratio % IS levels from baseline) was described using a semi-physiological model accounting for cell maturation, disease progression and existing resistance.

Simulations performed using an asciminib population PK model revealed that a dose of 40 mg BID maintains Ctroughs above the clinical (0.07 to 61 ng/mL) threshold in ≥95% of chronic phase CML patients without T315I mutation having failed ≥ 2 TKI or intolerant to TKIs. The estimates from this clinical study were found to be similar to the threshold trough concentration required for 90% inhibition of pSTAT5 derived from a preclinical PK-PD KCL-22 mouse xenograft model (free IC90: 30 to 121 ng/mL, after correction for protein binding) and *in vitro* gIC50 assessed in the KCL-22 cell line (1 ng/mL = 2.1 nM after correction for protein binding).

Simulations performed using asciminib population PKPD model revealed that chronic phase CML patients having failed ≥ 2 TKI or intolerant to TKIs are likely to exhibit a 1 log10 reduction of (%) BCR-ABL1 mRNA transcript levels from baseline of ~33% (CI95%: 24-42%) at 6 months, and ~42% (CI95%: 32-52%) at 12 months at a dose of 20 mg BID and ~41% (CI95%: 31-51%) at 6 months, and ~53% (CI95%: 43-63%) at 12 months at a dose of 40 mg BID.

Additional preliminary exposure response analyses (i.e. exploring the relationship between PK and both safety and efficacy) support the selected dose.

Please refer to the latest [Asciminib Investigator's Brochure] for more details

Food effect

The effect of food on asciminib PK was characterized in a Phase I study [CABL001A2101] in healthy volunteers. Food was found to influence the pharmacokinetics of asciminib. When administered with a low-fat meal, the exposure (AUC) decreased by approximately 30%. The

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overall exposure decreased by approximately 65% when administered with a high-fat meal. Therefore, asciminib will be administered in a fasted state.

1.2 Purpose

Thanks to the advances in CML treatments, many of these patients can now have life expectancy similar to the general population. However, there is a significant proportion of patients who unfortunately experience treatment failure due to either resistance or intolerance. When considering patients treated with frontline imatinib, 31% exhibit treatment failure and progress to second-line treatment; of those, half of them progress to third-line treatment (Akard, 2013). On patients starting treatment with 2nd generation TKI (2G-TKI), treatment failure rate is at 13% and when they move on to second-line treatment, around 60% of them exhibit disease progression and move on to third-line treatment.

Given the poor outcomes of patients that progress after successive lines of therapy, there remains an unmet need for new compounds that can provide CML patients optimal disease management. It is worthwhile mentioning the lack of defined treatments recommendations once patients move on to second-line treatment and beyond. NCCN guidelines recommend treating patients with any of the 2G-TKIs if imatinib was given as the frontline agent; if 2G-TKI was used for first-line treatment, any 2G-TKI can be considered for subsequent treatment, although some experts advocate for ponatinib if the reason for treatment discontinuation was related to resistance (Hochhaus, 2020).

In addition, patients harboring T315I mutation have few treatment choices since this mutation confers resistance to all TKIs with the exception of Ponatinib. Unfortunately, Ponatinib is associated with high risk of cardiovascular complications and many of these patients are then not eligible for treatment. Based on data from ongoing study [CABL001X2101], 53.8% of CML-CP patients with this mutation who had not been previously treated with Ponatinib were able to achieve MMR by 6 months (Hughes, 2020). Therefore, asciminib represents a promising agent for this CML-patient population that the current study is attempting to address.

2 Objectives and endpoints

Table 2-1 Objective(s) Endpoint(s)

Primary Objective(s)	Endpoint(s) for primary objective(s)
• To evaluate safety profile of monotherapy asciminib in CML-CP in 3L and beyond, for Cohorts A and B	• AEs, SAEs and laboratory evaluation for 24 Weeks.
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate safety profile of monotherapy asciminib in CML-CP in all Cohorts A, B and C	• AEs, SAEs and laboratory evaluation for cohort A, and Cohort C, for 48, 72 weeks
• To estimate the rate of patients with hematologic and molecular response by specific time points for Cohort A, B and C	• Rate of CHR, MR2, MMR, by 12, 24, 48, 72 weeks of therapy
• To estimate the rate of patients with deep molecular response	• Rate of MR4, MR4.5 by 48, 72 weeks of therapy

Table 2-1 Objective(s)	Endpoint(s)
by specific time points for Cohort A, B and C	
• To estimate time to hematologic and molecular response	• Time to CHR, MR2, MMR, MR4, MR4.5
• To evaluate the duration of hematologic and molecular response	• Duration of CHR, MR2, MMR, MR4 and MR4.5
• To Evaluate the progression free survival (PFS) during 72 weeks	• PFS during 24, 48 and 72 weeks
• To Evaluate Overall Survival (OS) during 72 weeks	• OS during 24, 48 and 72 weeks

[redacted]

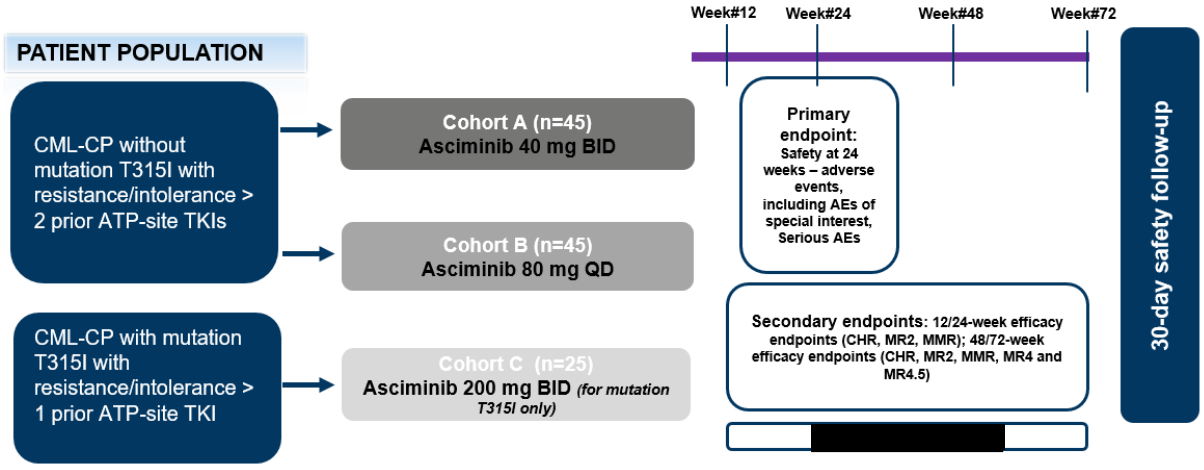
3 Study design

This study will be a multicenter Phase IIIb open-label, three-cohort study of asciminib in patients with CML-CP without T315I mutation who have had at least 2 prior TKIs and CML-CP harboring the T315I mutation with at least 1 prior TKI. The primary outcome is to evaluate the safety profile of asciminib with AEs, SAEs and laboratory studies' assessment at 24 weeks of therapy. The secondary endpoints will consist of:

- Additional Safety endpoints including the AES, SAEs and laboratory tests leading to treatment discontinuation on weeks 48 and 72
- Efficacy measures such as duration, estimated time for achievement and rates of CHR, MR2, MMR, MR4, MR4.5 by 12, 24, 48, 72 weeks of therapy
- Survival measures such as PFS and OS during 72 weeks of therapy

[redacted]

Figure 3-1 Study design



Patient Selection

For patients without T315I mutation, patients will be selected randomly between cohort A, where patients will be given asciminib at 40 mg twice daily (BID) and cohort B, where patients will receive asciminib at 80 mg daily (QD) to minimize selection bias. Data from [CABL001X2101] study showed encouraging efficacy and safety findings in 40 mg twice daily and 80 mg daily-treated patients.

On cohort C, patients harboring the T315I mutation will be treated on the dose of 200 mg twice daily (BID). The higher dose required for that patient population is related to its required concentration to attain optimal blockade of the kinase activity. Patients will continue therapy until disease progression, unacceptable toxicity or elective treatment discontinuation.

4 Rationale

4.1 Rationale for study design

Asciminib (ABL001) is a potent BCR-ABL1 allosteric inhibitor currently being developed by Novartis for the treatment of CML. Unlike drugs such as imatinib, nilotinib, dasatinib, bosutinib and ponatinib, which bind to the ATP-site of the ABL kinase domain, asciminib binds to the myristoyl pocket and consequently, restores the negative regulation of the kinase activity[1]. Given this unique mechanism of action, it has been proven to have activity against BCR-ABL1 mutations that are known to confer resistance to the ATP-binding site TKIs (tyrosine kinase inhibitors). Moreover, the selective binding of asciminib is predicted to reduce toxicities, which is an encouraging feature for patients where side effects from previous treatments were the reason for drug discontinuation. Based on phase I data, asciminib has been proven safe and effective in patients who had more than 2 lines of therapy, with 32% and 44% of those achieving MMR in 6 and 12 months, respectively. The incidence of grade 3/4 treatment emergent AEs were mostly less than 10%, which implies a favorable safety profile in a heavily pre-treated CML population.

The ongoing ASCEMBL study is a phase III study, which is investigating the efficacy of treatment with asciminib versus bosutinib in CML-CP patients with at least 2 prior therapies. The release of interpretable results is expected to be in 2020 with subsequent data presentation and submission to health authorities. Despite its phase III design with randomization, questions remain such as safety and efficacy on a larger patient population including those carrying the T315I mutation and of a daily dosing schedule. A once daily regimen could be more convenient as we believe it will greatly improve patient's adherence as well as quality of life. For that dosing schedule, the dose of 80 mg was selected based on similar efficacy and safety profile when compared to 40 mg twice daily from early phase data[3].

The study currently proposed is a phase IIIb open-label study patients with CML-CP without T315I mutation who have had at least 2 prior TKIs and CML-CP harboring the T315I mutation with at least 1 prior TKI with the aim of gaining further efficacy and safety data with asciminib monotherapy on a larger population of patients.

The study will contain the following cohorts:

- Cohort A asciminib 40 mg BID
- Cohort B asciminib 80 mg QD
- Cohort C asciminib 200 mg BID, exclusively for those harboring the T315I mutation

Random Selection of patient

As above, patients with CML-CP without T315I mutation will be randomly selected to either cohort A or B (both primary). Patients in those 2 cohorts will be selected randomly to minimize selection bias at the time of patient allocation. Additionally, there will be a separate cohort (cohort C) enrolling patients harboring the T315I mutation to strengthen the body of evidence generated in the [CABL001X2101] study, which has already treated 58 patients with that mutation in the asciminib extension cohort at 200 mg bid showing encouraging antileukemic activity and well tolerated safety profile.

4.2 Rationale for dose/regimen and duration of treatment

The dose and regimen of asciminib selected for cohort A is 40 mg BID and cohort B is 80 mg QD. This dose is supported by pharmacokinetic, efficacy and safety data available from the ongoing [CABL001X2101] study.

During escalating doses of asciminib 10 mg to 200 mg on a continuous BID schedule in study [CABL001X2101], the 40 mg BID dose was shown to be active and well tolerated in CML-CP patients.

With respect to efficacy, no clear evidence of dose-response relationship was observed across dose levels when considering Complete Cytogenetic Response (CCyR) or MMR. However, as described below, PK-PD population modeling using change from baseline of BCR-ABL1 mRNA levels as a PD endpoint suggest a higher probability of achieving ≥1 log reduction at 6 and 12 months with 40 mg BID versus 20 mg BID.

