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TITLE: A study of treatment-free remission in chronic phase chronic myeloid leukemia in combination with asciminib and tyrosine kinase inhibitors

SHORT TITLE: ASTER-A

Corresponding Organization: *The Korean Society of Hematology Chronic Myeloid Leukemia Working Party*

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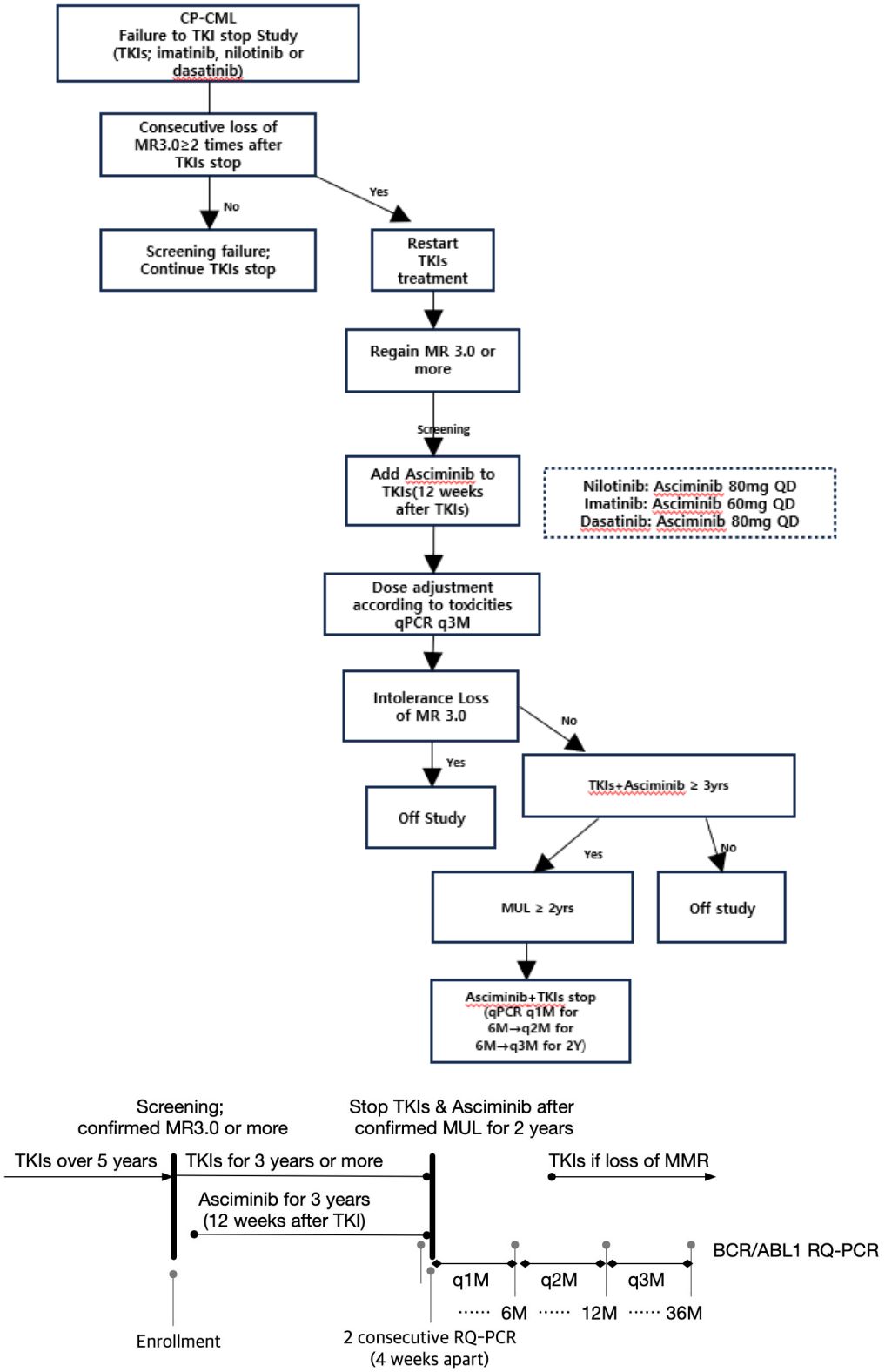
SYNOPSIS

Title	**A study of treatment-free remission in chronic phase chronic myeloid leukemia in combination with asciminib**
Background and Rationale	Tyrosine kinase inhibitors (TKIs) havebeen standard of treatment in chronic phase (CML-CP)as a first line therapy and its efficacy and safety have been consistantly proved for a long time use.[1-6] Recent study suggested that patients who took imatinib for 10 years or more had a tendency of increasing renal insufficiency. Nilotinib and dasatinib have increased risk of peripheral artery occlusive disease and pulmonary complications, respectively.[3,4,7] This raised reasonable suspicion for the long-term safety of all TKIs. Recently we come to know that chronic phase CML (CP-CML) patients could expect as good survial as normal population in the era of tyrosine kinase inhibitor (TKI) therapy, and STIM and KIDS trial showed that some patients who were in sustainable MR4.5 for several years (usually over 2 years) could stop imatinib safely. This means that the ultimate goal of CP-CML treatment could be remission free survival (RFS) beyond prolongation of survival.[8,9] Despite of those promising data, 30-60% patients who had stopped imatinib loss their MR3.0 response and had to restart imatinib almost within 6 months although re-challenging imatinib after loss of MR3.0 made almost all patients regain MR4.5.[8-10] There is a small report for second stop trial of imatinib after failure of first imatinib stop study.[11] Among 16 patients, 4/16 (25%) remained in major molecular response (MMR) and 2/16 (12.5%) remained in molecularly undetectable leukemia (MUL). This result implies that second trial of imatinib stopping is quite disappointing and there needs to be another approach for second cessation trial. The disadvantages of life long TKIs are not only discomforts and adverse events but also the increasing burden of total cost in health care system. Therefore, successful second TKIs stop is mandatory to achieve. Asciminib (ABL001) is a potent, specific, orally bioavailable BCR-ABL1 inhibitor that is distinct from approved other ABL1 kinase inhibitors, that does not bind to the ATP-binding site of the kinase.[12-14] Asciminib is a suitable candidate drug for adding to TKIs for the purpose of molecular relapse free survival (MRFS) since asciminib was active in heavily pretreated patients with CML who had resistance to or unacceptable side effects from TKIs, including patients who failed to ponatinib and those with a T315I mutation.[15] Also asciminib can give an additional synergistic effect with TKIs to ensure profound BCR/ABL1 suppression for successful second TKI stop. We expect that patients who lost MR3.0 after stopping TKIs, thus failed to maintain treatment-free remission can achieve second sustainable MR4.5 by sustainable MR4.5 for more than 3 years once regained and prolong MRFS by adding asciminib to TKIs. Patients will be restarted on TKIs when they fail sustaining MR3.0 after cessation because restarting TKIs when loss of MR3.0 is reasonable in this situation.[16] Hypothesis • This trial will evaluate the efficacy and safety of combined therapy of asciminib and TKIs in patients who attempt second cessation of TKIs after first cessation trial failure. • The hypothesis of this trial is that asciminib can achieve at least 40% sustainable MR3.0 after stopping CML therapy in CP-CML patients who have lost MR3.0 after 1 or more previous cessation trial of TKIs.
Objective of study	To evaluate the efficacy of asciminib adding on tyrosine-kinase inhibitors (TKI) to achieve treatment-free remission (TFR) in chronic myeloid leukemia (CML) patients in chronic phase who failed prior cessation study of TKI

End points	**Primary end point:** 1. To evaluate the cumulative incidence of sustained MR3.0 or less by 1 year of cessation of TKI and asciminib **Secondary end points:** 1. To evaluate the re-achievement rate of MR4.5 adding asciminib on TKI. 2. To evaluate molecular relapse-free survival (MRFS), overall survival (OS), time to loss of MR3.0/4.0/4.5, and treatment-free survival (TFS) 3. To evaluate safety profiles of additional asciminib on TKI. 4. To analyze prognostic factors to predict the successful TFR after combination therapy of asciminib and TKI.
Target Population	Patients with CML-chronic phase (CML-CP) who failed previous trial of TKI cessation.
Inclusion criteria	1. 19 year or older 2. CP-CML patients who are taking current TKIs (imatinib, nilotinib or dasatinib) for 5 years or more 3. Patients who have failed maintaining MR3.0 after 1 or more cessation trial of TKIs. 4. Patients who regained MR3.0 or deeper molecular response by TKIs retrial after TKI cessation failure at the time of screening 5. Taking TKIs over 12 weeks for the retrial of TKIs after TKI cessation failure 6. Patients who agree with stopping asciminib and TKIs after maintaining 2 year-duration of MR4.5 7. Adequate end organ function as defined by: • Total bilirubin (TBL) < 3 x upper limit of normal (ULN); patients with Gilbert's syndrome may only be included if TBL ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN • Creatinine clearance (ClCr) ≥ 30 mL/min as calculated using Cockcroft-Gault formula • Serum lipase ≤ 1.5 x ULN. For serum lipase > ULN - ≤ 1.5 x ULN, value must be considered not clinically significant and not associated with risk factors for acute pancreatitis 8. Patients who can sign the informed consent of their own free will
Exclusion criteria	1. Patients who experienced grade 3 or higher adverse events with TKIs (imatinib, dasatinib, and nilotinib). 2. Patients who are receiving any other investigational agents. 3. Patients who currently have uncontrolled infections 4. Patients who previously received Chimeric antigen receptor T-cell (CAR-T cell) therapy, allogeneic hematopoietic stem cell transplantation (allo-HSCT) or biologic therapy. 5. Patients with clinically significant cardiovascular disease or gastrointestinal dysfunction. 6. Patients who have a history of thromboembolic episodes within 3 months prior to the study enrollment. 7. Patients with active hepatitis B or C with uncontrolled disease activity. 8. Patients who have active malignancies requiring treatment other than CML. 9. Patients with any severe and/or uncontrolled medical conditions or other conditions that could adversely impact on

	patients' ability to participate in the study. 10. Patients with psychiatric illness/social situations that would limit compliance with study requirements. 11. Pregnant women are excluded from this study Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with asciminib and TKIs, breastfeeding should be discontinued if the mother is treated with asciminib and TKIs.
TFR eligibility	1. Patients have received asciminib along with one of TKIs over 3 years 2. MUL duration is over 2 years. 3. MUL is confirmed (2 consecutively at least 4 weeks apart).
Study procedures	• Patients will start Asciminib in addition to previously treated TKIs when eligibility is confirmed after taking signed informed consent. • Asciminib treatment ▫ Asciminib (80mg qd for nilotinib; 60mg qd for imatinib; 80mg qd for dasatinib) will be added at 12 weeks after the re-initiation of TKIs. ▫ Patients will be dropped out from this study if patients are intolerant to asciminib 20mg qod or loss of MR3.0 occurs twice consecutively. • Cessation of Asciminib and TKIs for TFR ▫ When a patient achieves molecularly undetectable leukemia (MUL; at least MR4.0 detection limit) and there is no loss of MUL for 2 years, the patient will stop asciminib and TKIs. RQ-PCR will be performed 2 times consecutively, 4 weeks apart for the confirmation of MUL just prior to stopping Asciminib and TKIs. ▫ The duration of asciminib and TKIs treatment should be 3 years or more and the duration of sustained MUL should be 2 years or more before stopping asciminib and TKIs. If a patient fails achieving MUL after 3 years of TKIs and asciminib combination, the patient will be dropped from the study. ▫ TKIs only without asciminib will be restarted, or other treatment can be tried when loss of MR3.0 is found consecutively 2 times after stopping asciminib and TKIs by above condition. **Therapeutic schedules**



Study design	A prospective, multi-center, open-label, single arm, phase II study
Outcomes and	**Efficacy evaluation**

measures	- CBC, Chemistry at every visit - BCR-ABL1 RQ-PCR^{is} every month for 6 months, then every 2 months for next 6 months, and then every 3 months until loss of MR3.0 or 36 months from the cessation of asciminib and TKI combination. **Safety evaluation** NCI-CTCAE v5.0
Statistical considerations	**Sample size calculations:** The sample size is calculated based on Simon's exact sing-stage phase II design assuming that P0=0.25; P1=0.4; α-error=0.05; β-error=0.2. The final number of patients required will be 69 with consideration of 10% of drop-out rate.
Total planned number of patients	69 patients from at least 10 centres of Korea

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1. OBJECTIVES & END POINTS

1.1 Objective of study

1.1.1 To evaluate the efficacy of asciminib adding on tyrosine-kinase inhibitors (TKI) to achieve treatment-free remission (TFR) in chronic myeloid leukemia (CML) patients who failed prior cessation study of TKI

1.2 Primary endpoint

1.2.1 To evaluate the cumulative incidence of sustained MR3.0 or less by 1 year of cessation of TKI and asciminib

1.3 Secondary Objectives

1.3.1 To evaluate the re-achievement rate of MR4.5 adding asciminib on TKI.

1.3.2 To evaluate molecular relapse-free survival (MRFS), overall survival (OS), time to loss of MR3.0/4.0/4.5, and treatment-free survival (TFS).