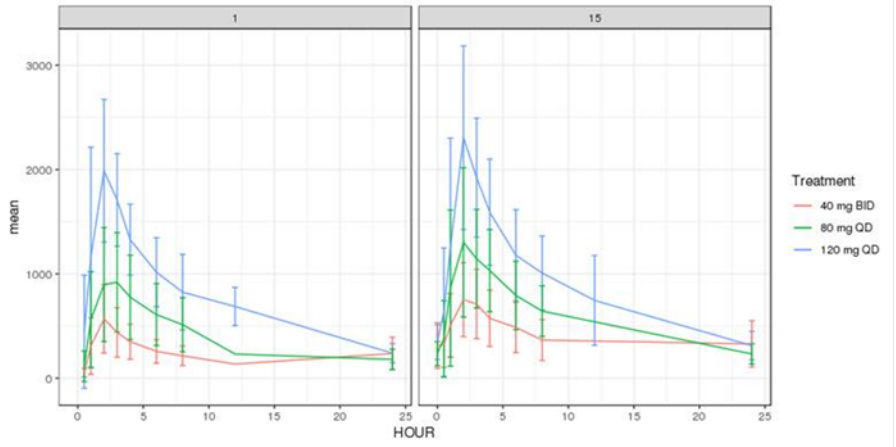
With respect to safety, asciminib has been regarded as safe with mild toxicities even for patients who required higher doses of the drug. Most of the toxicities observed were limited to grade 1 and 2 [CABL001X2101]. Two patients developed pancreatitis after intra-patient dose escalation

[redacted]

to 80 mg BID from 40 mg BID and in one patient at the dose of 150 mg BID. Generally there is a trend for higher rates of discontinuation due to AE, DLT (dose limiting toxicity) and grade 3/4 AE with increasing doses.

With respect to overall exposure, the dose of 40 mg BID and 80 mg QD are expected to result in concentrations consistently above IC90 *in vitro* concentrations. The estimates from study [CABL001X2101] were found to be above the threshold trough concentration required for 90% inhibition of pSTAT5 derived from a preclinical PK-PD KCL-22 mouse xenograft model (free IC90: 30 to 121 ng/mL, after correction for protein binding) and *in vitro* gIC50 assessed in the KCL-22 cell line (1 ng/mL = 2.1 nM after correction for protein binding). Additionally, clinical data from the study on patients taking 40 mg BID and 80 mg QD were obtained and as seen on Figure 4.1, it showed similar results when it comes to pharmacokinetic parameters.

Figure 4-1 Pharmacokinetic data of 40 mg BID and 80 mg QD



A preliminary population PK-PD model has been developed using data from the [CABL001X2101] study (cut-off 2 May 2016). The time course of molecular response (change in BCR-ABL1 ratio % IS levels from baseline) was described using a semi-physiological model accounting for cell maturation, disease progression and existing resistance. Simulations performed (with 100 patients) using asciminib population PK-PD model revealed that at a dose of 40 mg BID, ~41% (CI95%: 31-51%) of chronic phase CML patients having failed ≥ 2 TKI or intolerant to TKIs are likely to exhibit a 1 log10 reduction of (%) BCR-ABL1 mRNA transcript levels from baseline at 6 months, and 53% (CI95%: 43-63%) at 12 months, and predicting higher probability of achieving BCR-ABL1 mRNA ≥ 1 log reduction at 6 and 12 months with 40 mg BID versus 20 mg BID.

Additional preliminary PK-efficacy and PK-safety analyses to assess the exposure-response relationship for asciminib were conducted (Section 1.1.2.2). The efficacy measure used was Molecular Response (MR), which is defined as a decline in BCR-ABL1 transcript levels in clinical blood samples of patients with Chronic Myeloid Leukemia (CML). MR was evaluated as both a continuous variable (BCR-ABL1 transcript levels) and categorical variable (whether or not adequate decline in BCR-ABL1 was achieved). The safety measures used were occurrence of Common Toxicity Criteria (CTC) grade 2, 3 or 4 laboratory values for lipase and amylase.

[redacted]

Reviewing the totality of the efficacy, safety, and pharmacokinetic data derived from the [CABL001X2101] study, the recommended dose for asciminib in this phase 3 study is 40 mg BID.

Please refer to the latest [Asciminib Investigator's Brochure] for more details

200 mg BID Dose Rationale for Patients harboring the T315I mutation

Asciminib maintained activity against all BCR-ABL1 constructs, regardless of mutation, at concentrations below 50 nM. The most striking example of the difference between asciminib and nilotinib, was the activity against the BCR-ABL1 expressing cell line with a T315I mutation. Asciminib inhibited the proliferation of cells with T315I mutation in the low nanomolar range, in contrast with the exception of ponatinib ATP competitive BCR-ABL inhibitors were, inactive at concentrations 600 nM (Figure 4-2) (Schoepfer et al 2018; Report RD-2013-50447).

Figure 4-2 Comparison of the effects of Asciminib with those of ATP-competitive BCR-ABL inhibitors approved for the treatment of CML on Luc-Ba/F3 cells engineered to express drug-resistant BCR-ABL mutants

Luc-BaF3 BCR-ABL1	Asciminib	Bosutinib	Dasatinib	Imatinib	Nilotinib	Ponatinib
wt	0.61 ± 0.21	204 ± 32	0.30 ± 0.04	90.5 ± 19.2	3.52 ± 1.07	0.37 ± 0.04
G250H	0.74 ± 0.27	146 ± 24	0.29 ± 0.03	77.1 ± 11.8	3.71 ± 1.61	0.34 ± 0.07
Q252H	10.9 ± 3.53	243 ± 44	0.98 ± 0.40	455 ± 54.9	18.9 ± 4.71	1.89 ± 0.57
Y253H	1.71 ± 0.75	177 ± 78	0.42 ± 0.08	836 ± 171	132 ± 52	1.21 ± 0.32
E255K	2.35 ± 0.71	356 ± 69	1.44 ± 0.45	838 ± 64	36.9 ± 8.5	2.60 ± 0.75
E255V	1.17 ± 0.54	278 ± 49	0.77 ± 0.31	874 ± 92	61.6 ± 13.2	1.93 ± 0.79
T315I	7.64 ± 3.22	642 ± 100	2562 ± 516	9645 ± 710	2262 ± 891	1.60 ± 0.48
E355G	9.33 ± 2.14	128 ± 30	0.21 ± 0.01	149 ± 6.4	4.82 ± 1.60	0.28 ± 0.17
F359V	11.5 ± 4.87	195 ± 46	0.33 ± 0.05	249 ± 87	29.6 ± 11.2	1.63 ± 0.50
E459K	3.01 ± 1.37	140 ± 25	0.25 ± 0.09	201 ± 44	9.21 ± 3.41	0.64 ± 0.27

Growth inhibition is expressed as mean GI_{50} values (nM ± SD; n = 3)

Source: (Schoepfer et al 2018)

Based on exposures required for in vitro activity against T315I mutation preclinically, higher doses of asciminib (> 160 mg BID) may drive BCR-ABL % IS and major molecular response in CML patients with T315I mutation. A 200 mg BID dose was overall deemed safe by BLRM and the safety profile was seen to be similar between patients with and without the T315I mutation.

4.3 Purpose and timing of interim analyses/design adaptations

See Section 12.8

[redacted]

4.4 Risks and benefits

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-drug induced adverse events are provided in Section 6.5.4. Patients who have failed 2 prior TKIs are at increased risk of progression to more advanced phases of CML such as CML-AP and CML-BC. Currently available therapeutic agents in this setting are non-curative and patients remain at risk of progressing after short duration of remissions (Khoury 2012).

An important potential risk for patients enrolling on the 80 mg QD arm is the possibility of having either higher toxicity or reduced efficacy. However, as mentioned above, the evidence to date of such dose on a similar population of patients in the study [CABL001X2101] suggests that asciminib is an active and safe agent. Further, the adverse event profile of asciminib is similar qualitatively to that observed with other TKIs targeting BCR-ABL1 (Section 1.1.2.2). The risk of 80 mg QD of asciminib not being effective has been mitigated in that patients will be observed closely for evidence of efficacy, based on assessment of hematologic and molecular response data, which will permit rapid decision making as to discontinuation of therapy if necessary.

Another relevant risk is the potential for higher rates of toxicity in patients harboring the T315I mutation, who will be receiving the dose of 200 mg BID. As previously mentioned, our [CABL001X2101] study where more than 50 patients with that mutation were treated with that dose showed encouraging safety data and so, it is fairly unlikely that more AEs will be occurring in this patient population.

Other risks to subjects 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.

The currently available information suggests that there is equivalence between the two arms with respect to benefit / risk to enable inclusion of patients in this study.

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

5 Study Population

One hundred and fifteen (115) patients with CML-CP without T315I mutation who have had at least 2 prior TKIs and CML-CP harboring the T315I mutation with at least 1 prior TKI will be considered for the current study. Previous medical records should be used to confirm the patient's mutational status/history.

The definition of CML-CP will be according to the European Leukemia Network (ELN) criteria (Hochhaus, 2020), 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.

[redacted]

5.1 Inclusion criteria

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

1. Written informed consent must be obtained and signed prior to participation in the study
2. Male or female patients with a diagnosis of CML-CP ≥ 18 years of age
3. Patients must meet all of the following laboratory values at the screening visit:
   - < 15% blasts in peripheral blood or bone marrow
   - < 30% blasts plus promyelocytes in peripheral blood or bone marrow
   - < 20% basophils in the peripheral blood
   - ≥ 50 x 10^9/L (≥ 50,000/ mm^3) platelets
   - Transient prior therapy related thrombocytopenia (< 50,000/mm^3 for ≤ 30 days prior to screening) is acceptable
   - No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly
4. Mutation Analysis testing performed at screening.
5. Prior treatment with a minimum of:
   - 2 prior ATP-site TKIs (i.e. imatinib, nilotinib, bosutinib, dasatinib or ponatinib) in case of absence of T315I mutation
   - 1 prior ATP site TKI (i.e. imatinib, nilotinib, bosutinib, dasatinib or ponatinib) in case of presence of T315I mutation
6. Failure (adapted from the 2020 ELN Recommendations) or intolerance to the most recent TKI therapy at the time of screening
   - Failure for CML-CP patients (CP at the time of initiation of last therapy) is defined as meeting at least <u>one</u> of the following criteria.
     - Three months after the initiation of therapy: >10% BCR-ABL1 on International Scale (IS) if confirmed within 1-3 months
     - Six months after the initiation of therapy: BCR-ABL1 ratio > 10% IS
     - Twelve months after initiation of therapy: BCR-ABL1 ratio > 1% IS
     - At any time after the initiation of therapy, loss of CHR, MR2
     - At any time after the initiation of therapy, the development of new BCR-ABL1 mutations which potentially cause resistance to current treatment
     - At any time 12 months after the initiation of therapy, BCR-ABL1 ratio ≥ 1% IS or loss of MMR
     - At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cells: CCA/Ph+
   - Intolerance is defined as:
     - Non-hematologic intolerance: Patients with grade 3 or 4 toxicity while on therapy, or with persistent grade 2 toxicity, unresponsive to optimal management, including dose adjustments (unless dose reduction is not considered in the best interest of the patient if response is already suboptimal)

[redacted]

- Hematologic intolerance: Patients with grade 3 or 4 toxicity (absolute neutrophil count [ANC] or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by manufacturer

7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2
8. Evidence of typical BCR-ABL1 transcript [e14a2 and/or e13a2] at the time of screening which are amenable to standardized RQ-PCR quantification.
9. Adequate end organ function, within 12 days before the first dose of asciminib treatment. Patients with mild to moderate renal and hepatic impairment are eligible if:
    - Total bilirubin ≤ 3.0 x ULN with any AST increase
    - Serum lipase ≤ 1.5 x ULN. For serum lipase > ULN - ≤ 1.5 x ULN, value should be considered not clinically significant and not associated with risk factors for acute pancreatitis
    - Creatinine clearance ≥ 30 mL/min as calculated using Cockcroft-Gault formula
10. Patients must avoid consumption of grapefruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.
11. Patients must have the following electrolyte values (as per central laboratory tests) within normal limits or corrected to be within normal limits with supplements prior to first dose of study medication:
    - Potassium (potassium increase of up to 6.0 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits)
    - Total calcium (corrected for serum albumin); (calcium increase of up to 12.5 mg/dl or 3.1 mmol/L is acceptable at study entry if associated with creatinine clearance within normal limits)
    - Magnesium, with the exception of magnesium increase > ULN – 3.0 mg/dL; > ULN - 1.23 mmol/L associated with creatinine clearance (calculated using Cockcroft-Gault formula) within normal limits.