1.3.3 To evaluate safety profiles of additional asciminib on TKI.

1.3.4 To analyze prognostic factors to predict the successful TFR after combination therapy of asciminib and TKI.

2. BACKGROUND

2.1 Study background

2.1.1 Tyrosine kinase inhibitors (TKIs) have been standard of treatment for chronic myeloid leukemia (CML) as a first line therapy and its efficacy and safety have been consistently proved for a long time use.[1-6] In the era of TKIs, life expectancy of chronic phase CML (CP-CML) patients approaches that of general population.[17]

2.1.2 Long-term follow-up of IRIS study reported that 45% of patients had to stop imatinib and 12% of among those discontinued imatinib due to intolerance.[18] About 10% of patients who treated with second generation TKI (2G-TKI) such as dasatinib and nilotinib also discontinued TKI due to toxicities.[19,20] Another study suggested that patients who took imatinib for 10 years or more had a tendency of increasing renal insufficiency. Nilotinib and dasatinib also have increased risk of peripheral artery occlusive disease and pulmonary complications, respectively.[3,4,7] This raised reasonable suspicion for the long-term safety of all TKIs.

2.1.3 With successful treatment outcomes, the balance between disease control and quality of life with issues of long-term safety led to conduct the trials of discontinuation of TKI. Early trials, such as STIM, and KIDS trial showed that some patients who were able to maintain sustainable MR4.5 for several years (usually over 2 years) could stop imatinib safely. This lifted the ultimate goal of CP-CML treatment up to molecular relapse survival (MRFS) from prolongation of survival.[8,9]

2.1.4 Despite of those promising data, 30-60% patients who had stopped imatinib loss their MR3.0 response and had to restart imatinib almost within 6 months although re-challenging imatinib after loss of MR3.0 made almost all patients regain MR4.5.[8-10] The largest trial of TKI discontinuation which included 758 patients who maintained MR4.0 at

least 1 year reported treatment-free remission (TFR) of 50% at 24 months.[21]

2.1.5 There is a small report for second discontinuation trial of imatinib after failure of first imatinib TFR study.[11] Among 16 patients, 4/16 (25%) remained in major molecular response (MMR) and 2/16 (12.5%) remained in molecularly undetectable leukemia (MUL). This result suggested that second attempt of imatinib discontinuation is quite disappointing and other approach for second cessation trial is warranted. The disadvantages of life long TKIs are not only affecting on quality of life and adverse events but also the increasing burden of total cost in health care system. Therefore, successful second TKIs stop is worthy the goal to achieve.

2.1.6 Asciminib (ABL001) is a potent, allosteric, orally bioavailable BCR-ABL1 inhibitor binding a myristoyl site of the BCR-ABL1 protein, locking BCR-ABL1 into an inactive conformation that is distinct from approved other ABL1 kinase inhibitors.[12-14] Asciminib was active in heavily pretreated patients with CML who had resistance to or unacceptable side effects from TKIs, including patients who failed to ponatinib and those with a T315I mutation.[15] Asciminib is a suitable candidate drug adding its potent activity to other TKIs to achieve deeper molecular response translating into molecular relapse free survival (MRFS). Also, asciminib can give an additional synergistic effect with other TKIs to ensure profound BCR/ABL1 suppression for successful second TKI stop given its different mechanism of action.

2.1.7 The phase I trial of asciminib combined with dasatinib or nilotinib showed the 4 of 13 and 5 of 14 achieved MMR by 48 weeks without baseline MMR in patients who failed at least 2 prior lines of TKIs.[22] Combination of asciminib and imatinib also demonstrated promising efficacy with 42% of MMR by 48 weeks.[23]

2.1.8 We expect that patients who lost MR3.0 since stopping TKIs, thus failed to maintain TFR can achieve second sustainable MR4.5 and prolong MRFS by adding asciminib to TKIs with condition of sustainable MR4.5 for more than 3 years once regained. Patients will restart TKIs when they fail sustaining MR3.0 after cessation because restarting TKIs when loss of MR3.0 is reasonable in this situation.[16]

2.2 Hypothesis

2.2.1 This trial will evaluate the efficacy and safety of combined therapy of asciminib and TKIs in patients who attempt second cessation of TKIs after first cessation trial failure.

2.2.2 The hypothesis of this trial is that asciminib can achieve at least 40% sustainable MR3.0 after stopping CML therapy in CP-CML patients who have lost MR3.0 after 1 or more previous cessation trial of TKIs.

3. STUDY DRUG INFORMATION

3.1 Drug substance – physical and chemical properties

3.1.1 The free-base form of asciminib has been used for early clinical investigation with capsules. Following polymorphism evaluation, a

hydrochloride form was identified as better suited for development and is used for late phase clinical development with tablets

3.1.2 The molecular formula for ABL001 free base is $C_{20}H_{18}ClF_2N_5O_3$ (relative molecular weight 449.8). The molecular formula for ABL001 HCl salt is $C_{20}H_{18}ClF_2N_5O_3$. HCl (relative molecular weight 486.3).

3.2 Drug product – pharmaceutical properties

3.2.1 Description and composition

3.2.1.1 Film-coated tablets and capsules of asciminib hydrochloride may be used in the clinic.

3.2.2 Storage condition

3.2.2.1 Asciminib drug products packaged in either high density polyethylene (HDPE) bottles or PCTFE-PVC/Alu blister pack, and should not be stored above 25 °C and should be protected from moisture. Please refer to clinical labels and/or the Pharmacy Manual for current shelf life, in-use period, and additional storage instructions, as applicable.

3.2.3 Hazards and precautions

3.2.3.1 Asciminib is a potent investigational new drug that has not been fully evaluated. Exercise appropriate hygiene and clinical practice precautions.

3.3 Pharmacokinetics, metabolism, and pharmacodynamics in humans

3.3.1 Relative bioavailability and food effect assessments in healthy subjects

3.3.1.1 Study CABL001A2101 evaluated the relative bioavailability of the two asciminib tablet formulations in comparison to the clinical supply formulation (CSF) of capsule (used in the first-in-human study X2101) in healthy subjects.

3.3.1.2 The effect of food was assessed using the tablet formulations. Median Tmax was around 2 hr. and was similar between the three formulations under fasted condition. The concentration-time profiles revealed comparable rate and extent of absorption of asciminib when administered as tablet containing the HCl salt form/CSF capsule or free form tablet variant /CSF capsule under fasted conditions.

3.3.1.3 Tablets made from asciminib HCl salt versus CSF capsule under fasted condition indicated similar exposure: The exposures were 11%-12% higher in the tablet variant as compared to the capsule. The geometric mean ratios (GMRs) for AUCinf, AUClast, and Cmax were 1.12 (90% CI: 0.998, 1.25), 1.12 (90% CI: 1.00, 1.26), and 1.11 (90% CI: 0.949, 1.29), respectively.

3.3.1.4 Tablets made with asciminib free form variant versus CSF capsule under fasted condition: The exposures were 18%-22% higher in the tablet variant as compared to the capsule. The GMRs for AUCinf, AUClast, were 1.18 (90% CI: 1.05, 1.33) and 1.18 (90% CI: 1.05, 1.33), respectively. There was a 22%

increase in asciminib peak concentration Cmax with GMR of 1.22 (90% CI: 1.05, 1.42).

3.3.1.5 Study CABL001A2104 evaluated the relative bioavailability of orally administered asciminib CSF capsule and the final market image (FMI) tablet formulation in healthy subjects under fasted condition. The concentration-time profiles revealed similar rate and extent of absorption of asciminib when administered either as a tablet or as capsule under fasted conditions. The median Tmax was 2 hr. and 3 hr. for tablet and capsule formulations, respectively.

3.3.1.6 The bioavailability of tablet formulation was similar to that of the capsule formulation. The GMR (tablet vs capsule) and 90% CIs for AUCinf, AUClast and Cmax were 1.00 (90% CI: 0.909, 1.10), 1.01 (90% CI: 0.911, 1.11), and 0.909 (90% CI: 0.805, 1.03), respectively.

3.3.1.7 In conclusion, the systemic exposure in terms of Cmax and AUC was similar between the FMI tablet and the capsule formulation. Therefore, the capsule formulation was switched to the FMI tablet in study X2101 without dose adjustment. A negative food effect was observed following low and high fat meals (CABL001A2101, CABL001E2101). Low-fat and high-fat meals decreased the bioavailability of asciminib by ~30% and ~60%, respectively

3.3.2 Absorption and distribution

3.3.2.1 Based on PBPK modeling, asciminib is believed to be almost completely absorbed in humans.

3.3.2.2 The estimated fraction absorbed (Fa) was approximately 100% in humans. Based on PBPK modeling, the estimated absolute bioavailability was 73% (DMPK-R2000208).

3.3.2.3 Asciminib is poorly soluble in aqueous solution and possesses a high permeability; hence, asciminib was classified as a BCS class II compound. However, in vitro dissolution experiments across the physiological pH range (2-stage dissolution) a pronounced super saturation effect of asciminib was observed, explaining the almost complete fraction absorbed (ARD000059).

3.3.2.4 The apparent volume of distribution (Vz/F) was geo-mean (CV%) 89.0 L (6.1%) based on the human ADME study (Study CABL001A2102) and based on popPK analysis, for a typical individual (70 kg male), the combined volumes of central and peripheral compartments were approximately 111 L (V1 (+/- SE): 46.5 (1.71) + V2: 64.5 (7.92)), suggesting distribution into tissues.

3.3.3 Pharmacokinetics

3.3.3.1 The PK profile of asciminib has been evaluated as single agent in patients with CML and Ph+ ALL at a dose range between 10

mg to 280 mg b.i.d. and 80 mg to 200 mg q.d., as well as in healthy subjects.

3.3.3.2 Asciminib was rapidly absorbed following single dose and repeated administration with a median time to reach maximum plasma concentration (Tmax) of 2 to 3 hr., independent of dose.

3.3.3.3 Systemic exposure of asciminib, after oral administration of a single dose and multiple doses, as measured by Cmax and AUC, increased in a slightly more than dose proportional manner. Steady state was reached by day 3 (CABL001A2106).

3.3.3.4 The apparent terminal elimination half-life (T1/2) was estimated to be between 7 and 15 hr., the apparent clearance (CL/F) of asciminib was 4.34 L/hr. (based on non-compartmental PK analysis of a single dose of 80 mg in hADME study [CABL001A2102] in healthy subjects).

3.3.3.5 Based on population PK, the asciminib clearance for a typical individual was 6.31 L/hr. for a total daily dose of 80 mg.

3.3.3.6 Plasma concentrations of asciminib generally declined in a bi-phasic manner. No time dependent PK was observed.

3.3.3.7 In Study X2101, the geometric mean average accumulation ratio at steady state (Cycle 2 Day 1) ranged from 1.65 to 2.29 for the b.i.d. dosing (1.65 at 40 mg b.i.d. and 1.92 at 200 mg b.i.d.) and from 1.12 to 1.30 for the q.d. dosing (1.30 at 80 mg q.d.) (Study X2101-Table 14.2-11.1.1).

3.3.3.8 Generally, the variability of exposure was low to moderate with inter-subject variability (CV %) ranging from approximately 17% to 69% for AUClast and from 14% to 74% for Cmax.

3.3.3.9 The intrasubject variability ranged from 13.3% to 28.9% for Cmax and 5.6 to 22.7% for AUClast.

3.3.3.10 The inter-subject geoCV% in Study X2101 Cycle 2 Day 1 at 40 mg b.i.d. was 49.6% and 48.9% for AUClast and Cmax. In line with that, the inter-subject geoCV% in A2301 at 40 mg b.i.d. was 47.8% and 46.7% for AUClast and Cmax.

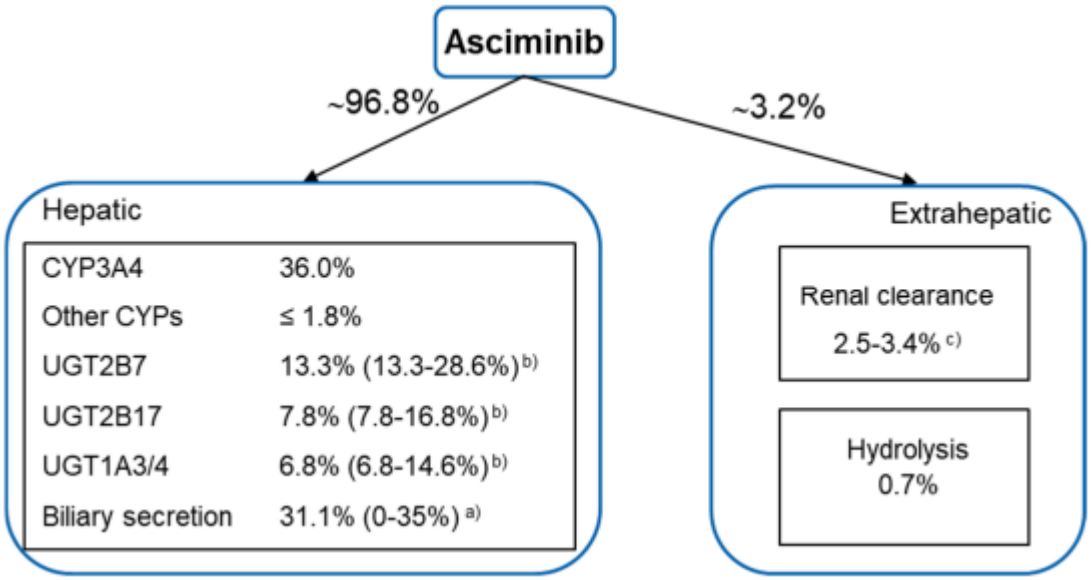
3.3.3.11 There was no apparent difference in PK between the patients with CML-CP harboring the T315I mutation compared to the patients with disease not harboring the T315I mutation and between patients with CML and ALL.

3.3.4 Metabolism

3.3.4.1 In human CYP3A4, UGT2B7, UGT2B17 and UGT1A3/4 were estimated to contribute to 36.0%, 13.3%, 7.8% and 6.8%, respectively, of the total clearance of asciminib based on *in vitro* human hepatocyte clearance and enzyme reaction phenotyping studies and clinical human ADME data (DMPK R1709012), (CABL001A2102). Based on PBPK simulations biliary secretion via BCRP was estimated to contribute to total

systemic clearance with about 31.1% (DMPK-R2000208).

3.3.4.2 Schematic description of disposition pathways



3.3.4.3 Asciminib is eliminated via parent drug excretion and metabolism.

3.3.4.4 The metabolism of asciminib involved the following primary biotransformation pathways: oxidation at the pyrrolidinol ring, direct glucuronidation, O-dealkylation, and amide hydrolysis. Oxidative opening of the pyrrolidinol ring, led to the formation of several metabolites (M29.5, M37, M39 and M43.3), which accounted for approximately 17% of the dose elimination in human excreta.

3.3.4.5 About 7% of the radioactivity excreted were M30.5, M44 contributed with 0.8% (CABL001A2102).

3.3.4.6 No major metabolite was identified (<10% of total drug-related material).

3.3.5 Excretion/Elimination

3.3.5.1 Following oral administration, the absorbed asciminib is mainly cleared through hepatic metabolism and biliary secretion through the fecal pathway with renal excretion playing a minor role. Following a single oral dose of 80 mg of [^{14}C] labelled asciminib to healthy subjects, 80% of the radiolabeled material was excreted into feces and 11% into urine (Study CABL001A2102).

3.3.5.2 In feces, asciminib was the major component, accounting accounted for 53.7% to 58.5% of the administered radioactive dose, with an average value of 56.7%.

3.3.5.3 In human, asciminib in feces is believed to originate from biliary secretion of unchanged asciminib via BCRP and direct glucuronide metabolites as indicated by results from bile-duct cannulated rats. The glucuronides are assumed to be back-

converted to the parent drug by intestinal bacteria, as evidenced by stability investigations of asciminib glucuronides in human feces, where an almost complete back-conversion was observed (DMPK R2000268).

3.3.6 Drug-drug interactions

3.3.6.1 Interaction potential with inhibitors and inducers of CYP3

3.3.6.1.1 A drug-drug interaction study (CABL001A2107) in healthy volunteers assessed the interaction of strong CYP3A inhibitors and inducers with asciminib (single dose of 40 mg).

3.3.6.1.2 Following multiple doses of the strong CYP3A inducer rifampicin, the geo-mean AUCinf, AUClast of single dose asciminib decreased by 14.9% and 12.7%, respectively, with co-administration of rifampicin. Cmax was increased by 9% when asciminib is administered with rifampicin.

3.3.6.1.3 Following multiple doses of the strong CYP3A4 inhibitor clarithromycin, the geo-mean AUCinf, AUClast, and Cmax of single dose asciminib increased by 36%, 37%, and 19%, respectively with co-administration of clarithromycin.

3.3.6.1.4 These data suggest only a weak interaction of asciminib with CYP3A inhibitors and inducers.

3.3.6.2 Interaction potential with P-gp inhibitors

3.3.6.2.1 A drug-drug interaction study (CABL001A2107) in healthy volunteers assessed the interaction of a P-gp inhibitor with asciminib (single dose of 40 mg). Following multiple doses of the P-gp inhibitor quinidine, the geo-mean AUCinf, AUClast, and Cmax of single dose asciminib decreased by 12.9%, 16.0%, and 11.3%, respectively with co-administration of quinidine.

3.3.6.2.2 These data suggest no relevant interaction of asciminib with P-gp inhibitors.

3.3.6.3 Interaction potential with acid-reducing agents

3.3.6.3.1 Study CABL001A1101 assessed the effect of multiple doses of rabeprazole, a proton pump inhibitor, on the PK of a single oral dose (fasted) of 40 mg asciminib in healthy subjects.

3.3.6.3.2 Coadministration of rabeprazole (regarded as the worst-case scenario with regards to pH alteration) in combination with a single 40-mg oral dose of asciminib had no effect on the bioavailability of asciminib, hence asciminib can be administered with acid reducing

agents.

3.3.6.4 Interaction potential with BCRP inhibitors

3.3.6.4.1 Asciminib is a substrate of BCRP *in vitro* with an apparent Km of 1.83 μM, an intra-cellular Km of 0.14 μM was calculated. At clinically relevant doses, i.e., 40 mg, the intestinal asciminib concentrations are high (356 μM). Therefore, intestinal BCRP is expected to be almost completely saturated and co-administration of a BCRP inhibitor is unlikely to impact the absorption of asciminib.

3.3.6.4.2 In the dedicated DDI study (CABL001E2101) with asciminib (40 mg single dose) and imatinib (400 mg q.d.), an inhibitor of CYP3A4, BCRP and UGT2B7 resulted in an asciminib AUC increase of 2.08-fold. Based on PBPK predictions, the interaction potential of BCRP inhibitors (using imatinib only with BCRP inhibition in the model) on asciminib decreases with increasing doses of asciminib due to saturation of BCRP (DMPK-R2001088).

3.3.6.4.3 In summary, co-administration of asciminib with BCRP inhibitors are not expected to result in a clinically relevant asciminib exposure increase.

3.3.6.5 Interaction potential with UGT inhibitors

3.3.6.5.1 Imatinib and nilotinib are both moderate CYP3A4 and UGT inhibitors (UGT2B17 and UGT1A3/4) as well as BCRP inhibitors. In addition, imatinib has been shown to be a potent P-gp inhibitor. The PK of asciminib in combination with imatinib and nilotinib was assessed in CML patients in study X2101. In addition, a dedicated DDI study evaluated the effect of imatinib on the PK of asciminib (40 mg single dose) in healthy subjects (CABL001E2101). Collectively, an approximately 2-fold increase in asciminib exposure when administered together either with imatinib or nilotinib.

3.3.6.5.2 In conclusion, co-administration of strong UGT inhibitors is not expected to result in clinically relevant asciminib exposure changes.

3.3.6.6 Interaction potential with UGT inducers

3.3.6.6.1 In the CABL001A2107 study, a small decrease of approximately 15% in asciminib exposure was observed with rifampicin, which is besides CYP3A4 at least partly also inducing UGT1A3/4, UGT2B7 and UGT2B17 enzymes.

3.3.6.6.2 In conclusion, the low asciminib exposure reduction by rifampicin suggests that UGT induction did not

relevantly influence the PK of asciminib.

3.3.6.7 Imatinib interaction in healthy subjects

3.3.6.7.1 Study CABL001E2101 assessed the effect of multiple doses of imatinib on the pharmacokinetics of a single oral dose (low-fat meal) of 40 mg asciminib in healthy subjects.

3.3.6.7.2 The analysis showed that the exposure of asciminib was higher when administered in combination with imatinib compared to when asciminib was administered alone.

3.3.6.7.3 The asciminib exposure (AUCinf) was approximately 108% higher and Cmax was 59% higher when administered in combination with imatinib compared to when administered alone. The Tmax was not impacted by the co-administration of imatinib. The effect of imatinib on asciminib may result from the inhibition of several metabolism and transport pathways that are involved in the disposition of asciminib. Considering the positive effect of imatinib (400 mg q.d.) on asciminib exposure, 40 mg q.d. and 60 mg q.d. given with low-fat meal are being evaluated in the add-on phase 2 study (E2201).

3.3.6.8 Asciminib in combination with nilotinib in CML-CP/-AP

3.3.6.8.1 Asciminib PK: Following administration of the first oral dose of asciminib on Cycle 1 Day 1 and after repeated administration of asciminib at steady state, asciminib was rapidly absorbed with a median Tmax of 2-3 hr. across all cohorts and independent of study day. Accumulation of asciminib exposure was observed at steady state (Cycle 2 Day 1) with the geometric mean accumulation ratio of 2.03 and 2.28 when administered at 20 mg b.i.d. and 40 mg b.i.d., respectively in combination with nilotinib 300 mg b.i.d.