5.2 Exclusion criteria

Patients eligible for this study must not meet any of the following criteria:

1. Known second chronic phase of CML after previous progression to AP/BC
2. Previous treatment with a hematopoietic stem-cell transplantation
3. Cardiac or cardiac repolarization abnormality, including any of the following:
    - History within 6 months prior to starting study treatment of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG)
    - 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 at screening ≥450 msec (male patients), ≥460 msec (female patients)

[redacted]

- 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 wwwcrediblemeds.org/ that cannot be discontinued or replaced 7 days prior to starting study drug 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, pulmonary hypertension)
5. History of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis
6. Known presence of significant congenital or acquired bleeding disorder unrelated to cancer
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. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or gastric bypass surgery)
9. Previous treatment with or known/ suspected hypersensitivity to asciminib or any of its excipients.
10. Treatment with medications that meet one of the following criteria and that cannot be discontinued at least one week prior to the start of treatment with study treatment;
    - For Cohort A (40 mg BID) and for Cohort B (80 mg QD) patients not harboring the T315I mutation
      - strong inducers of CYP3A
    - For Cohort C (200 mg BID for patients harboring the T315I mutation)
      - strong inducers of CYP3A
      - strong inhibitors of CYP3A
11. Participation in a prior investigational study within 30 days prior to randomization or within 5 half-lives of the investigational product, whichever is longer
12. Pregnant or nursing (lactating) women
13. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

[redacted]

- Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy) total hysterectomy or bilateral tubal ligation 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 sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject.
- Use of oral, 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 and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking study medication. In the case of oophorectomy alone, women are considered post-menopausal and not of child-bearing potential only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

14. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 3 days after stopping study (only for patients treated with asciminib). A condom is required for all sexually active male participants on asciminib treatment to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, these male participants must not donate sperm for the time period specified above.
15. If a patient is presenting with symptoms suggestive of possible COVID-19 infection, we advise ruling it out by appropriate testing recommended by health authorities.
    - Nucleic acid amplification tests for viral RNA (polymerase chain reaction), in order to measure current infection with SARS-CoV-2
    - Antigen tests for rapid detection of SARS-CoV-2
    - Antibody (serology) tests to detect the presence of antibodies to SARS-CoV-2

6 Treatment

6.1 Study treatment

The investigational treatments for this study are asciminib (40 mg BID, 80 mg QD or 200 mg BID). Novartis will supply asciminib to the investigational site as 20 mg and 40 mg tablets.

6.1.1 Asciminib Dosing Regimen

Asciminib will be supplied as 20 mg or 40 mg strength tablets will be administered orally in accordance with the assigned cohort.

[redacted]

Cohort A	Cohort B	Cohort C
40 mg BID	80 mg QD	200 mg BID

Asciminib tablets should be ingested as follows:

- Asciminib should be administered in the fasted state: avoid food for at least 2 hours before the dose is taken and for at least 1 hour after the dose is taken. Water is permitted during this period.
- Asciminib should be taken with approximately 8 ounces (240 mL) of water.
- Asciminib should be swallowed whole and not chewed or crushed.
- If vomiting occurs within the first hour after taking the drug, re-dosing is allowed before the next scheduled dose.
- If the patient does not take asciminib within 6 hours after the approximate time of the usual dosing time, that dose should be skipped and treatment should continue with the next daily dose at the prescribed level.

6.1.2 Investigational drugs

Table 6-1 Investigational and control drug

Investigational (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
ABL001 20 mg	Tablet	Oral use	Open Label; 30 ct bottle	Sponsor (Local)
ABL001 40 mg	Tablet	Oral use	Open Label; 30 ct bottle	Sponsor (Local)

6.1.3 Additional study treatments

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

6.1.4 Treatment Cohorts

This is an open label, three-cohort, multi-center phase IIIb study of asciminib (ABL001) monotherapy in previously treated patients with chronic myeloid leukemia on chronic phase (CML-CP) with and without T315I mutation

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

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

6.1.5 Guidelines for continuation of treatment

Not Applicable see Section 6.5.2

[redacted]

6.1.6 Treatment duration

The patients are treated in the study up to end of study treatment period defined as up to 72 weeks after the last patient receives the first dose. Patients may be discontinued from treatment with the study drug at any time due to unacceptable toxicity, disease progression and/or at the discretion of the investigator or the patient.

6.1.6.1 Treatment beyond disease progression

Not Applicable

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug and including over-the-counter treatment and nutritional or vitamin supplements) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the "Concomitant Medications/Significant non-drug therapies" section of the eCRF.

Chronic medication should be maintained at the same dose and schedule throughout the study period, as medically feasible.

All prior antineoplastic surgery, chemotherapy, biologic, immunologic and radiation therapy must be recorded in the "Prior antineoplastic therapy" section of the eCRF.

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient 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 platelet transfusions for patients with anemia and with thrombocytopenia.

Permitted concomitant therapy

Drugs that affect gastric pH

Asciminib does not have a pH-dependent solubility. Drugs that elevate gastric pH will not affect asciminib absorption. All acid reducing agents are allowed.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

The *in vivo* potential of asciminib to interact with sensitive CYP3A4/5, CYP2C8 and CYP2C9 substrates has been evaluated and would indicate a minimal or negligible risk (Section 1.1.2.1). Therefore CYP3A4/5, CYP2C8 and CYP2C9 substrates with narrow therapeutic index (NTI) should be used with caution.

As CYP3A4/5 inhibitors may decrease the metabolism of asciminib and resulting in increased plasma concentrations and increased exposure, we recommend using them with caution at asciminib 40 mg BID and 80 mg QD. Note: at asciminib 200 mg BID the use of strong CYP3A4/5 inhibitors should be avoided (see 6.2.2).

[redacted]

In recombinant cellular expression systems, asciminib was identified as a substrate of BCRP (Km ≈ 4 μM) and P-gP (Km could not be estimated due to insufficient saturation of efflux activity). Inhibitors of BCRP and P-gP may increase asciminib concentration. Based on human ADME study, P-gp may represent maximally 24% of the total clearance resulting in modest increase in AUC. Therefore, both BCRP and P-gp inhibitors should be administered with caution. If a medication listed in Section 16 appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.

6.2.1.2 Use of bisphosphonates

The use of bisphosphonates regardless of indication is allowed.

6.2.2 Prohibited medication

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 patients. These patients may remain in the current study after consultation with Novartis. The administration of other tyrosine kinase inhibitors indicated for treatment of CML are **not** allowed.

Strong CYP3A inducers

Any strong CYP3A inducers should be discontinued 7 days before the first dose of study medications.

Every effort should be made NOT to concomitantly administer strong CYP3A inducers during the study. If administration of a strong CYP3A inducer cannot be avoided during the study and cannot be switched to an alternative therapy, investigator should exercise caution while patient is on study treatment.

Cohort C only (200 mg BID): Strong CYP3A inhibitors

Any strong CYP3A inhibitors should be discontinued 7 days before the first dose of study medications.

Every effort should be made NOT to concomitantly administer strong CYP3A inhibitors. CYP3A inhibitors may decrease the metabolism of asciminib and resulting in increased plasma concentrations and increased exposure. If administration of a strong CYP3A inhibitor cannot be avoided during the study and cannot be switched to an alternative therapy that does not strongly inhibit CYP3A, asciminib must be interrupted.

A list of cytochrome P450 isoenzymes and CYP3A inhibitors may be found at medicine.iupui.edu/CLINPHARM/ddis/clinical-table.

A classification of CYP3A SmPC can be found in Section 16, Table 16-2.

Further information can also be found in the following reference (Venkatakrishnan et al 2001).

[redacted]

UGT1A/2B inducers

The use of strong inducers of UGT1A/2B is prohibited during the study.

If administration of UGT1A/2B inducer cannot be avoided during the study and cannot be switched to an alternative therapy, temporary interruption of study treatment is NOT needed.

QT prolonging agents

As far as possible avoid co-administering drugs with a "Known", "Possible" or "Conditional" risk of Torsades de Pointes (per wwwcrediblemeds.org/) during the course of the study:

- If concomitant administration of drugs with a "Known risk of Torsades de Pointes" is required and cannot be avoided, study drug must be interrupted. If, based on the investigator assessment and clinical need, study treatment is resumed, close ECG monitoring is advised.
- If during the course of the study, concomitant administration of a drug with "Possible risk" or "Conditional risk of Torsades de Pointes" is required, based on the investigator assessment and clinical need, study treatment may be continued under close ECG monitoring to ensure patient safety.

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

Herbal medications

Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

6.2.3 Rescue medication

Not Applicable

6.2.4 Other Concomitant medications

Anti-emetics

Use of anti-emetics is allowed. Prophylactic anti-emetics should be started only once the patient experiences nausea or vomiting, at the discretion of the investigator. It is recommended that patients use drugs that do not cause QT prolongation. Please note that some anti-emetics have a known risk for Torsade de Pointes and are prohibited (refer to Section 6.2.1.1 and Section 16 Appendix 1).

Contraceptives

Hormonal contraceptives are allowed as contraception methods. Highly effective contraception should be maintained throughout the study and for 7 days after study treatment discontinuation.

Anticoagulation agents

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

[redacted]

Therapeutic doses of warfarin sodium (Coumadin®) or any other coumadin-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-platelet pro-drugs such as clopidogrel, ticlopidine and prasugrel, which require metabolic activation by CYP3A4 and CYP2C9. While the weak reversible *in vitro* inhibition potential of asciminib is unlikely to translate into clinical significance as the steady-state plasma concentrations at the maximum therapeutic doses are significantly lower than the experimentally determined inhibition constants, patients using anti-platelet 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.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned 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 enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center 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.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.3.2 Treatment assignment

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

6.4 Treatment blinding

Not Applicable

[redacted]

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted.

6.5.1 Dose escalation guidelines

Dose escalation beyond the dose of 40 mg BID, 80 mg QD or 200 mg BID (for patients harboring the T315I mutation) is not permitted

6.5.2 Dose modifications

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

These dose modifications are summarized in Table 6-2. The dose reduction indicated as "recommendations" is provided to assist investigators in the event the patient experiences toxicity. However, deviations from "mandatory" dose interruptions and/or reductions are not allowed and mandatory interruptions or reductions must be strictly followed. Re-escalation to asciminib 40 mg BID is permitted if a change in the patient's individual benefit/risk assessment at the lower dose level is seen. Re-escalation will be allowed only once for any given patient. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-2. Any dose changes must be recorded on the Dosage Administration Record eCRF.

A patient must discontinue treatment with Asciminib 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 patient requires a dose interruption of > 28 days for each non-hematologic toxicity, then the patient must be discontinued from the 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 TKI interruption and adequate management (including hematopoietic growth factors), then the patient must be discontinued from the study treatment.

These dose changes must be recorded on the appropriate case report form (CRF).

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

Dose modifications for asciminib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**	
Worst toxicity CTCAE Grade 5	**Asciminib**
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 TKI interruption and adequate management (including hematopoietic growth factors), then the patient 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 –	**Recommendation**: Maintain dose level

Dose modifications for asciminib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**	
Worst toxicity CTCAE Grade 5	**Asciminib**
1.0 x 10^9/L)	
Grade 3 (ANC < 1.0 – 0.5 x 10^9/L)	**Mandatory**: Hold 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 (ANC < 0.5 x 10^9/L)	**Mandatory**: Hold 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 109/L, fever ≥ 38.5°C)	**Mandatory:** Hold dose until resolved, then reduce dose ↓ 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

[redacted]

Dose modifications for asciminib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**		
Worst toxicity CTCAE Grade 5	**Asciminib**	
Grade 3 (PLT < 50 - 25 x 10^9/L)	**Mandatory:** Hold 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:** Hold 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:** For recurrent Grade 3-4 cytopenias: If resolved to ≤ Grade 2 in ≤ 14 days, then maintain dose level If resolved in > 14 days, then reduce asciminib and imatinib dose ↓ 1 dose level	
Non-hematologic adverse reactions except where further specified in individual sections		
Grade 1	**Recommendation**: Maintain dose level	**Recommendation:** Maintain dose level
Grade 2	**Recommendation:** Hold dose until resolved to ≤ Grade 1, then maintain dose level	
Grade 3	**Mandatory:** Hold dose until resolved to ≤ Grade 1, then reduce dose ↓ 1 dose level	
Grade 4	**Mandatory**: Permanently discontinue patient from study drug treatment.	
Investigations (Renal)		
Serum creatinine		
Grade 1 (> ULN - 1.5 x ULN)	**Recommendation:** Maintain dose level	
Grade 2 (> 1.5 - 3.0 x ULN)	**Recommendation:** Hold dose until resolved to ≤ Grade 1 or baseline, then maintain dose level	
Grade 3 (> 3.0 - 6.0 x ULN)	**Mandatory:** Permanently discontinue patient from study drug treatment.	
Grade 4 (> 6.0 x ULN)	**Mandatory:** Permanently discontinue patient from study drug treatment.	
Investigations (Hepatic)		
Isolated total Bilirubin elevation		
> ULN – 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	**Recommendation:** Maintain dose level	
> 1.5 - 3.0 x ULN if baseline was normal; > 1.5 - 3.0 x baseline if baseline was abnormal	**Recommendation:** Hold dose. Monitor LFTs[b] 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; if baseline was normal; > 3.0 - 10 x baseline if baseline was abnormal*	**Mandatory:** Hold dose. Monitor LFTs[b] 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 patient from study drug treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.	
> 10.0 x ULN; if baseline was normal; > 10 x baseline if baseline was abnormal*	**Mandatory:** Permanently discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.	
Isolated AST or ALT elevation		

[redacted]

Dose modifications for asciminib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**	
Worst toxicity CTCAE Grade 5	**Asciminib**
> ULN - 3.0 x ULN if baseline was normal; 1.5-3.0 x baseline if baseline was abnormal	**Recommendation:** Maintain dose level
> 3.0 - 5.0 x ULN if baseline was normal; 3.0 - 5.0 x baseline if baseline was abnormal	**Recommendation:** Maintain dose level. Repeat LFTs[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 LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN if baseline was normal or 1.5 - 3.0 x baseline if baseline was abnormal

Dose modifications for asciminib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**	
Worst toxicity CTCAE Grade 5	**Asciminib**
> 5.0 - 10.0 x ULN if baseline was normal; 5.0 - 10.0 x baseline if baseline was abnormal	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN if baseline was normal or 1.5 - 3.0 x baseline if baseline was abnormal: Then If resolved in ≤ 14 days, maintain dose level If resolved in > 14 days, reduce dose ↓ 1 dose level
> 10.0 - 20.0 x ULN if baseline was normal; > 10.0 - 20.0 x baseline if baseline was abnormal	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN if baseline was normal or 1.5 - 3.0 x baseline if baseline was abnormal. Then reduce dose ↓ 1 dose level.
> 20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	**Mandatory:** Hold dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3 x ULN (or ≤ 5 x ULN for patients with baseline value > 3.0 -5.0 x ULN), then resume treatment at reduce dose ↓ 1 dose level. Only 1 dose reduction is allowed; if reoccurs at > 5 x ULN, discontinue patient from study drug treatment.

[redacted]

Dose modifications for asciminib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**	
Worst toxicity CTCAE Grade 5	**Asciminib**
Combined [c] elevations of AST or ALT and total bilirubin	
For patients with normal baseline ALT and AST and total bilirubin value: AST or ALT >3.0 x ULN combined with total bilirubin >2.0 x ULN without evidence of cholestasis[d] For patients with elevated baseline AST or ALT or total bilirubin value [AST or ALT>2 x baseline AND > 3.0 x ULN]	**Mandatory:** Permanently discontinue patient from study drug treatment. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b]), or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Refer to Section 6.5.3 for additional follow-up evaluations as applicable.
Investigation (metabolic)	
Asymptomatic amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 x ULN)	**Recommendation:** Maintain dose level, measure 2x week
Grade 2 (> 1.5 - 5.0 x ULN)	**Recommendation:** Maintain dose level, measure 2x week
Grade 3 (> 5.0 x ULN)	**Mandatory:** Hold 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., MRI, CT scan or ultrasound).
Grade 4 (> 5.0 x ULN and with signs and symptoms)	**Mandatory:** Permanently discontinue patient from study drug treatment. Obtain appropriate imaging (i.e., MRI, CT scan or ultrasound).

[redacted]

Dose modifications for asciminib **Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment**	
Worst toxicity CTCAE Grade 5	**Asciminib**
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 current antihypertensive drug or change treatment plan as per investigator assessment
Systolic BP ≥160 mm Hg or Diastolic BP ≥100 mm Hg	**Mandatory:** Hold dose until resolved ≤ Grade 1/baseline, then reduce dose ↓ 1 dose level. Initiate antihypertensive drug/increase the dose of current antihypertensive drug or change treatment plan as per investigator assessment
CTCAE Grade 4	**Mandatory:** Permanently discontinue patient from study drug treatment.
Gastro intestinal	
Pancreatitis	
Grade 2 (radiologic findings for pancreatitis as per CTCAE v5, for increased enzymes please see table for asymptomatic amylase and/or lipase elevation)	**Mandatory:** If asymptomatic radiologic pancreatitis, hold treatment until recovery of the radiologic findings. If treatment delay is ≤ 21 days, then reduce dose ↓ 1 dose level. 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 patient from study drug 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:** Hold dose until resolved to ≤ grade 1, then maintain dose level. If diarrhea returns as ≥ grade 2, then hold dose until resolved to ≤ grade 1, then reduce dose ↓ 1 dose level
Grade 3	**Recommendation:** Hold dose and discontinue patient from study drug treatment
Grade 4	**Mandatory:** Permanently discontinue patient from study drug treatment

[redacted]

Dose modifications for asciminib

Please note that if a patient requires a dose interruption of > 28 days for each toxicity, then the patient must be discontinued from the study treatment

Worst toxicity CTCAE Grade 5	**Asciminib**
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:** Hold dose until resolved to Grade ≤ 1, then: If resolved in ≤ 7 days, then reduce dose ↓ 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then discontinue patient from study drug treatment
Grade 4, despite skin toxicity therapy	**Mandatory:** Permanently discontinue patient from study drug treatment.
General disorders and administration site conditions	
Fatigue/ Asthenia	
Grade 1 or 2	**Recommendation:** Maintain dose level
Grade 3	**Recommendation:** Hold 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 Adverse Events (CTCAE Version 5)

[b] Core LFTs consist of ALT, AST, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN).

[c] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold

If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin 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 hold 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 ALP elevation (>2.0 x ULN and R value <2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with 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 total bilirubin > 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, patients will be discontinued permanently from study treatment.

*** Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea

[redacted]

Table 6-3 Dose reduction steps for asciminib

Dose reduction*

	Starting dose level – 0	Dose level – 1
Asciminib 40 mg BID	40 mg tablet BID (total daily dose 80 mg)	20 mg tablet BID (total daily dose 40 mg)
Asciminib 80 mg QD	40 mg tablet + 40 mg tablet = 80 mg once daily	40 mg tablet once daily
Asciminib 200 mg BID	40 mg tablet x 5 = 200 mg BID	40 mg tablet x 5 = 200 mg once daily
*Dose reduction should be based on the worst toxicity demonstrated at the last dose.		
Asciminib dose reduction below total daily 40 mg is not allowed. 20 mg tablets will be dispensed to patients in the instance of dose reduction.		

6.5.2.1 Dose adjustments for QTcF prolongation

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

1. Assess the quality of the ECG recording and the QT value and repeat if needed
2. Interrupt study treatment until confirmed resolution of QTcF and as per dose reduction guidelines for non-hematological AEs.
3. Determine the serum electrolyte levels (in particular hypokalemia and hypomagnesemia). If abnormal, correct abnormalities before resuming study treatment.
4. Review concomitant medication associated with QT prolongation, including drugs with a "Known", "Possible", or "Conditional risk of Torsades de Pointes" (refer to wwwcrediblemeds.org/), and drugs with the potential to increase the risk of study drug exposure related QT prolongation.
5. Check the dosing schedule and treatment compliance

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

- Interrupt study treatment
- Repeat ECG and confirm ECG diagnosis by a cardiologist or central ECG lab
- If QTcF confirmed > 500 msec:
  - Correct electrolytes, eliminate culprit concomitant treatments, and identify 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 msec
- After resolution to ≤ 480 msec, consider re-introducing treatment at reduced dose, and increase ECG monitoring (e.g., pre dose and 2 hours post dose after one week and two weeks of treatment re-introduction)
- If QTcF remains ≤ 500 msec after dose reduction, continue planned ECG monitoring during subsequent treatment
- If QTcF recurs > 500 msec after dose reduction, discontinue subject from trial

[redacted]

6.5.3 Follow-up for toxicities

Patients whose treatment is permanently discontinued due to a study drug related adverse event or clinically significant laboratory value, must 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 patients must be followed up for adverse events and serious adverse events for 30 days following the last dose of study treatment.

6.5.3.1 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 as 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, GLDH, prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase.

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, 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, or elevation of the liver-specific ALP isoenzyme in participants with 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 ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury. For children, there are caveats to calculating the R-ratio as normal levels of ALP are higher than in adults with standard ranges varying by developmental age. 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 (livertox.nih.gov/rucam.html).

Table 6-8 Provides guidance on specific clinical and diagnostic assessments that can be performed to rule out possible alternative causes of observed LFT abnormalities.

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
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, TSH; CVD / ischemic hepatitis – ECG, prior hypotensive episodes; T1D / glycogenic hepatitis).

[redacted].

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 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 LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should be reported as SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Total daily dose of study treatment administered with start and end date will be collected on the Dosage Administration Record eCRF page. Name, start and end dates of any Concomitant

[redacted]

Medications and Surgical and Medical procedures will be collected on the Prior and Concomitant medications and Surgical and Medical procedures eCRFs respectively.

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each dispensing patient visit.

6.6.2 Emergency breaking of assigned treatment code

Not Applicable

6.6.3 Special Considerations for COVID-19 infection

All patients that who present with COVID-19 infection or who become COVID-19 positive on treatment should be placed immediately on treatment break or delay while a determination is made about the next steps

A request to start or continue treatment of COVID-19 positive patients should be considered in the context of medical necessity to start or continue treatment with the study drug.

Many patients with previous COVID-19 infection may be appropriate to be considered eligible for inclusion in the study if tested negative after initial infection

6.7 Preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Each study site will be supplied with study drug in packaging as described under investigational drugs section.