3.3.6.8.2 Steady state was reached by Cycle 1 Day 15 as similar exposures were observed on Cycle 1 Day 15 and Cycle 2 Day 1. No time-dependent PK was observed. At steady state of asciminib 40 mg b.i.d. in combination with nilotinib 300 mg b.i.d. (Cycle 2 Day 1), the geometric mean Cmax and AUCtau of asciminib were 1113 ng/mL and 7908 ng.hr/mL, respectively, vs 793 ng/mL and 5262 ng.hr/mL for single agent asciminib 40 mg b.i.d. Hence, comparing the exposure of single agent asciminib 40 mg b.i.d. vs asciminib 40 mg b.i.d. in combination with 300 mg nilotinib b.i.d., Cmax and AUCtau of asciminib in combination appeared to be moderately increased by

1.4- and 1.5-fold, respectively (Cycle 2 Day 1).

3.3.6.8.3 Nilotinib PK: Following administration of the first oral dose of nilotinib on Cycle 1 Day 1 and after repeated administration of nilotinib at steady state, nilotinib was rapidly absorbed with a median Tmax of approximately 1-3 hr. across all cohorts and independent of study day. At steady state (Cycle 2 Day 1), the geometric mean Cmax and AUClast of nilotinib 300 mg b.i.d. when given in combination with asciminib 20 mg b.i.d. were 996 ng/mL and 5890 ng.hr/mL, respectively and in combination with asciminib 40 mg b.i.d. were 1082 ng/mL and 5870 ng.hr/mL, respectively. Hence, there was no change in the nilotinib Cmax and AUClast when administered in combination with asciminib 40 mg b.i.d. vs 20 mg b.i.d.

3.3.6.8.4 Overall, considering sample size and variability, there was no relevant difference in nilotinib exposure across the different dose groups. Accumulation of nilotinib exposure was observed at steady state (Cycle 2 Day 1) with the geometric mean accumulation ratio of 2.48 when administered in combination with asciminib 40 mg b.i.d.

3.3.6.9 Asciminib in combination with imatinib in CML-CP/-AP

3.3.6.9.1 Asciminib PK: Following administration of the first oral dose of imatinib on Cycle 1 Day 1 and after repeated administration of asciminib at steady state, asciminib was rapidly absorbed with a median Tmax of approximately 1.5-4 hr. across all cohorts and independent of study day. Asciminib exposure did not appear to accumulate at steady state (Cycle 2 Day 1) as indicated by the geometric mean accumulation ratio of approximately 1.0 for asciminib when administered at 40 to 80 mg q.d. in combination with imatinib 400 mg q.d.; the ratio was 2.54 when asciminib administered at 40 mg and b.i.d. regimen. At steady state of asciminib 40 mg b.i.d. in combination with imatinib 400 mg q.d. (Cycle 2 Day 1), the geometric metric mean Cmax and AUCtau of asciminib were 981 ng/ml and 9841 ng.hr/mL (n=5 for Cmax and n=3 for AUCtau), respectively, vs 793 ng/ml and 5262 ng.hr/mL for single agent asciminib 40 mg b.i.d. Based on very limited data, comparing the exposure of single agent asciminib 40 mg b.i.d. (fasted) vs asciminib in combination with imatinib 400 mg q.d. (fed), Cmax and AUCtau of asciminib in combination appeared to be moderately increased by 1.2- and 1.9-fold (Cycle 2

Day 1), respectively.

3.3.6.9.2 Imatinib PK: The Tmax for imatinib in combination with asciminib was approximately 2-4 hr. across cohorts, and independent of study day. Accumulation of imatinib exposure was observed at steady state (Cycle 2 Day 1) with the geometric mean accumulation ratio of 3.20 and 1.81 when administered with asciminib 40 mg and 60 mg q.d., respectively.

3.3.6.9.3 Overall, considering sample size and variability, there was no clinically relevant difference in imatinib exposure across the different dose groups. The overall increase of asciminib when co-administered with imatinib or nilotinib could be explained by their potential to inhibit BCRP, CYP3A4, UGT2B17 and UGT1A3/4. Both nilotinib and imatinib are UGT inhibitors and moderate CYP3A4 inhibitors. In addition, imatinib has been shown to be a potent P-gp and BCRP inhibitor.

3.3.6.10 Asciminib in combination with dasatinib in CML-CP/-AP

3.3.6.10.1 Asciminib PK: Following administration of the first oral dose of asciminib on Cycle 1 Day 1 and after repeated administration of asciminib at steady state, asciminib was rapidly absorbed with a median Tmax of approximately 2 hr. across all cohorts and independent of study day. Accumulation of asciminib exposure was observed at steady state (Cycle 2 Day 1) with the geometric mean accumulation ratio of 1.22 to 2.04 when administered at 40 mg b.i.d., 80 mg q.d. or 160 mg q.d. in combination with dasatinib 100 mg q.d. At steady state of asciminib 40 mg b.i.d. in combination with dasatinib100 mg q.d. (Cycle 2 Day 1), the geometric mean Cmax and AUCtau of asciminib were 823 ng/mL and 5243 ng.hr/mL (n=9 for Cmax and n=7 for AUCtau), respectively, vs 793 ng/mL and 5262 ng.hr/mL for single agent asciminib 40 mg b.i.d. Comparing the exposure of single agent asciminib 40 mg b.i.d. (fasted) vs asciminib in combination with dasatinib 100 mg q.d., there was no difference observed in Cmax and AUCtau of asciminib in combination with dasatinib.

3.3.6.10.2 Dasatinib PK: The Tmax for dasatinib in combination with asciminib was approximately 0.5-1.5 hr. across cohorts, and independent of study day. Accumulation of dasatinib exposure was observed at steady state (Cycle 2 Day 1) with the geometric mean accumulation ratio of 0.83 to 1.21 when administered

with asciminib 40 mg b.i.d., 80 mg q.d. or 160 mg q.d. Overall, considering sample size and variability, there was no clinically relevant difference in dasatinib exposure across the different dose groups.

3.3.7 Pharmacokinetics in special patient populations

3.3.7.1 Hepatic impairment

3.3.7.1.1 Study CABL001A2103 assessed the effect of varying degrees on hepatic impairment on the PK of asciminib. Compared to the control group: i) mild hepatic impairment group exhibited a trend to slightly higher exposure with 22% higher AUCinf, 21% higher AUClast, 26% higher Cmax, although considered globally comparable to normal subjects; ii) moderate hepatic impairment group had similar exposure; iii) severe hepatic impairment group had 66% higher AUCinf, 55% higher AUClast, 29% higher Cmax.

3.3.7.1.2 Median asciminib Tmax were similar in normal, mild, moderate groups (2 hr.) and slightly shorter (1.5 hr.) in severe hepatic impairment group Protein binding of asciminib was similar across groups. Based on the unbound fraction of asciminib and compared to the control group: i) the mild hepatic impairment group had 15% higher AUCinf, 14% higher AUClast, 19% higher Cmax; ii) moderate hepatic impairment group had similar exposure; iii) severe hepatic impairment group had 51% higher AUCinf, 44% higher AUClast, 20% higher Cmax.

3.3.7.1.3 Treatment with asciminib 40 mg was well tolerated in healthy subjects and in subjects with varying degrees of hepatic impairment.

3.3.7.2 Renal impairment

3.3.7.2.1 Study CABL001A2105 assessed the effect of severe renal impairment on the PK of asciminib. The exposure of asciminib as assessed by AUClast and AUCinf, which were 49% (geo mean ratio [90% CI]: 1.49 [1.01, 2.20]) and 56% (geo mean ratio [90% CI]: 1.56 [1.05, 2.30]) higher in the severe renal impairment cohort compared to the normal renal function cohort.

3.3.7.2.2 The Cmax and Tmax values were similar in both cohorts, suggesting there was no difference in the absorption of the drug.

3.4 Safety in humans

3.4.1 Asciminib single agent

3.4.1.1 The most common AEs reported in at least 50 patients among the 200 with CML-CP or AP-CML treated with asciminib single

agent when considering all doses and all grades were fatigue (29.0%), headache, lipase increase, nausea (26.0%, each) and diarrhea (25.5%).

3.4.1.2 Serious adverse events suspected to be drug related by system organ class, preferred term, and treatment single agent asciminib in CML-CP and CML-AP

All subjects N=200	
Primary system organ class	**SAE**
Preferred term	**n (%)**
Number of subjects with at least one event	18 (9.0)
Blood and lymphatic system disorders	3 (1.5)
Thrombocytopenia	2 (1.0)
Febrile neutropenia	1 (0.5)
Cardiac disorders	5 (2.5)
Angina pectoris	2 (1.0)
Atrial fibrillation	1 (0.5)
Pericardial effusion	1 (0.5)
Acute coronary syndrome	1 (0.5)
Cyanosis	1 (0.5)
Myocardial infarction	1 (0.5)
Gastrointestinal disorders	4 (2.0)
Pancreatitis	2 (1.0)
Pancreatitis acute	2 (1.0)
General disorders and administration site conditions	3 (1.5)
Non-cardiac chest pain	2 (1.0)
Immune system disorders	1 (0.5)
Hypersensitivity	1 (0.5)
Investigations	1 (0.5)
Platelet count decreased	1 (0.5)
Musculoskeletal and connective tissue disorders	2 (1.0)
Myalgia	1 (0.5)
Bone pain	1 (0.5)
Fibromyalgia	1 (0.5)
Osteonecrosis	1 (0.5)
Nervous system disorders	3 (1.5)
Cerebrovascular accident	1 (0.5)
IIIrd nerve paralysis	1 (0.5)
Ischemic stroke	1 (0.5)
Respiratory, thoracic, and mediastinal disorders	4 (2.0)
Dyspnea	1 (0.5)
Pleural effusion	2 (1.0)
Bronchospasm	1 (0.5)
Pleurisy	1 (0.5)
Skin and subcutaneous tissue disorders	1 (0.5)
Urticaria	1 (0.5)
Numbers (n) represent counts of subjects. Sort SOC by alphabetical order, and then PTs within each SOC by descending frequency in 'All grades' column. Only AEs occurring during treatment or within 30 days of the last study medication are reported. MedDRA version 23.0, CTCAE version 4.03	

3.4.2 Asciminib and imatinib combination

3.4.2.1 Asciminib has been studied in 25 patients with CML-CP or CML-AP at dose levels of 40 mg b.i.d., 40 mg q.d., 60 mg q.d.,

80 mg q.d. in combination with imatinib 400 mg q.d. Twelve patients (48.0%) discontinued study treatment. The most frequent primary reason for discontinuation was physician's decision due to lack of efficacy (16.0%). Adverse events leading to treatment discontinuation were reported in 2 patients (8.0%). Dose limiting toxicities (DLT) have been reported in six out of 25 evaluable patients (24.0%) treated with a combination of asciminib and imatinib as follows:

3.4.2.1.1 • Pancreatitis, n=2 (40 mg b.i.d., 80 mg q.d.),
3.4.2.1.2 • Abdominal pain, n=1 (60 mg q.d.),
3.4.2.1.3 • Nausea, n=1 (60 mg q.d.),
3.4.2.1.4 • Lipase increase, n=1 (80 mg q.d.).
3.4.2.1.5 • Neutrophil count decreased, n=1 (40 mg q.d.)

3.4.2.2 Based on totality of data, asciminib 40 mg and 60 mg q.d. doses have been recommended in combination with imatinib 400 mg q.d. in CML-CP or CML-AP patients for further development.

3.4.2.3 The safety profile from these cohorts and for the overall population is presented below. All 25 patients were evaluable for safety. Overall, by cut-off date, the median duration of exposure was longer for asciminib (129.3 weeks) than with imatinib (84.9 weeks) No on-treatment deaths were reported.

3.4.2.4 Nausea was the most common AE reported in patients with CML-CP or CML-AP treated with a combination of asciminib and imatinib (all cohorts) regardless of relationship to study drug or suspected to be related to study drug.

3.4.2.5 In this clinical trial, 40-60 mg of asciminib per day was confirmed to be similar to 40 mg bid administration when used with imatinib in previous studies, so asciminib 60 mg qd is used.

3.4.2.6 Serious adverse events suspected to be related to study drug by system organ class, preferred term, and treatment – asciminib in combination with Imatinib in CML-CP and CML-AP

All subjects **N=25**	
Primary system organ class	**SAE**
Preferred term	**n (%)**
Number of subjects with at least one event	4 (16.0)
Gastrointestinal disorders	1 (4.0)
Pancreatitis	1 (4.0)
Hepatobiliary disorders	1 (4.0)
Hepatitis	1 (4.0)
Investigations	1 (4.0)
Neutrophil count decreased	1 (4.0)
Musculoskeletal and connective tissue disorders	1 (4.0)
Myopathy	1 (4.0)
Numbers (n) represent counts of subjects. Sort SOC by alphabetical order, and then PTs within each SOC by descending frequency in 'All grades' column. Only AEs occurring during treatment or within 30 days of the last study medication	

are reported. MedDRA version 23.0, CTCAE version 4.03.

3.4.3 Asciminib and nilotinib combination

3.4.3.1 Asciminib has been studied in 26 patients with CML-CP or CML-AP at dose levels of 20 mg b.i.d. or 40 mg b.i.d. in combination with nilotinib 300 mg q.d. Eleven patients (42.3%) discontinued study treatment. The most frequent primary reason for discontinuation was physician's decision (26.9%, mainly due to lack of efficacy). Only one patient (3.8%) discontinued study treatment due to adverse events.

3.4.3.2 Dose limiting toxicities (DLT) have been reported in one out of sixteen evaluable patients (6.3%) treated with a combination of asciminib with nilotinib as follow: • maculopapular rash (asciminib 20 mg b.i.d. + nilotinib 300 mg b.i.d.).

3.4.3.3 Based on the safety and tolerability data, PK data, preliminary efficacy observed, the combined dose of asciminib 40 mg b.i.d. + nilotinib 300 mg b.i.d. was recommended for expansion cohort to collect additional safety and tolerability data. All 26 patients enrolled were evaluable for safety.

3.4.3.4 In this clinical trial, the dose of asciminib is set to 80 mg qd when administered in combination with nilotinib.

3.4.3.5 Overall, by cut-off date, the median duration of exposure was similar for both study drugs (36.6 weeks with asciminib and 34.8 weeks with nilotinib). No on-treatment deaths occurred. Lipase increased (38.5%), myalgia (34.6%), pruritus (30.8%), abdominal pain, amylase increase, and thrombocytopenia (26.9%, each) were the most common AEs reported in at least 7 patients with CML-CP or CML-AP treated with a combination of asciminib and nilotinib (all cohorts) regardless of relationship to study drug.

3.4.3.6 Serious adverse events suspected to be drug related by system organ class, preferred term, and treatment – asciminib in combination with nilotinib in CML-CP and CML-AP

All subjects N=26	
Primary system organ class	**SAE**
Preferred term	**n (%)**
Number of subjects with at least one event	3 (11.5)
Cardiac disorders	2 (7.7)
Angina pectoris	1 (3.8)
Atrial fibrillation	1 (3.8)
Atrioventricular block	1 (3.8)
Metabolism and nutrition disorders	1 (3.8)
Hyponatremia	1 (3.8)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (3.8)
Myelodysplastic syndrome	1 (3.8)
Respiratory, thoracic, and mediastinal disorders	1 (3.8)
Pleural effusion	1 (3.8)
Vascular disorders	1 (3.8)
Peripheral arterial occlusive disease	1 (3.8)

Numbers (n) represent counts of subjects. Sort SOC by alphabetical order, and then PTs within each SOC by descending frequency in 'All grades' column. Only AEs occurring during treatment or within 30 days of the last study medication are reported. MedDRA version 23.0, CTCAE version 4.03.

3.4.4 Asciminib and dasatinib combination

3.4.4.1 Asciminib has been studied in 23 patients with CML-CP or CML-AP at dose levels of 40 mg b.i.d., 80 mg q.d. and 160 mg q.d. in combination with dasatinib 100 mg q.d. Six patients (26.1%) discontinued study treatment; half of them due to physician's decision and the other half due to adverse events.

3.4.4.2 Dose limiting toxicities (DLT) have been reported in 2 out of 22 evaluable patients (9.1%) treated with a combination of asciminib and dasatinib as follows:

3.4.4.2.1 lipase increased (asciminib 40 mg b.i.d. + dasatinib 100 mg q.d.)

3.4.4.2.2 thrombocytopenia (asciminib 160 mg q.d. + dasatinib 100 mg q.d.)

3.4.4.3 Based on the overall safety, PK, and preliminary efficacy data, asciminib at 80 mg q.d. + dasatinib at 100 mg q.d. was selected as RDE in this combination and recruitment was ongoing at time of the safety cut-off date.

3.4.4.4 In this clinical trial, asciminib 80 mg qd is set when combined with dasatinib.

3.4.4.5 All 23 patients were evaluable for safety. Overall, by cut-off date the median duration of exposure was longer for asciminib (102.3 weeks) than with dasatinib (79.4 weeks). No on-treatment deaths were reported.

3.4.4.6 Fatigue (34.8%), thrombocytopenia (30.4%), abdominal pain, cough, lipase increase, nausea, and pleural effusion (26.1%, each) were the most common AEs reported in at least 6 patients with CML-CP or CML-AP treated with a combination of asciminib and dasatinib (all cohorts) regardless of relationship to study drug.

3.4.4.7 Serious adverse events suspected to be drug related by system organ class, preferred term, and treatment – asciminib in combination with dasatinib in CML-CP and CML-AP

All subjects N=43	
Primary system organ class	**SAE**
Preferred Term	**n (%)**
Number of subjects with at least one event	7 (16.3)
Blood and lymphatic system disorders	1 (2.3)
Febrile neutropenia	1 (2.3)
Gastrointestinal disorders	2 (4.7)
Pancreatitis	2 (4.7)
Investigations	4 (9.3)
Lipase Increased	2 (4.7)
Blood Alkaline Phosphatase increased	1 (2.3)
Gamma-glutamyl transferase increased	1 (2.3)

Alanine aminotransferase increased	2 (4.7)
Aspartate aminotransferase increased	2 (4.7)
Blood alkaline phosphatase increased	1 (2.3)
Nervous system disorders	1 (2.3)
Cerebrovascular accident	1 (2.3)

- Preferred terms are sorted in descending frequency of 'All grades' column, as reported in the 'All subjects' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- Only AEs occurring during treatment or within 30 days of the last study medication are reported.
- AEs occurred after the intra-patient dose escalation are summarized under the patient's initial treatment group.

MedDRA version 23.0, CTCAE version 4.03.

4. ELIGIBILITY

4.1 Inclusion Criteria

4.1.1 19 year or older

4.1.2 CP-CML patients who are taking current TKIs (imatinib, nilotinib or dasatinib) for 5 years or more.

4.1.3 Patients who have failed maintaining MR3.0 after 1 or more cessation trial of TKIs.

4.1.4 Patients who regained MR3.0 or deeper molecular response by TKIs retrial after TKI cessation failure at the time of screening

4.1.5 Taking TKIs over 12 weeks for the retrial of TKIs after TKI cessation failure

4.1.6 Patients who agree with stopping asciminib and TKIs after maintaining 2year-duration of MR4.5

4.1.7 Adequate end organ function as defined by:

4.1.7.1 Total bilirubin (TBL) < 3 x upper limit of normal (ULN); patients with Gilbert's syndrome may only be included if TBL ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN

4.1.7.2 Creatinine clearance (ClCr) ≥ 30 mL/min as calculated using Cockcroft-Gault formula

4.1.7.3 Serum lipase ≤ 1.5 x ULN. For serum lipase > ULN - ≤ 1.5 x ULN, value must be considered not clinically significant and not associated with risk factors for acute pancreatitis

4.1.8 Patients who can sign the informed consent of their own free will

4.2 Exclusion Criteria

4.2.1 Patients who experienced grade 3 or higher adverse events with TKIs (imatinib, dasatinib, and nilotinib).

4.2.2 Patients who are receiving any other investigational agents.

4.2.3 Patients who currently have uncontrolled infections

4.2.4 Patients who previously received Chimeric antigen receptor T-cell (CAR-T cell) therapy, allogeneic hematopoietic stem cell transplantation (allo-HSCT) or biologic therapy.

4.2.5 Patients with clinically significant cardiovascular disease or gastrointestinal dysfunction

4.2.6 Patients who have a history of thromboembolic episodes within 3

months prior to the study enrollment.

4.2.7 Patients with active hepatitis B or C with uncontrolled disease activity.

4.2.8 Patients who have active malignancies requiring treatment other than CML.

4.2.9 Patients with any severe and/or uncontrolled medical conditions or other conditions that could adversely impact on patients' ability to participate in the study.

4.2.10 Patients with psychiatric illness/social situations that would limit compliance with study requirements.

4.2.11 Pregnant women are excluded from this study Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with asciminib and TKIs, breastfeeding should be discontinued if the mother is treated with asciminib and TKIs

4.3 TFR eligibility

4.3.1 Patients have received asciminib along with one of TKIs over 3 years

4.3.2 MUL duration is over 2 years after TKIs+asciminib.

4.3.3 MUL is confirmed (2 consecutively at least 4 weeks apart).

5. TREATMENT PLAN

5.1 General principle

5.1.1 The patient will be enrolled when achieving MR3.0 or deeper molecular response after re-initiation of TKIs.

5.1.2 The TKIs are the same drug and dose when attempting TKI cessation.

5.1.3 Asciminib will be added to the each TKIs when confirming MR3.0 or deeper molecular response and the duration of re-initiation of TKIs are at least 12 weeks.

5.1.4 The change of concurrent TKI or dosage during this trial is not recommended.

5.2 Agent Administration

5.2.1 Treatment will be administered on an outpatient basis.

5.2.2 Reported adverse events and potential risks are described in Section 3.4 and 10.1.

5.2.3 Appropriate dose modifications are described in Section 5.9.

5.2.4 No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's CML.

5.2.5 The study treatment will be the combination of asciminib and one of concurrent TKIs.

5.3 Asciminib

5.3.1 Asciminib will be started after failure of TKIs cessation trial and subsequent re-achievement of MR3.0 or deeper molecular response.

5.3.2 Asciminib (80mg qd for nilotinib; 60mg qd for imatinib; 80mg qd for dasatinib) will be added to each concurrent TKI.

5.3.3 Patients will be dropped out from this study if patients are intolerant to asciminib 20mg qod or loss of MR3.0 occurs.

5.3.4 Tyrosine-kinase inhibitors allowed for co-treatment: imatinib, dasatinib,

and nilotinib

5.3.5 Asciminib should be added at least 12 weeks after TKI resumed.

5.4 Concurrent TKIs

5.4.1 The principle of choosing TKI for re-initiation after TFR failure is to start the same TKI that patients have took when trying TFR.

5.4.2 Concurrent TKIs will be started at least 12 weeks prior to the start of asciminib.

5.4.3 The dosage each TKI

5.4.3.1 The dosage will be the same as the dose of re-initiation of TKI.

5.4.3.2 The change of concurrent each TKI dose combined with asciminib will be permitted at the discrete of attending physician.