A unique medication number is printed on the study medication label.

The IRT will select the study treatment to dispense to the subject. The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the package to the subject, site personnel will detach the outer part of the label from the package and affix it to the subject's source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment 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 study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

[redacted]

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 subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects 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.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, 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.

6.7.1.2 Handling of additional treatment

Not Applicable

6.7.2 Instruction for prescribing and taking study treatment

See Section 6.1.1

7 Informed consent procedures

Eligible subjects 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 subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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 subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject 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 subject.

[redacted]

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male subjects on asciminib treatment must be informed that if a female partner becomes pregnant while the male subject is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

No eCRF will be used as a source document.

(S) is defined as "Source"

(D) is defined as "Data Based"

[redacted]

Table 8-1 Assessment schedule

	Category	Protocol Section 8	Screening Phase	Treatment Phase														
Visit name			**Screening/ Baseline (Day -21 to -1)**	**Week 1 Day 1**	**Week 2 Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**
Obtain Informed Consent	D		X (Screening window -56 days)															
Eligibility checklist/registration	D		X															
Cohort Assignment	D	6.3.2	X															
Demography	D	8.2	X															
Inclusion/exclusion criteria	D	5.1	X															
Medical History	D	8.2	X															
Disease History	D	8.2	X															
Mutation status	D	8.2	X															
Prior antineoplastic therapy	D	8.2	X															
Prior TKI therapy	D	8.2	X															

[redacted]

	Category	Protocol Section 8	Screening Phase	Treatment Phase														
Visit name			**Screening/ Baseline (Day -21 to -1)**	**Week 1 Day 1**	**Week 2 Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**
Prior/concomitant medications	D	6.2	X	Continuous														
Physical examination	S	8.3	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Extramedullary Involvement	D	8.3	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance status	D	8.3	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Height	D	8.3	X															
Weight	D	8.3	X	X				X			X			X			X	
Vital signs	D	8.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments																		
Hematology	D	8.3.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	D	8.3.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry-Hemoglobin A1c	D	8.3.1	X	Week 12 and as clinically indicated														
Serum Pregnancy test (if applicable)	D		X			X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis markers	D		X															

[redacted]

	Category	Protocol Section 8	Screening Phase	Treatment Phase													
Visit name			**Screening/ Baseline (Day -21 to -1)**	**Week 1 Day 1**	**Week 2 Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**
Liver assessments	D			as clinically indicated													
Efficacy assessments																	
Blood collection for BCR-ABL1 quantification by RQ-PCR	D	8.4.1	X			X		X			X			X			X	
[redacted]																	
Hematologic Response Assessment	D	8.4.1						X			X			X			X	
Cardiac Assessments																	
ECG	D	8.3.2	X	X	X	X	X[α]	X			X			X			X	

[redacted]

	Category	Protocol Section 8	Screening Phase	Treatment Phase														
Visit name			**Screening/ Baseline (Day -21 to -1)**	**Week 1 Day 1**	**Week 2 Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**
Cardiovascular risk factor assessments (including Family History)	D	8.3.2	X															
Echocardiogram	D	8.3.2	X							X*								
Pulmonary Function Test	D	8.3.2	X*							X*								
Adverse events / SAE	D	10.1	X	Continuous														
[redacted]																		

[redacted]

	Category	Protocol Section 8	Screening Phase	Treatment Phase														
Visit name			**Screening/ Baseline (Day -21 to -1)**	**Week 1 Day 1**	**Week 2 Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**
[redacted]																		
Asciminib Drug administration	D	6.1		Continuous														
Progression Status	D							X			X						X	
[redacted]																		

	Category	Protocol Section 8	Treatment Phase				EOT /Early Discontinuation	30 days Safety follow-up
Visit Name			**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	
Prior/concomitant medications	D	6.2	Continuous					

[redacted]

	Category	Protocol Section 8	Treatment Phase				EOT /Early Discontinuation	30 days Safety follow-up
Visit Name			**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	
Physical examination	S	8.3	X	X	X	X	X	
Extramedullary Involvement	D	8.3	X	X	X	X	X	
ECOG Performance	D	8.3	X	X	X	X	X	
Weight	D	8.3		X			X	
Vital signs	D	8.3	X	X	X	X	X	
Laboratory assessments								
Hematology	D	8.4.1	X	X	X	X	X	
Chemistry	D	8.4.1	X	X	X	X	X	
Chemistry-Hemoglobin A1c	D	8.4.1	as clinically indicated					
Serum Pregnancy test (if applicable)	D	8.3	X	X	X	X	X	
Liver assessments	D		as clinically indicated					
Efficacy assessments								
Blood collection for BCR-ABL1 quantification by RQ-PCR	D	8.4.1		X[β]			X	

[redacted]

	Category	Protocol Section 8	Treatment Phase				EOT /Early Discontinuation	30 days Safety follow-up
Visit Name			**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	
[redacted]								
Hematologic Response Assessment	D	8.4.2					X	
Cardiac Assessments								
ECG	D	8.3.2		X			X	
Cardiovascular risk factor assessments (including Family History)	D	8.3.2					X	
Echocardiogram	D	8.3.2					X*	
Adverse events / SAE	D	10.1.1	Continuous					
[redacted]								

[redacted]

	Category	Protocol Section 8	Treatment Phase				EOT /Early Discontinuation	30 days Safety follow-up
Visit Name			**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	
[redacted]								
Asciminib Drug administration	D		Continuous					
Antineoplastic therapies since discontinuation of study treatment	D							X
Progression status	D						X	
[redacted]								

X = assessment to be recorded in the clinical database or received electronically from a vendor

S = assessment to be recorded in the source documentation only

α = only applicable to Cohort C

* = If clinically indicated

** = Upon confirmed loss of MMR and/or End of Treatment

β = only applicable if the visit is in-person

Study visits from Week 2 Day 1 will have an allowed “visit window” of +/- 2 day for Week 2 Day 1. Study visits from Week 4 to Week 72 (EOT) will have an allowed “visit window” of +/- 7 days.

[redacted]

8.1 Screening

Molecular pre-screening

Not Applicable

Screening

Written informed consent must be obtained before any study specific medical procedures are performed. All screening/baseline assessments should occur within 21 days before Week 1 Day 1.

During the screening visit, inclusion and exclusion criteria will be assessed. Screening assessments to confirm eligibility must be performed prior to randomization. The results of the real time quantitative polymerase chain reaction (RQ-PCR) must be available prior to randomization and first dose of study treatment.

For details of assessments required during screening please refer to Table 8-1.

Laboratory baseline assessments (including hematology, chemistry and serum pregnancy test), physical examination including extramedullary involvement, performance status, ECG, height, weight and vital signs, evaluation of all relevant medical history including cardiovascular risk factors, CML disease history, including prior TKI therapy and antineoplastic medication and prior and concomitant medication must be performed prior to the first dose of study treatment. Patients 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 the first dose of study drug.

A patient who has a laboratory test (peripheral blood test) 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 approximately 2 weeks of the original screening visit date. In this case, the subject will not be required to sign another Informed Consent Form (ICF), and the original patient 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 patient 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 patient after a patient has screen failed, however, a new patient ID number will be assigned. All required screening activities must be performed when the patient is re-screened for participation in the study. An individual patient may be re-screened up to three times for the study. Once the number of patients screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the patients who screen failed will not be permitted to re-screen.

8.1.1 Eligibility screening

Following registration 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.

[redacted]

Please refer and comply with detailed guidelines in the IRT manual. The investigator site will then be allowed to assign treatment to the participant. For treatment assignment, please see Section 6.3.2

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable 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 phase (see SAE section for reporting details).

Participants who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition Case Report Form.

8.1.3 Treatment Period

All patients will be given the opportunity to receive study treatment until the end of study treatment period as defined in Section 6.1.

During the treatment phase, the patients will receive either asciminib treatment 40 mg BID, 80 mg QD or 200 mg (if T315I Mutation).

The dose can be modified, if required from the perspective of tolerance, following the guidance in Section 6.5. Treatment will be administered until patient experiences treatment failure, unacceptable toxicity, disease progression, death, lost to follow-up and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent.

The patients are advised to adhere to the food restrictions during the treatment (fasting status regarding study treatment administration, avoidance of prohibited concomitant medication).

8.1.4 Visit Windows

Study visits from Week 1 Day 1 to Week 2 Day 1 should be completed on the designated date [with an allowed “visit window” of +/- 2 day for Week 1 Day 1 and Week 2 Day 1]. All visits up until Week 4 day 1 need to be performed live by the treating physician on the site.

Study visits from Week 4 to Week 72 (EOT) should be completed every 4 weeks on the designated date [with an allowed “visit window” of +/- 7 days]. After Week 4 day 1, remote visits can be performed using tele-medicine approach with the exception of visits on Weeks 12, 24, 36, 48 and 72.

A delayed visit will have no impact on the next planned visit. The next visit should be completed as scheduled in order to avoid accumulation of additional weeks.

8.2 Participant demographics/other baseline characteristics

Patient demographics and baseline characteristics collected will include the following: date of birth, gender (and child bearing potential for female), race and ethnicity, height, weight, all relevant medical history including cardiovascular disease history, CML disease history,

[redacted]

including mutation status, and prior and concomitant medication including prior TKI therapy and antineoplastic medication.

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

Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the subject's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the patient's eCRF.

The central reading of the screening ECGs as well as the results of the RQ-PCR must be available prior to the first dose of study treatment to evaluate eligibility and to stratify the patient.

8.3 Safety and tolerability

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the patient's eCRF.

For details on AE collection and reporting, refer to AE section.

Table 8-4 Assessments

Assessment	Specification
Physical examination	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 about the physical examination must be present in the source documentation at the study center and will be collected on the following visits as specified in Table 8-1 : Screening Week 1 Day 1, Week 4 With the exception of Weeks 12, 24, 36, 48 and 72, Physical examination can be omitted for the remainder of the protocol. Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF. 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. liver and spleen size, any other organ involvement).
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature and must be performed at the following visits as specified in Table 8-1: • Screening

[redacted]

Assessment	Specification
	• Week 1 Day 1 • Week 2 Day 1 • Week 4 With the exception of Weeks 12, 24, 36, 48 and 72, Vital Signs can be omitted if for the remainder of the protocol
Height and weight	Height in centimeters (cm) will be measured at screening only. Body weight (to the nearest 0.2 pounds [lb] in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 8-1: • Screening • Week 1 Day 1 With the exception of Weeks 12, 24, 36, 48 and 72, Height and Weight can be omitted for the remainder of the protocol

Performance status:

ECOG Performance status scale (Table 8-5) will be used as described in the Table 8-1:

- Screening
- Week 1 Day 1
- Every 4 weeks from Week 4 to Week 72 (End of treatment) or early discontinuation in case of premature discontinuation.
- More frequent examinations may be performed at the investigator's discretion, if medically indicated.

ECOG Performance status scale will be used as described in Table 8-5.

Table 8-5 Table ECOG Performance Status Scale

Description	Grade
Fully active, able to carry on all pre-disease activities without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light housework, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead.	5

8.3.1 Laboratory Evaluations

Central laboratory will be used for analysis of hematology and clinical chemistry as specified in the visit schedules in Table 8-1 and Table 8-6 . Details on the collections, shipment of the samples and reporting of results by the central laboratory are provided to investigators in the [CABL001AUS04 Laboratory Manual]. The time windows granted for laboratory evaluations are identical with the corresponding visit time windows for each visit.

Local laboratory analysis are allowed only if there is a clinical suspicion of abnormal laboratory values which is supported by a reported adverse event.

[redacted]

When abnormal laboratory values or test results constitute an adverse event (i.e. induces clinical signs/symptoms or requires therapy) they must be recorded on the Adverse Events eCRF. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant (e.g. cause study discontinuation or constitutes in and of itself a Serious Adverse Event) or require therapy (e.g., any hematologic abnormality that requires transfusion or cytokine treatment); and should be recorded on the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them. Refer to the visit schedule for the collection frequency.

8.3.1.1 Hematology

Hematology labs are to be analyzed at each scheduled visit by a central laboratory as specified in Table 8-1 and Table 8-6 . Hematology includes assessment of hemoglobin, platelets count, red blood cells, total white blood cell count (WBC) and a full manual differential count including basophils, eosinophils, lymphocytes, monocytes, neutrophils, promyelocytes, myelocytes, metamyelocytes, blast and other cells (Table 8-6).

8.3.1.2 Clinical chemistry

Blood chemistry labs are to be analyzed at each scheduled visits by a central laboratory as specified in Table 8-1 and Table 8-6 . Chemistry includes albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), total calcium, total calcium (corrected for albumin), creatinine, creatinine clearance, creatine kinase, potassium, magnesium, sodium, phosphate (inorganic phosphorus), direct bilirubin, indirect bilirubin, total bilirubin, total cholesterol, LDL cholesterol, HDL cholesterol, total protein, triglycerides, blood urea, Blood Urea Nitrogen (BUN), uric acid, amylase, lipase and fasting glucose.

HbA1c is analyzed at screening/baseline, week 12 and as clinically indicated.

The hepatitis markers HbsAg, HbcAb/anti-Hbc are analyzed at screening/baseline (Table 8-6).

Table 8-6 Clinical laboratory parameters collection plan

Test Category	Test Name	Frequency
Hematology	Hemoglobin, platelets, red blood cells, white blood cells, WBC morphology with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils, promyelocytes, myelocytes, metamyelocytes, blast and other)	Screening/baseline, Week 1 Day 1, Week 2 Day 1, every 4 weeks from week 4 up to Week 72 (EOT) and as clinically indicated
Chemistry	Hemoglobin A1c	Screening/baseline, Week 12 and as clinically indicated
Chemistry	Creatinine clearance	Screening/baseline

[redacted]

Test Category	Test Name	Frequency
Chemistry	Albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), total calcium, total calcium (corrected for albumin), creatinine, creatine kinase, potassium, magnesium, sodium, phosphate (inorganic phosphorus), direct bilirubin, indirect bilirubin, total bilirubin, total cholesterol, LDL cholesterol, HDL cholesterol, total protein, triglycerides, blood urea or Blood Urea Nitrogen (BUN), uric acid, amylase, lipase, glucose (fasting)	Screening/baseline, Week 1 Day 1, Week 2 Day 1, every 4 weeks from week 4 up to week 72, (EOT), and as clinically indicated
Hepatitis markers	HbsAg, HbcAb /anti-Hbc	Screening/baseline
Serum Pregnancy test (if applicable)	Serum ß-HCG testing	Screening/baseline, every 4 weeks up to week 72 (EOT), unscheduled

8.3.2 Cardiac Assessments

8.3.2.1 Electrocardiogram (ECG)

After the subject has rested approximately 10 minutes in a semi-supine position, standard 12-lead ECGs must be obtained in triplicate with a recommended minimal interval of 5 minutes between each ECG at the time points specified in Table 8-1, and Table 8-5. In this case recording of ECGs should be planned according to the true time of blood sample [redacted] rather than to the scheduled time point.

A standard 12 lead ECG will be performed:

- For Cohort A, B and C at screening and/or baseline, Week 1 day 1, Week 2 Day1, Week 4 Day 1, Week 12 Day 1, Week 24 Day 1, Week 36 Day 1, Week 48 Day 1, Week 60 Day 1, Week 72 Day 1 (end of study).
- Cohort C will require additional Week 8 Day 1 ECG in addition to the schedules mentioned above.

Table 8-2 ECG collection plan

Week (or Cycle)	Time	ECG Type	Number of ECGs (per Visit)
Screening/Baseline Day -21 to -1 / (all patients)	3 serial ECGs at the screening visit	12 Lead	3
Week 1 Day 1	3 serial ECGs at 2 h post dose	12 Lead	3
Week 2 Day 1	3 serial ECGs pre-dose and at 2, 3, 4 h post dose	12 Lead	12

[redacted]

Week (or Cycle)	Time	ECG Type	Number of ECGs (per Visit)
Week 4 Day 1	3 serial ECGs pre-dose	12 Lead	3
Week 8 Day 1*	3 serial ECGs pre-dose	12 Lead	3
Week 12 Day 1	3 serial ECGs pre-dose	12 Lead	3
Week 24 Day 1	3 serial ECGs pre-dose	12 Lead	3
Week 36 Day 1	3 serial ECGs pre-dose	12 Lead	3
Week 48 Day 1	3 serial ECGs pre-dose	12 Lead	3
Week 60 Day 1+	3 serial ECGs pre-dose	12 Lead	3
Week 72 Day (end of study) 1	3 serial ECGs 30 min post-dose	12 Lead	3
Unscheduled or Unplanned sample	3 serial ECGs	12 Lead	3
30 min +/- 5min allowed * Week 8 day 1 assessment is only applicable to Cohort C and in-person visit + only applicable to in-person visit			

All ECGs performed will be independently reviewed. Instructions for the collection and transmission of these ECGs to the independent central reader will be provided in the [CABL001AUS04 ECG Manual].

Three serial ECGs (triplicate) should be performed ½ hour prior to dosing for pre-dose assessment. The serial ECGs should be taken approximately 5 minutes apart. All 3 ECGs for each time point should be sent to central ECG reader. Readings for QTc prolongation will be based on the average seen in the scans for each time point. The enrollment of patients has to be based on centrally assessed QTcF time. If one of the 3 serial ECGs prior to dosing on day 1 shows a QTcF ≥ 450 msec (male) or ≥ 460 msec (female) by automated reading, an immediate manual central reading must be requested by either contacting the medical monitor or by calling central ECG reader. The patient may not be dosed if the average of the manually read ECGs confirms a QTcF ≥ 450 msec (male) or ≥ 460 msec (female).

Dose adjustments in case of QT prolongation should be performed per Section 6.5.2.1

Additional unscheduled ECGs may be repeated 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. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator.

All ECGs, including unscheduled triplicate safety ECGs with clinically relevant findings, collected during the study should be transmitted to the central core ECG laboratory for review.

[redacted]

The results of the centrally assessed ECGs are automatically transferred into the clinical database.

Clinically significant ECG abnormalities present at screening should be reported on the Medical History eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

8.3.2.2 Echocardiogram

Echocardiograms will be performed to monitor cardiac safety. Assessments are scheduled at screening/baseline, and if clinically indicated at Week 20 and end of treatment visits. Echocardiogram is the only acceptable assessment for cardiac safety. The echocardiogram will be performed at the discretion of the treating physician locally if he/she recommends assessing the left ventricular ejection fraction due to potential concerns for cardiac safety. Any clinically significant findings will be collected and reported in the database (i.e. reported as adverse events).

8.3.2.3 Cardiovascular risk factor assessment

Cardiovascular events (CVE) including ischemic heart disease, peripheral arterial occlusive disease and ischemic cerebrovascular events have been reported in CML patients receiving TKI therapies as specified in Table 8-1. Since the study treatment in the trial is TKIs (asciminib), the cardiovascular risk factors (hypertension, tobacco use, raised blood glucose (diabetes), physical inactivity, unhealthy diet, cholesterol/lipids, overweight and obesity) of each patient will be collected prior to randomization and end of treatment. This will also include the patients Family History.

8.3.2.4 Pulmonary function test

Pulmonary function test will only be performed if clinically indicated by treating physician. The pulmonary function test with the plethysmograph includes the assessment of the lung volumes FEV1, FVC, FEV1/FVC, TLC and VC. In addition the DLCO to evaluate the gas exchange will be assessed at the same time of testing if indicated. Any clinically significant findings will be collected and reported in the database (i.e. reported as adverse events).

8.3.3 Pregnancy and assessments of fertility

All women of childbearing potential have to complete a serum pregnancy test at the screening visit, at every monthly visit until end of treatment visit. Pregnancy testing is not required for patients 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. Refer to Table 8-1 and Table 8-6 of the Visit evaluation schedules. Serum pregnancy test will be performed by a central laboratory.

Pregnancies diagnosed in female patients participating in the study (including female partners of male patients) should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the Oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) Department.

[redacted]

During the whole study, women of childbearing potential should employ the use of highly effective contraception. Highly effective contraception methods are defined in Section 5.2.

Sexually active males on asciminib treatment must use a condom during intercourse while taking the drug and for at least 3 days after stopping treatment and should not father a child within this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. In addition, male participants must not donate sperm for the time period specified above.

8.3.4 Other safety evaluations

Not Applicable

8.3.5 Appropriateness of safety measurements

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

8.4 Efficacy

8.4.1 Molecular Response

Molecular response (MR) BCR-ABL1 will be assessed in all patients assigned Cohort A, B and C. The molecular response for all patients are to be assessed centrally.

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

MR2 and related variables are defined as the following:

- Rate of MR2 where MR2 is defined as a ≥ 2 log reduction in BCR-ABL1 transcripts compared to the standardized baseline equivalent to ≤ 1% BCR-ABL1/ABL % by international scale as measured by RQ-PCR, confirmed by duplicate analysis of the same sample
- Time to MR2 defined as the time from the date of start of study treatment to the date of the first documented MR2
- Duration of MR2 defined as the time from the date of first documented MR2 to the earliest date of loss of MMR, progression to AP or BC, or CML-related death

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

- Rate of Major Molecular Response (MMR) where MMR is defined as a ≥ 3.0 log reduction in BCR-ABL1 transcripts compared to the standardized baseline equivalent to ≤ 0.1 % BCR-ABL1/ABL % by international scale as measured by RQ-PCR, confirmed by duplicate analysis of the same sample
- Time to MMR defined as the time from the date of start of study treatment to the date of the first documented MMR,
- Duration of MMR defined as the time from the date of first documented MMR to the earliest date of loss of MMR, progression to AP or BC, or CML-related death.

[redacted]

MR4 and related variables are defined as the following:

- Rate of MR4 where MR4 is defined as a ≥ 4 log reduction in BCR-ABL1 transcripts compared to the standardized baseline equivalent to ≤ 0.01% BCR-ABL1/ABL % by international scale as measured by RQ-PCR, confirmed by duplicate analysis of the same sample
- Time to MR4 defined as the time from the date of start of study treatment to the date of the first documented MR4,
- Duration of MR4 defined as the time from the date of first documented MMR to the earliest date of loss of MR4, progression to AP or BC, or CML-related death.

MR4.5 and related variables are defined as the following:

- Rate of MR4.5 where MR4.5 is defined as a ≥ 4.5 log reduction in BCR-ABL1 transcripts compared to the standardized baseline equivalent to ≤ 0.0032% BCR-ABL1/ABL % by international scale as measured by RQ-PCR, confirmed by duplicate analysis of the same sample
- Time to MR4.5 defined as the time from the date of start of study treatment to the date of the first documented MR4.5
- Duration of MR4.5 defined as the time from the date of first documented MMR to the earliest date of loss of MR4.5, progression to AP or BC, or CML-related death

Loss of Responses

Loss of MR2 is defined as increase of BCR-ABL1/ABL to > 1% by international scale (IS). BCR-ABL less than 1% according to the IS can be regarded as an equivalent to CCyR. Loss of MR2 must be confirmed by subsequent sample analysis within 4 to 6 weeks.