5.4.4 The concurrent TKIs will be one of Imatinib, Nilotinib, or Dasatinib

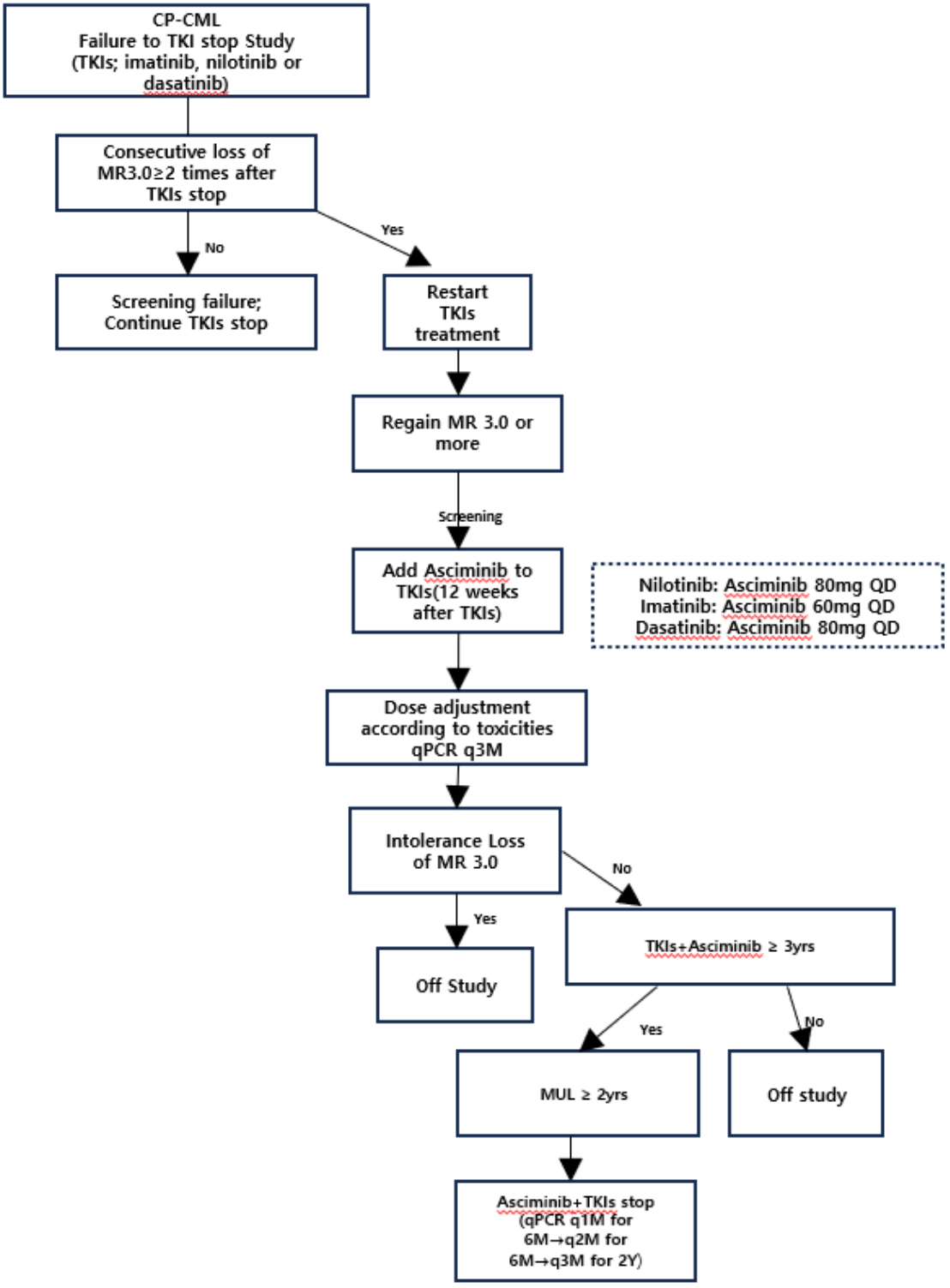
5.4.5 Change of TKIs

5.4.5.1 The change of concurrent TKIs when combined with asciminib is not recommended.

5.4.5.2 The change of concurrent TKIs when combined with asciminib will be permitted at the discrete of attending physician among

imatinib, nilotinib or dasatinib.

5.5 Treatment scheme



5.6 Duration of Therapy

5.6.1 In the absence of treatment delays due to adverse event(s), treatment

may continue until one of the following criteria applies:

5.6.2 Fulfillment of the criteria for cessation of therapy to attempt TFR

5.6.2.1 When a patient achieves molecularly undetectable leukemia (MUL; at least MR4.0 detection limit) and there is no loss of MUL for 2 years, the patient will stop asciminib and TKIs.

5.6.2.2 RQ-PCR will be performed 2 times consecutively, 4 weeks apart for the confirmation of MUL just prior to stopping Asciminib and TKIs.

5.6.2.3 The minimum duration of asciminib and TKIs treatment should be 3 years or longer and the duration of sustained MUL should be 2 years or longer before stopping asciminib and TKIs.

5.6.2.4 If a patient fails achieving MUL after 3 years of TKIs and asciminib combination, the patient will be dropped from the study.

5.6.3 Disease progression: loss of MR3.0 twice a month apart, consecutively or progression to accelerated phase or blast crisis while on asciminib and TKIs

5.6.4 Intercurrent illness that prevents further administration of treatment

5.6.5 Unacceptable adverse event(s)

5.6.6 Patient decides to withdraw from the study

5.6.7 General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

5.6.8 Patient non-compliance

5.6.9 Pregnancy

5.6.9.1 All women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed, or late menstrual period) at any time during study participation.

5.6.10 Termination of the study by sponsor

5.6.11 The drug manufacturer can no longer provide the study agent

5.6.12 The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.7 Reinitiation of CML therapy

5.7.1 TKIs will be restarted, or other treatment without asciminib can be tried when loss of MR3.0 is detected consecutively 2 times after discontinuation of asciminib and TKIs by above condition.

5.8 Duration of Follow-Up

5.8.1 Patients will be followed 30 days after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

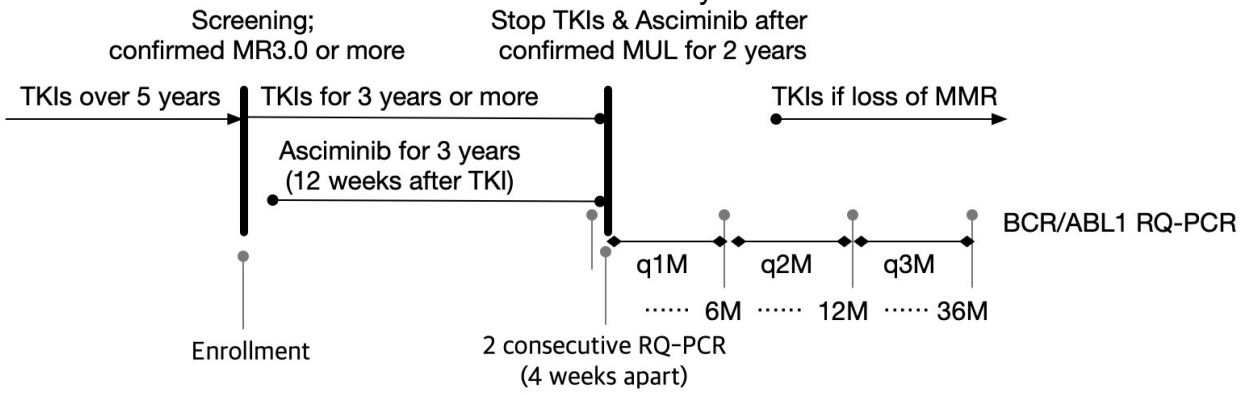
5.9 BCR/ABL1 RQ PCR

5.9.1 While on asciminib and TKIs, BCR/ABL1 RQ PCR will be performed

every 3 months.

5.9.2 After discontinuation of asciminib and TKIs to attempt TFR, RQ PCR should be repeated every month for 6 months, then every 2 months for next 6 months, and then every 3 months for 2 years.

5.9.3 BCR/ABL1 RQ PCR will be analyzed at the central lab.



5.10 Dosing delays/dose modifications

5.10.1 Dose Escalations: For asciminib, dose escalation beyond the standard dose (80mg qd for nilotinib; 60mg qd for imatinib; 80mg qd for dasatinib) is not permitted.

5.10.2 Dose Modifications: For patients who do not tolerate their protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated (depending on the specific event and grade) to allow continuation of study treatment. Dose reduction will be based on worst toxicity demonstrated at the last dose. Asciminib dose reduction below 20 mg qod will not be allowed. The dose can be reduced by 1 dose level in a stepwise manner (dose level 0 to -1; dose level -1 to -2; dose level -2 to -3).

5.10.3 Asciminib dose level

Dose level	Nilotinib	Imatinib	Dasatinib
0	80mg qd	60mg qd	80mg qd
-1	40mg qd	40mg qd	40mg qd
-2	20mg qd	20mg qd	20mg qd
-3	20mg qod	20mg qod	20mg qod

5.10.4 Patients must discontinue treatment with either agent if, after treatment is resumed at a lower dose level, the toxicity recurs at the same or worse severity—except for recurrence of cytopenias.

5.10.5 If a patient requires a dose interruption of >28 days for each nonhematologic toxicity, they must discontinue study treatment.

5.10.6 If a hematologic toxicity (cytopenia grade 3/4) lasts for >42 days without recovery to grade ≤2, despite TKI interruption and adequate management (including hematopoietic growth factors), the patient

must discontinue study treatment.

5.10.7 adjustment of nilotinib capacity by extending the QT interval

ECGs QTc > 480 msec	1. Stop nilotinib to measure serum potassium and magnesium, and correct it to a normal level if it is below the normal lower limit. You need to check which drugs are administered together. 2. QTcF <450 msec, within 20 msec of the target base value, start over with the previous capacity within two weeks. 3. If QTcF falls between 450 and 480 msec after two weeks, the dose is reduced to 400 mg once a day. 4. If the dose reaches QTcF > 480 msec even though 400 mg is reduced to one dose a day, stop the nilotinib. 5. ECG follow-up tests shall be performed within 7 days of capacity adjustment.

5.10.8 Criteria for dose reduction/interruption and reinitiation of asciminib and bosutinib treatment for adverse drug reactions