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

Mutational Analysis (T315I mutation)

Mutational analysis will be performed at a Novartis designated laboratory by Sanger sequencing for T315I mutation at Screening if T315I mutational analysis is not confirmed and upon confirmed loss of MMR and/or at end of treatment. Please see Section 8.5.3.

The blood samples will be taken as described in Table 8-1, and Table 8-6 .

[redacted]

Table 8-3 Blood samples (efficacy secondary endpoint)

Sample Type	Volume	Visit	Time point
Blood for BCR-ABL1 quantification by RQ-PCR	20 mL	Screening/Baseline	Pre-dose
	20 mL	Week 4	Pre-dose
	20 mL	Week 12	Pre-dose
	20 mL	Week 24	Pre-dose
	20 mL	Week 36	Pre-dose
	20 mL	Week 48	Pre-dose
	20 mL	Week 60[β]	Pre-dose
	20 mL	(Week 72) End of Treatment	Anytime
Blood for BCR-ABL1 Mutation analysis by Sanger Sequencing	5 mL	Screening	Pre-dose
	No sample collected - testing is performed on the "Blood for BCR-ABL1 quantification by RQ-PCR" sample	Upon confirmed loss of MMR and/or End of Treatment	Anytime

β = only applicable if the visit is in-person

During the study, peripheral blood samples will be collected into PAXgene™ Blood RNA tubes for all RQ-PCR assessments. Detailed instructions for the collection, handling, and shipment of RQ-PCR and mutation samples are outlined in the [CABL001AUS04 Laboratory Manual].

8.4.2 Hematologic Response

Hematologic response assessments are to be done locally at the site. The hematology parameters required to be evaluated are listed in Table 8-6.

A complete hematologic response (CHR) is defined as all of the following present for ≥ 4 weeks:

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

Loss of CHR

Loss of CHR is defined if patients exhibit:

- WBC count >10 x 10^9/L
- Platelet count >450 x 10^9/L
- Basophils >5%
- Any blasts and promyelocytes in peripheral blood
- Myelocytes + metamyelocytes > 5% in peripheral blood

[redacted]

8.5 Additional assessments

[redacted]

8.5.3 Biomarkers

At the screening the selection of patient in each cohort will based on the mutational status of T315I during screening as mentioned in the visit schedule Table 8-1. Patient's BCR-ABL1 mutation status needs to be available and results have to be done within 6 months of screening.

In addition, mutational analysis will be performed at screening to confirm the historical T315I mutational record if available.

[redacted]

8.5.4 Imaging

Not Applicable

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the subject or the investigator.

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

Patients who discontinue the study treatment for an adverse event suspected to be related to study drug or an abnormal laboratory value suspected to be related to study drug must be followed as described in Section 8

Patients may also be discontinued from the study treatment if any of the following occurs:

- discovery of patient ineligibility
- errors in treatment compliance [study treatment, other prescribed or non-prescribed medications]
- missed/unscheduled/off schedule/incomplete/incorrect assessments
- major protocol deviation
- use of prohibited treatment refer to Section 15-Appendices
- any other protocol deviation that results in a significant risk to the patient's safety

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

- In the event of detection of new T315I mutations during the study, the patient **must** be discontinued from the study treatment. The Novartis Managed Access Program (MAP) ABL001A02401M Cohort will be available for those patients without a reasonable alternative options if treating physician and patient still choose to pursue treatment with Asciminib.
- In the event of a pregnancy during study, if a patient wants to pursue the pregnancy then patient **must** be discontinued from the study treatment. However, in the event of a spontaneous miscarriage or in the event of elective abortion, the patient is permitted to continue study treatment.
- In the event of treatment failure the patient must be discontinued from the study treatment. The following events will constitute 'treatment failure', defining failure of a third line treatment:
  - No CHR at three months after initiation of therapy or thereafter
  - BCR-ABL1 ratio > 10% IS at 24 weeks after initiation of therapy or thereafter
  - BCR-ABL1 ratio > 1% IS at 48 weeks after initiation of therapy or thereafter
  - Loss of CHR, MR2 at any time after initiation of therapy

[redacted]

  - Detection of new BCR-ABL1 mutations which potentially cause resistance to study treatment (asciminib) at any time after initiation of therapy
  - Confirmed loss of MMR in 2 consecutive tests (Section 8.5) (BCR-ABL1 > 0.1%)
- In the event of disease progression the patient must be discontinued from the study treatment. 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 the peripheral blood or bone marrow aspirate
  - ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate
  - ≥ 20% basophils in the peripheral blood
  - Thrombocytopenia (<100 x 109/L) that is unrelated to therapy
  - Blast crisis (BC) as defined by any of the following:
  - ≥ 30% blasts in peripheral blood or bone marrow aspirate

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section,). Where possible, they should return for the assessments indicated in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/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 subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

9.1.2 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore, and
- Does not want any further visits or assessments, and
- Does not want any further study related contacts

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 his/her consent and record this information.

[redacted]

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

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.

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 assessment table.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, 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.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- 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 study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen by treating physician as soon as possible and treated as a prematurely withdrawn participant. 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 sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

The patients are treated in the study up to end of study treatment period defined as up to 72 weeks after the last patient receives the first dose unless patients have discontinued treatment earlier. The end of the study will occur when the last patient enrolled (40 mg BID, 80 mg QD or 200 mg BID cohort) into the study completes 72 weeks of treatment or experience treatment failure**.**

[redacted]

The primary analysis (cut-off date) is defined as the date when all patients (in Cohort A, B and C) have been on study treatment for 24 weeks (Section 12) or discontinued earlier. Subsequent to this analysis, the primary clinical study report (CSR) will be developed. Following the cut-off date for the primary CSR, the study will remain open. Patients who are ongoing at the time of the primary analysis will continue to receive the study treatments (asciminib) during the study treatment period as defined above. The end of study treatment analysis will be conducted with a cut-off date 30 days after the end of study treatment period to ensure all available treatment data from all patients in the study is analyzed and summarized in a final CSR.

After the end of the study treatment period the assigned study treatment will be made available to patients who in the opinion of the Investigators are still deriving clinical benefit. This may be outside of this study through alternative options including, but not limited to, an expanded access/compassionate use /managed access program or access to commercial supplies in applicable countries.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Adverse events 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.

Adverse events 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].

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

[redacted]

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) 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. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 10.1.2 and which seriousness criteria have been met
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)

If the event worsens the event should be reported a second time in the eCRF 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 eCRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Natural progression or deterioration of the malignancy under treatment (including loss of response, progression to accelerated phase or blast crisis and death due to disease progression), will be recorded as part of the efficacy evaluation and should NOT be reported as an AE/SAE.

Signs and symptoms clearly associated with the disease under study should NOT be reported as AEs unless they are newly emergent (i.e. not previously observed in the patient), judged by the Investigator to be unusually severe or accelerated, or if the Investigator considers deterioration of disease-related signs and symptoms to be caused directly by the study drug. If

[redacted]

there is any uncertainty about an AE being due solely to the disease under study, it should be reported as an AE or SAE as appropriate.

10.1.2 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 subject 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
- 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 subject'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 subject 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 subject 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 or abuse (please refer to the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met

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

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

[redacted]

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

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. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

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 Novartis study treatment, an oncology Novartis 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 drug 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 Directive 2001/20/EC or as per national regulatory requirements in participating countries.

10.1.4 Pregnancy reporting

To ensure subject 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 the Novartis Chief Medical Office and Patient Safety (CMO&PS). 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.

Pregnancy outcome should be collected for the female partners of any male who receivedasciminib treatment in this study. Consent to report information regarding pregnancy outcome should be obtained from the mother.

For all pregnancies with live birth and/or unknown outcome the newborn has to be followed up to obtain infant health status and development up to twelve months after delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

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

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 CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse 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.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

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

10.2 Additional Safety Monitoring

Not Applicable

10.2.1 Data Monitoring Committee

Not Applicable

[redacted]

10.2.2 Steering Committee

The Steering Committee (SC) will be established comprising 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 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.

10.2.3 Adjudication committee

Not Applicable

11 Data Collection and Database management

11.1 Data collection

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 (recorded on CRFs) (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.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Data collected by third parties (biochemistry, PCR assessments, [redacted]) will be sent electronically to Novartis.

11.2 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

[redacted]

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 CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis (or delegated CRO) representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. 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 (or delegated CRO). 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.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

[redacted]

12 Data analysis and statistical methods

Data from all participating centers will be combined. Data from all centers participating in this study will be aggregated for analyses. A contract Research organization will conduct all analyses and will report data from all centers.

The primary analysis of the primary endpoint will be performed after all patients have completed 24 week follow-up from the first dose of study medication or discontinued earlier. Selected efficacy and safety analysis will be updated annually. A final Clinical Study Report (CSR) will be produced once all patients complete the study.

All AEs, SAEs and other safety parameters will be summarized by cohort. No inferential tests for safety analyses will be performed. All primary, secondary [redacted] variables will be summarized descriptively by Cohort. Categorical data will be presented in frequencies and percentages. For continuous data descriptive statistics (mean, standard deviation, median 25th and 75th percentiles, min and max) will be provided. As appropriate, 95% confidence intervals will also be reported. Kaplan Meier's estimates will be reported for the time to event variables.

Detail analysis methods will be available in the Statistical Analysis Plan (SAP).

12.1 Analysis sets

The analysis sets to be used are defined as below. The FAS will be used as the primary efficacy analysis set. The Safety Set will be used for all the safety analysis.

The screened patients comprises all patients who have signed informed consent/assent and screened in the study. The enrolled comprises all patients who are enrolled in the study. Enrollment is defined as the point at which the patient meets all inclusion/exclusion criteria, and the patients'

12.1.1 Full Analysis Set (FAS)

The FAS comprises all patients to whom study treatment has been assigned Patients will be analyzed according to the treatment regimen.

12.1.2 Safety Set (SS)

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

12.1.3 Per-Protocol Set (PPS)

The PPS consists of a subset of the patients in the FAS without any major deviation, and who are compliant with requirements of the clinical study protocol (CSP).

The detailed exclusion criteria of PPS will be determined prior to the primary/final analysis based on the identified major protocol deviations.

[redacted]

12.1.5 Other analysis sets

Not Applicable

12.1.6 Efficacy/evaluable set

Not Applicable

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively for the FAS. Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term.

12.3 Treatments

The duration of exposure will be summarized for study treatment and for each study cohort A, B and C. The dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized for each study drug component by descriptive statistics.

The number of participants will be summarized by study treatment and by study cohort.

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

12.4 Primary objective / analysis of the primary endpoint(s)

Primary Objective(s)

To evaluate safety profile of monotherapy asciminib in CML-CP in 3L and beyond for Cohorts A, and B

Primary objective is to assess the safety profile of ABL001 (40 mg and 80 mg). For all primary safety analyses, the Safety Set will be used, unless stated otherwise.

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

12.4.1 Statistical hypothesis, model, and method of analysis

No formal hypothesis testing is planned for this study. Analyses of the safety data are described in Section 12.7.

12.4.2 Handling of missing values/censoring/discontinuations

Missing data for measures of safety and efficacy will not be imputed.

12.4.3 Supportive analyses

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

[redacted]

- Age: (< 65 years; ≥ 65 years)
- Patients with resistance
- Previous treatment with Ponatinib
- By number of prior TKI therapies

Data will be only summarized within each subgroup.

Additionally, as the study is ongoing during COVID 19 pandemic, in order to address the impact of COVID-19 (if any) on discontinuation, protocol deviations, disease status, dose interruptions, AEs and labs assessments and on missing data will be explored.

As appropriate, a sensitivity analysis will be performed on the primary efficacy evaluating the impact of COVID-19 on the study.

12.5 Secondary objectives / analysis of secondary endpoints

12.5.1 Secondary objective(s)

Secondary Objective(s)

- To estimate the rate of hematologic and molecular responses at specific time points for Cohort A, B and C
- Rate of CHR, MR2, MMR, MR4, MR4.5 in 12, 24, 48, 72 weeks of therapy
- To estimate time to hematologic and molecular response
- Time to CHR, MR2, MR4, MR4.5 in 12, 24, 48, 72 weeks of therapy
- To evaluate the duration of hematologic and molecular response
- Duration of MR1, MR2, MMR, MR4 and MR4.5
- To evaluate Progression Free Survival (PFS)
- To evaluate Overall Survival (OS)

12.5.2 Secondary objectives

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

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

For secondary efficacy analysis, proportion of patients achieving the response levels will be presented together with an exact 95% Clopper-Pearson confidence interval.

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

[redacted]

  - No evidence of extramedullary disease, including spleen and liver
- The rate of molecular response (MR2) by 12, 24, 48 and 72 weeks after the start of first study medication. **MR2** is defined as ≥ 2 log reduction of BCR-ABL transcript from standardized baseline or ≤ 1% BCR-ABL/ABL % by international scale, measured by real-time quantitative PCR (RQ-PCR).
- The rate of major molecular response (MMR) by 12, 24, 48 and 72 weeks after the start of first study medication. **MMR** is defined as ≥ 3 log reduction of BCR-ABL transcript from standardized baseline or ≤ 0.1% BCR-ABL/ABL % by international scale, measured by real-time quantitative PCR (RQ-PCR).
- The rate of molecular response (MR4) after the star by 12, 24, 48 and 72 weeks after the start of first study medication. **MR4** is defined as ≥ 4 log reduction of BCR-ABL transcript from standardized baseline or ≤ 0.01% BCR-ABL/ABL % by international scale, measured by real-time quantitative PCR (RQ-PCR).
- The rate of the molecular response (MR4.5) by 12, 24, 48 and 72 weeks after the start of first study medication. **MR4.5** is defined as ≥ 4.5 log reduction of BCR-ABL transcript from standardized baseline or ≤ 0.0032% BCR-ABL/ABL % by international scale, measured by real-time quantitative PCR (RQ-PCR).

12.5.2.2 Time to CHR, MR2, MR4, MR4.5 in 12, 24, 48, 72 weeks of therapy

Time to achieving a response level is defined as the time from the date of the first dose of study medication to the first documented achievement of a response level.

Time to achieve a specific response level will be analyzed using the Kaplan-Meier Product-Limit method. Patients who are known to be without achieving that response level will be censored at the last adequate assessment. Estimates of the 25th, median and 75th percentile of the time to achieve a response level and their 95% confidence intervals will be provided, if applicable.

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

Duration of Response (DOR) is the time from the date of the first documented a molecular response level to the date of first documented loss of the response level or death due to any cause, whichever occurs first.

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

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

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

[redacted]

12.5.2.4 Progression Free Survival

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

For patients without progression, the time is censored at the latest date the patient was known to be alive and without progression (on or before the cut-off date).

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

12.5.2.5 Overall Survival

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

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

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

[redacted]

[redacted]

[redacted]

12.7 Safety objectives

12.7.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment received.

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

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to *x* days after last dose of study medication

12.7.2 Adverse events (AEs)

All information obtained on adverse events will be displayed by treatment and participant.

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period. The number (and percentage) of participants with treatment emergent AEs will be summarized by primary system organ class, preferred term and maximum severity (based on CTCAE grades). Separate summaries will be provided for study medication related adverse events, deaths, serious adverse events, adverse events leading to treatment discontinuation, and adverse events leading to dose adjustment. The number (and percentage) of participants with adverse events will be summarized by primary system organ class, preferred term and maximum severity.

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

The incidence of 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 and non-serious adverse events will be tabulated.

Selected summaries of adverse events will be produced for the overall safety period. 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, post-treatment and overall safety period will be flagged.

12.7.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per NCI CTCAE version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

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

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

The following summaries will be generated separately for hematology and biochemistry tests: For laboratory tests where grades are defined by CTCAE v5

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

Listing of all laboratory data with values flagged to show the corresponding CTCAE v5 grades if applicable and the classifications relative to the laboratory normal ranges will be presented.

12.7.4 Other safety data

ECG

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

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

Vital signs

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

- Number and frequency of patients who shift from non-notable at baseline to notable post- baseline (details about the definition of notable abnormal results will be given in the SAP)
- All information collected will be listed and notable values will be flagged.

[redacted]

12.8 Interim analysis

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

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

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

12.9 Sample size calculation

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

For all CML-CP with the exception of those harboring the T315I mutation, there will be randomization to eliminate selection bias at the time of cohort allocation. Those patients will be assigned to either Cohort A consisting of asciminib 40 mg BID patients or Cohort B consisting of asciminib 80 mg QD. For CML-CP patients harboring the T315I mutation, they will be assigned to Cohort C with asciminib 200 mg BID, which is the dose required for that patient population. It is worthwhile mentioning that randomization for cohorts A and B will be

pursued for patient selection only. The study is not powered to show differences in Primary and Secondary endpoints between study cohorts.

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

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

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

Additionally for Cohort C, approximately 25 patients will be enrolled.

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

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign 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. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient 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, EudraCT 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.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

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.

14.1 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.

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16 Appendices

16.1 Appendix 1 List of concomitant medications for patients on asciminib

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited in Section 6.2 for patients.

The following lists are based on the internal [Pharmacokinetic Sciences memorandum on Drug-Drug Interaction] (release date: January 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. **If a medication appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.**

Table 16-1 Prohibited concomitant medications for asciminib

Category	Drug Names
Strong inducers of CYP3A	carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort (Hypericum perforatum)[3]
UGT1A1/2B7 inducers	UGT1A1: carbamazepine, cigarette smoke, rifampicin, testosterone propiate, UGT2B7: Barbiturates
Cohort C only : Strong inhibitors of CYP3A	atazanavir/ritonavir[1], danoprevir/ritonavir[1], darunavir/ritonavir[1], elvitegravir/ritonavir[1], indinavir/ritonavir[1], lopinavir/ritonavir[1], saquinavir/ritonavir[1], tipranavir/ritonavir[1], ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[1], boceprevir, clarithromycin, cobicistat, conivaptan, grapefruit juice[2], idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, telaprevir, telithromycin, troleandomycin, voriconazole
Torsade de pointe (TdP) TdP/QT risk : Known	amiodarone, anagrelide, arsenic trioxide, astemizole (off us mkt), azithromycin, bepridil (off us mkt), chloroquine, chlorpromazine, cilostazol, cisapride (off us mkt), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on us mkt), donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, grepafloxacin (off market worldwide), halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (off mkt worldwide), mesoridazine (off mkt worldwide), methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl, pentamidine, pimozide, probucol (off mkt worldwide), procainamide (oral off us mkt), propofol, quinidine, sevoflurane, sotalol, sparfloxacin (off us mkt), sulpiride (not on us mkt), terfenadine (off us mkt), thioridazine, vandetanib
TdP/QT risk: Possible	alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine, asenapine, bedaquiline, bortezomib, buprenorphine, capecitabine, ceritinib, clomipramine, clozapine, crizotinib, cyamemazine (cyamepromazine) (Only on Non US Market), dabrafenib, dasatinib, degarilix, delamanid (off US mkt), desipramine, dexmedetomidine, dolasetron, eribulin, ezogabine, famotidine, felbamate, fingolimod, foscarnet, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, lapatinib, lenvatinib, leuprolide, lithium, mifepristone, mirabegron, mirtazapine, moexipril/hctz, nicardipine, nilotinib, norfloxacin, nortriptyline, ofloxacin, olanzapine, osimertinib, oxytocin, paliperidone, panabinostat, pasireotide, pazopanib, perflutren lipid microspheres, pipamperone (not on us mkt), promethazine, quetiapine, ranolazine, rilpivirine, risperidone, roxithromycin (on non us mkt), saquinavir, sertindole (on non us mkt), sorafenib, sunitinib, tacrolimus, tamoxifen, telavancin, telithromycin, tetrabenazine (orphan drug in us), tizanidine, tolterodine, toremifene, trimipramine, vardenafil, vemurafenib, venlafaxine, vorinostat, zotepine

[redacted]

Category	Drug Names
TdP/QT risk: Conditional	amantadine, amisulpride, amitriptyline, atazanavir, chloral hydrate, diphenhydramine, doxepin, fluoxetine, furosemide (frusemide), galantamine, hydrochlorothiazide, hydroxyzine, hydroxychloroquine, indapamide, itraconazole, ivabradine (on non us mkt), ketoconazole, loperamide, metoclopramide, metronidazole, nelfinavir, pantoprazole, paroxetine, posaconazole, quinine sulfate, ritonavir, sertraline, solifenacin, telaprevir, torsemide, trazodone, voriconazole, ziprasidone
[1] Combination ritonavir-boosted regimens are listed here in the DDI memo as strong CYP3A inhibitors (to avoid potential confusion), even though some are considered moderate CYP3A inhibitors in the UW DDI Database. [2] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparationdependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength). [3] Herbal product	

Table 16-2 Concomitant medications to be used with caution

Category	Drug Names
Cohorts A and B only: Strong inhibitors of CYP3A	atazanavir/ritonavir[1], danoprevir/ritonavir[1], darunavir/ritonavir[1], elvitegravir/ritonavir[1], indinavir/ritonavir[1], lopinavir/ritonavir[1], saquinavir/ritonavir[1], tipranavir/ritonavir[1], ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[1], boceprevir, clarithromycin, cobicistat, conivaptan, grapefruit juice[2], idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, telaprevir, telithromycin, troleandomycin, voriconazole
Narrow therapeutic index substrates of CYP2C8	paclitaxel
Narrow therapeutic index substrates of CYP2C9	phenytoin, warfarin
Narrow therapeutic index substrates of CYP3A	alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus, terfanadine
BCRP Inhibitors	abacavir, amprenavir, atorvastatin, ,curcumin[3], cyclosporine[3], daclatasvir, declatasvir[3], delavirdine, efavirenz, elbasvir, eltrombopag[3], elvitegravir[3], erlotinib, fluvastatin, fostamatinib, fumitremorgin, gefitinib, grazoprevir, lapatinib[3], ledipasvir[3], lopinavir, paritepravir[3], pitavastatin, rosuvastatin, simvastatin, sulfasalazine, tipranavir[3], velpatasvir, venetoclax
P-gp inhibitors	alogliptin, amiodarone[4], azithromycin[4], canaglifozin, captopril[4], carvedilol[4], clopidrogel, cremophor RH40, curcumin, diltiazem[4], dronedarone[4], elacridar[4], eliglustat, felodipine[4], fluvoxamine[4], fostamatinib, ginko[4,5], isavuconazole, ivacaftor, lopinavir, milk thistle (silymarin, silibinin)[4,5], nifedipine[4], nitredipine[4],ombitasvir, paritaprevir, propafenone, quercetin,[4], ritonavir[4], sequinavir[4], schisandra chinesis extract[4,5], simepravir, St. John’s wort extract (Hypericum perforatum)[4,5], suvorexant, talinolol[4], telaprevir[4], telmisartan[4], ticagrelor[4], tipranavir[4], tolvaptan[4], valspodar, vandetanib, verapamil[4], voclosporin, vorapaxar
[1] Combination ritonavir-boosted regimens are listed here in the DDI memo as strong CYP3A inhibitors (to avoid potential confusion), even though some are considered moderate CYP3A inhibitors in the UW DDI Database. [3] Evidence of *in vivo* DDI [4] Dual P-gp and CYP3A4 inhibitor [5] Herbal product	

[redacted]