Dose modifications*	
Worst toxicity CTCAE grade 4.03	**Asciminib**
Hematologic toxicity†	
Neutropenia	
Grade 1 (ANC <LLN-1.5 × 10^9/L) or grade 2 (ANC <1.5-1.0 × 10^9/L)	**Recommendation:** Maintain dose level
Grade 3 (ANC <1.0-0.5 × 10^9/L) or grade 4 (ANC <0.5 × 10^9/L)	**Mandatory:** Hold dose until resolved to grade ≤2 (recheck CBC 2 times/week), then: If resolved in ≤14 days, maintain dose level If resolved in >14 days, reduce dose 1 dose level
Febrile neutropenia (ANC <1.0 × 109/L; fever ≥38.5°C)	**Mandatory:** Hold dose until resolved, then reduce dose by 1 dose level
Thrombocytopenia	
Grade 1 (PLT <LLN-75 × 109/L) or grade 2 (PLT <75-50 × 109/L)	**Recommendation:** Maintain dose level
Grade 3 (PLT <50-25 × 109/L) or grade 4 (PLT <25 × 109/L)	**Mandatory:** Hold dose until resolved to grade ≤2 (recheck CBC 2 times/week), the If resolved in ≤14 days, maintain dose level If resolved in >14 days, reduce dose by 1 dose level
Recurrence of all cytopenias	**Recommendation:** Hold dose until resolved to grade ≤2, then maintain current dose level
Nonhematologic toxicity	
Grade 1	**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 by 1 dose level
Grade 4	**Mandatory:** Permanently discontinue patient from study drug treatment
Renal	
Serum creatinine	
Grade 1 (>ULN-1.5 × ULN)	**Recommendation:** Maintain dose level
Grade 2 (>1.5-3.0 × ULN)	**Recommendation:** Hold dose until resolved to grade ≤1 or baseline, then maintain dose level
Grade 3 (>3.0-6.0 × ULN) or grade 4 (>6.0 × ULN)	**Mandatory:** Permanently discontinue patient from study drug treatment
Hepatic	
Isolated total bilirubin elevation	
>ULN-1.5 × ULN	**Recommendation:** Maintain dose level
>1.5-3.0 × ULN	**Recommendation:** Hold dose. Monitor LFTs‡ weekly, or more frequently if clinically indicated, until resolved to ≤1.5 × ULN: If resolved in ≤14 days, maintain dose level If resolved in >14 days, reduce dose by 1 dose level
>3.0-10.0 × ULN§	**Mandatory:** Hold dose. Monitor LFTs‡ weekly, or more frequently if clinically indicated, until resolved to ≤1.5 × ULN: If resolved in ≤14 days, reduce dose by 1 dose level If resolved in >14 days, discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs‡), or more frequently if clinically indicated, until total bilirubin has resolved to baseline or stabilized over 4 weeks
>10.0 × ULN§	**Mandatory:** Permanently discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs‡), or more frequently if clinically indicated, until total bilirubin has resolved to baseline stabilized over 4 weeks
Isolated AST or ALT elevation	
>ULN-3.0 × ULN	**Recommendation:** Maintain dose level
>3.0-5.0 × ULN	**Recommendation:** Maintain dose level. Repeat LFTs‡ as soon as possible, preferably within 48 to 72 hours from awareness of the abnormal results; if abnormal laboratory values are confirmed, monitor LFTs‡ weekly, or more frequently if clinically indicated, until resolved to ≤3.0 × ULN
>5.0-10.0 × ULN	**Mandatory:** Hold dose. Repeat LFTs‡ as soon as possible, preferably within 48 to 72 hours from awareness of the abnormal results; monitor LFTs‡ weekly, or more frequently if clinically indicated, until resolved to ≤3.0 ULN, then: If resolved in ≤14 days, maintain dose level If resolved in >14 days, reduce dose by 1 dose level
>10.0-20.0 × ULN	**Mandatory:** Hold dose. Repeat LFTs‡ as soon as possible, preferably within 48 to 72 hours from awareness of the abnormal results; monitor LFTs‡ weekly, or more frequently if clinically indicated, until resolved to ≤ baseline and then reduce dose by 1 dose level
>20.0 × ULN	**Mandatory:** Permanent discontinuation
Combined¶ elevations of AST or ALT and total bilirubin	
For patients with normal baseline ALT and AST and	**Mandatory:** Permanently discontinue patient from study drug treatment. Repeat as soon as possible, preferably within 48 hours

total bilirubin value: AST or ALT >3.0 × ULN combined, with total bilirubin >2.0 × ULN without evidence of cholestasis# For patients with elevated baseline AST or ALT or total bilirubin value: AST or ALT >2 × baseline and >3.0 × ULN	from awareness of the abnormal results, then monitor LFTs‡ weekly or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilized over 4 weeks. Additional follow-up evaluations may be needed
Metabolic	
Asymptomatic amylase and/or lipase elevation	
Grade 1 (>ULN-1.5 × ULN) or grade 2 (>1.5-2.0 × ULN)	**Recommendation:** Maintain dose level; measure 2 times/week
Grade 3 (>2.0-5.0 × ULN)	**Mandatory:** Hold dose until resolved to grade ≤1 or baseline, then: If resolved in ≤7 days, reduce dose by 1 dose level If resolved in >7 days, discontinue treatment and obtain appropriate imaging (MRI, CT scan, or ultrasonography)
Grade 4 (>5.0 × ULN)	**Mandatory:** Permanently discontinue patient from study drug treatment. Obtain appropriate imaging (MRI, CT scan, or ultrasonography)
Vascular disorders	
Hypertension	
CTCAE grade 3	**Mandatory:** Hold dose until resolved to grade ≤1, then reduce dose by 1 dose level
CTCAE grade 4	**Mandatory:** Permanently discontinue patient from study drug treatment
Gastrointestinal	
Pancreatitis	
Grade 2 (radiologic findings for pancreatitis as per CTCAE v5.0)	**Mandatory:** If asymptomatic radiologic pancreatitis, hold treatment until recovery of the radiologic findings. If treatment delay is ≤21 days, reduce dose by 1 dose level. If treatment delay >21 days, discontinue treatment and keep monitoring with appropriate imaging (MRI, CT scan, or ultrasonography)
Grade ≥3	**Mandatory:** Permanently discontinue patient from study drug treatment. Obtain appropriate imaging (MRI, CT scan, or ultrasonography)
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, hold dose until resolved to grade ≤1 and then reduce dose by 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
Skin and subcutaneous tissue disorders	
Rash/photosensitivity	
Grade 1	**Recommendation:** Maintain dose level. Consider initiating 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, reduce dose by 1 dose level If resolved in >7 days (despite appropriate skin toxicity therapy), 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, maintain dose level If resolved in >7 days, reduce dose by 1 dose level

6. SUPPORTIVE CARE AND GENERAL CONCOMITANT MEDICATION GUIDELINES

6.1 Supportive care

6.1.1
A characteristic polymyalgia-like syndrome of musculoskeletal and/or joint pain beginning the first weeks or months after TKI discontinuation has been reported in about 20–30% of patients. This phenomenon is likely due to undefined off-target effect(s) of the TKI. In most patients the symptoms are mild and self-limited, but some patients may require temporary treatment with acetaminophen, nonsteroidal anti-inflammatory drugs or in some instances a short course of oral corticosteroids.

6.1.2 Management for cytopenia

6.1.2.1
G-CSF or GM-CSF will be permitted.

6.1.2.2
Transfusion will be permitted.

6.2 General concomitant medication

6.2.1
Except for prohibited and restricted medications detailed below (Section 6.2.3), subjects should continue their normal medications.

6.2.2
Vaccinations During Study: Investigators should also review each subject's vaccination status at periodic intervals to ensure that any needed booster vaccinations are administered at the optimal timing during the study. Please contact the PI for any questions.

6.2.3 Prohibited and restricted medications

6.2.3.1
Generally, there is no prohibited and restricted medications for asciminib.

6.2.3.2
Please refer to package insert for each concurrent TKI for prohibited and restricted medications.

7. STUDY CONDUCT

7.1 Schedule of assessment

7.1.1
The schedule of study assessments/procedures of this study is presented in 7.2 and 7.3. Assessments in the study are intended to be

conducted in clinic; they may be conducted remotely under extenuating circumstances (e.g., COVID-19 restrictions), which will be determined individually for each site and/or subject.

7.1.2 The study schedule has 2 phases

7.1.2.1 Asciminib phase

7.1.2.1.1 Screening: confirming MR3 or deeper molecular response

7.1.2.1.2 Baseline: Start asciminib along with TKIs

7.1.2.1.3 Asciminib: Asciminib for 3 years

7.1.2.2 TFR phase

7.1.2.2.1 Screening: confirming MUL (2 consecutively, 4 weeks apart)

7.1.2.2.2 Baseline: Stop TKIs+Asciminib

7.1.2.2.3 TFR: BCR/ABL1 RQ-PCR

7.1.2.2.4 End of treatment: TFR for 3 years

7.2 Table for study assessments/Procedures for Asciminib phase

Assessment/Procedure	Screening 1 (M-4 to D-1)	Baseline D1	Asciminib				Unscheduled Visit
			Mth 3	Mth 6	Mth 9	(Mth 12-36)	
Written informed consent	X						
Review eligibility criteria	X	X					
Demographics	X						
Medical & medication history	X						
Height, body weight & BMI	X						
Physical examination	X	X	X	X	X	X	X
Vital signs (ECG)	X	X	X	X	X	X	X
Hematology & chemistry	X	X	X	X	X	X	X
BCR/ABL1 RQ-PCR	X	X	X	X	X	X	
Pregnancy test	X	X					
HBV, HCV, HIV, testing	X						
Study drug administration		X	X	X	X	X	
Drug accountability		X	X	X	X	X	X
Record AEs, concomitant medications							

7.3 Table for study assessments/Procedures for TFR phase

Assessment/Procedure	Screening (D-56 to D-1)	Baseline D1	TFR			Unscheduled Visit	EOT
			Mth 1-6	Mth 7-12	Mth 15-36		

Review TFR eligibility criteria	X	X					
Physical examination	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Hematology & chemistry	X	X	X	X	X	X	X
MUL confirmation	X*						
BCR/ABL1 RQ-PCR, monthly			X				
BCR/ABL1 RQ-PCR, bimonthly				X			
BCR/ABL1 RQ-PCR, q 3M					X		
Stop study drug administration		X	X	X	X	X	
TKI stop syndrome survey		X	X	X	X	X	X
Record AEs							
* 2 consecutive MUL confirmations during the screening phase before stopping asciminib & TKIs							

8. STUDY VISITS

8.1 Asciminib phase

8.1.1 Screening

8.1.1.1 Subjects who are received TKIs after TKI cessation failure by the loss of MR3 and re-achieved MR3/deeper response after 12 weeks of re-initiation of TKIs may be screened for this study. Written informed consent must be obtained from each subject before initiation of any screening assessments or procedures. Signing of the informed consent form (ICF) may occur prior to the first on-study visit, which is defined as the visit where site-conducted procedures are first performed.

8.1.1.2 A 4-month window is provided to qualify subjects for the study requiring MR3 or deeper molecular responses. All screening procedures do not need to be completed on the same day, but all screening procedures must be completed, and the results reviewed and approved by the investigator (or designee) prior to asciminib start. An important consideration for the timing of the screening visit is the collection of BCR/ABL1 RQ-PCR results.

8.1.1.3 The following assessments will be performed at the screening visit(s):

8.1.1.3.1 Obtain written informed consent

8.1.1.3.2 Obtain demographic information

8.1.1.3.3 Review of inclusion-exclusion criteria

8.1.1.3.4 Medical history, including collection of CML history and confirmation of adequate molecular result status.

8.1.1.3.5 Review medication history, including prohibited and restricted medications (see Section 6.2.3). All medications administered specifically for CML and

within 30 days prior to screening visit for all other medications will be recorded.

8.1.1.3.6 Full physical examination

8.1.1.3.7 Height, weight, and body mass index (BMI) estimation

8.1.1.3.8 Vital signs (resting blood pressure and pulse rate, and temperature)

8.1.1.3.9 Blood collection for clinical laboratory evaluations (see 7.2): - Blood for hematology, clinical chemistry, Blood for HBV, HCV, HIV testing, Serum pregnancy test for female subjects of childbearing potential or who are postmenopausal for ≤ 2 years at screening, Blood collection for follicle-stimulating hormone (FSH) to confirm postmenopausal state in women who are postmenopausal for ≤ 2 years at screening

8.1.1.3.10 BCR/ABL1 RQ-PCR for confirming MR3 or deeper molecular response

8.1.2 Rescreening/Retesting

8.1.2.1 Rescreening of ineligible subjects, where there is a reasonable expectation that the subject will become eligible, is permitted up to 2 times. If a subject is unable to be qualified in the 4-month window, e.g., due to BCR/ABL1 RQ-PCR or acute illness, the screening window may be extended up to 28 additional days. Retesting of specific assessments without entirely rescreening a subject may be permitted with the approval of the sponsor medical monitor (or designee).

8.1.3 Baseline visit

8.1.3.1 Before any study drug is administered, the following assessments will be completed:

8.1.3.2 Review and update medical history, including CML history, as needed

8.1.3.3 Review and update medication history, including prohibited and restricted medications. Record all medications administered specifically for CML and all other medications since screening visit.

8.1.3.4 Targeted physical examination

8.1.3.5 Body weight

8.1.3.6 Vital signs (resting blood pressure and pulse rate, and temperature)

8.1.3.7 Blood collection for clinical laboratory evaluations (see 7.2): - Blood for hematology, clinical chemistry

8.1.3.8 A negative pregnancy test result must be recorded for the subject to receive study drug.

8.1.3.9 Review of inclusion-exclusion criteria (to confirm study

eligibility)
8.1.3.10 Review/record AEs since screening visit
8.1.4 Asciminib visit
8.1.4.1 All subjects will return to the clinic during Month 1 (± 7 days), Month 2 (± 7 day), Month 3 (± 7 days), and every 3 months (± 14 days) until 3 years of asciminib administration.
8.1.4.2 Subjects do not need to withhold any doses on clinic days or take a dose in the clinic unless the clinic visit falls during the subject's normal time of dosing.
8.1.4.3 The following assessments will be performed at each visit unless otherwise indicated:
8.1.4.3.1 Targeted physical examination
8.1.4.3.2 Body weight
8.1.4.3.3 Vital signs (resting blood pressure and pulse rate, and temperature)
8.1.4.3.4 Blood collection for clinical laboratory evaluations (see 7.2): - Blood for hematology, clinical chemistry and BCR/ABL1 RQ-PCR
8.1.4.3.5 Study drug dispensing and drug accountability review
8.1.4.3.6 Review/record AEs, concomitant medication use, including prohibited and restricted medications.

8.2 TFR Phase
8.2.1 Screening
8.2.1.1 Subjects who are received TKIs+asciminib and the duration of asciminib is over 3 years may be screened for this TFR phase.
8.2.1.2 Subjects who did not achieved MUL will be dropped out from this study when the subjects had received TKIs+asciminib for 3 years.
8.2.1.3 If subjects who have achieved MUL but the duration of MUL is less than 2 years, the subjects can receive TKIs+asciminib further until MUL duration reaches 2 years.
8.2.1.4 A 2-month window is provided to qualify subjects for the study requiring 2 consecutive MUL molecular responses (at least 4 weeks apart). All screening procedures do not need to be completed on the same day, but all screening procedures must be completed, and the results reviewed and approved by the investigator (or designee) prior to stopping TKIs+asciminib. An important consideration for the timing of the screening visit is the collection of BCR/ABL1 RQ-PCR results.
8.2.1.5 The following assessments will be performed at the screening visit(s):
8.2.1.5.1 Review of TFR eligibility criteria
8.2.1.5.2 Full physical examination
8.2.1.5.3 Vital signs (resting blood pressure and pulse rate, and temperature)
8.2.1.5.4 Blood collection for clinical laboratory evaluations (see

7.2): - Blood for hematology, clinical chemistry
8.2.1.5.5 BCR/ABL1 RQ-PCR for confirming 2 consecutive MUL (at least 4 weeks apart)

8.2.2 Rescreening/Retesting
8.2.2.1 Rescreening of ineligible subjects, where there is a reasonable expectation that the subject will become eligible, is permitted up to 2 times. If a subject is unable to be qualified in the 56-day window, e.g., due to BCR/ABL1 RQ-PCR or acute illness, the screening window may be extended up to 28 additional days. Retesting of specific assessments without entirely rescreening a subject may be permitted with the approval of the sponsor medical monitor (or designee).

8.2.3 Baseline visit
8.2.3.1 Before stopping TKIs+asciminib, the following assessments will be completed:
8.2.3.2 Targeted physical examination
8.2.3.3 Vital signs (resting blood pressure and pulse rate, and temperature)
8.2.3.4 Blood collection for clinical laboratory evaluations (see 7.3): Blood for hematology, clinical chemistry
8.2.3.5 Review of TFR eligibility criteria (to confirm TFR eligibility)

8.2.4 TFR visit
8.2.4.1 All subjects will return to the clinic during Month 1 (± 7 days), Month 2 (± 7 day), Month 3 (± 7 days), Month 4 (± 7 days), Month 5 (± 7 days), Month 6 (± 7 days), Month 8 (± 14 days), Month 10 (± 14 days), Month 12 (± 14 days), and every 3 months (± 14 days) until 3 years of TFR follow-up.
8.2.4.2 The following assessments will be performed at each visit unless otherwise indicated:
8.2.4.2.1 Targeted physical examination
8.2.4.2.2 Vital signs (resting blood pressure and pulse rate, and temperature)
8.2.4.2.3 Blood collection for clinical laboratory evaluations (see 7.2): - Blood for hematology, clinical chemistry
8.2.4.2.4 BCR/ABL1 RQ-PCR
8.2.4.2.5 Review/record AEs or TKI stop syndrome

8.3 Unscheduled visit
8.3.1 At the investigator's discretion, an unscheduled visit may be completed at any time during the study prior to the EOS visit. Depending on the reason for the visit, any of the below assessments may be performed as appropriate. If subjects attend an unscheduled visit to assess acute symptoms, all the following assessments should be performed. If applicable, dosing compliance should also be reviewed to ensure that the subject is taking the drug correctly. Any missed doses should be recorded.
8.3.1.1 Review/record AEs, concomitant medication use, including

prohibited and restricted medications
8.3.1.2 Vital signs (resting blood pressure, pulse rate, and temperature)
8.3.1.3 Targeted physical examination
8.3.1.4 Blood collection for clinical laboratory evaluations (see 7.2 and 7.3): - Blood for hematology, clinical
8.3.1.5 Consider testing for acute SARS-CoV-2 infection (the causative agent of COVID-19) in the correct setting.

8.4 End-of-Study visit

8.4.1 All subjects who complete the 3 years TFR phase visit will be asked to return to the clinic approximately 3 weeks (21 ± 3 days) for an EOS visit. In addition, any subject who discontinues study treatment over 3 years and did not achieved MUL will be asked to complete the same procedures at an ET visit approximately 3 months (21 weeks ± 3 days) after the date of the last dose of asciminib. The following assessments will be performed at the EOS/ET visit:
8.4.2 Targeted physical examination
8.4.3 Vital signs (resting blood pressure and pulse rate, and temperature)
8.4.4 Blood collection for clinical laboratory evaluations (see 7.3 and 7.3): - Blood for hematology, clinical chemistry
8.4.5 Drug accountability (if not completed earlier)
8.4.6 Review/record AEs, concomitant medication use
8.4.7 If an AE, including a clinically significant laboratory abnormality, is ongoing at the end of study visit, additional clinic visit(s) or telephone contact(s) may be warranted.

9. STUDY ASSESSMENTS

9.1 Demographic Information, Medical and Medication History

9.1.1 Demographic information, and medical and medication history will be captured for each subject participating in the study at the screening visit. Medical history, medication review, and review of inclusion and exclusion criteria and prohibited and restricted medications will also be updated and rechecked at baseline (Day 1) as outlined in Section 7. A CML history will be taken to document CML clinical characteristics and disease burden, including time since diagnosis and history of TKIs. Medication history will include details of all treatments administered specifically for CML (including any prior tyrosine kinase inhibitor therapies); all other medications will be documented beginning 30 days prior to screening

9.2 Contraception Requirements

9.2.1 The following represents the minimum contraception that should be used by study participants and their partners. Additional contraceptive requirements (e.g., requiring the female partners of male subjects to additionally use highly effective contraception) may be required by local site **practice** and/or the governing ethics committee. It is anticipated that that not all contraceptive methods may be available in all countries/regions, so the list should be modified accordingly. For the purposes of this study, females are considered fertile following

menarche and until becoming postmenopausal, unless permanently sterile (i.e., premenopausal with one of the following: documented hysterectomy, documented bilateral salpingectomy, or documented bilateral oophorectomy). Documentation can come from site personnel's review of the subject's medical records, medical examination, or medical history interview. Female participants must meet at least one of the following requirements:
1. Be a woman of nonchildbearing potential, either postmenopausal (defined as without menses for ≥ 12 months without an alternative medical cause with an FSH > 40 mIU/mL) or had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy. 2. Be a woman of childbearing potential (defined as a female following menarche and prior to becoming post-menopausal who has not had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) who agrees to use a highly effective contraceptive method while enrolled in the study and for a duration of 30 days after last dose of study drug. The following methods are acceptable: - surgical sterilization (i.e., bilateral tubal occlusion or vasectomy of the sole male partner and the vasectomized partner has received medical assessment of surgical success) - intrauterine device (IUD) or intrauterine system (IUS) - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal) - progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable) Women of childbearing potential who declare themselves sexually abstinent or exclusively having female sexual partners do not need to use highly effective contraception. Abstinence in this study is defined as true abstinence when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, she, with her partner, must meet the requirements listed above. Female subjects must abstain from egg donation throughout the study and for a duration of 30 days after last dose of study drug. Male participants must meet at least one of the following requirements: 1. Males with a female partner of childbearing potential (as defined above) must agree to use condoms while enrolled in the study and for at least 90 days after the last dose of study drug unless their partner is using a highly effective contraceptive method as defined above independent of the study. 2. Males who declare themselves sexually abstinent or having exclusively male partners are not required to use contraception. Abstinence in this study is defined as true abstinence when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, the criteria listed above must be met. Male subjects must abstain from sperm donation throughout the study and for a duration of 90 days after last dose of study drug. Methods of contraception, as applicable, for both male and female

participants should be documented in the source documentation.

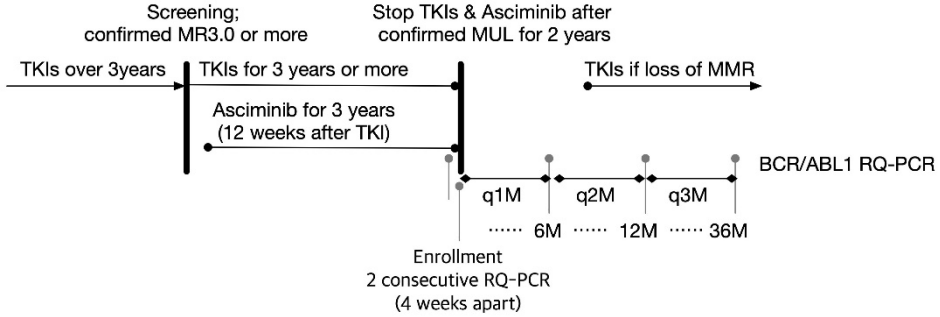
9.3 Efficacy/Effectiveness Assessments

9.3.1 Response monitoring

9.3.1.1 Response monitoring for TFR will start after 3 years of asciminib treatment.

9.3.1.2 Blood samples for BCR-ABL1 quantification by real-time quantitative polymerase chain reaction (RQ-PCR) will be collected at enrollment period (twice, 4 weeks apart) and at months 1, 2, 3, 4, 5, 6, 8, 10, 12 and every 3 months thereafter for more 2 years after cessation of asciminib/TKIs; samples will be analyzed at a central laboratory.

9.3.1.3 Flow for BCR/ABL1 monitoring



9.4 BCR/ABL1 monitoring laboratory

9.4.1 BCR/ABL1 RQ-PCR will be tested in the central laboratory.

9.4.2 All BCR/ABL1 RQ-PCR sample should be transported to the central laboratory.

9.5 Definitions of time-dependent variables

9.5.1 Molecular relapse-free survival: MRFS is defined as the duration of time from the cessation of treatment to time of reoccurrence of BCR/ABL1 transcript at the detectable level by RQ-PCR.

9.5.2 Treatment-free survival: TFS is defined as the duration of time from the cessation of treatment to time of reinitiation of CML therapy resulting from loss of MR3.0 or MMR (major molecular response) by RQ-PCR.

9.5.3 Overall survival: OS is defined as the duration of time from the cessation of treatment till death from any causes.

9.6 Safety assessment

9.6.1 Vital Signs

9.6.1.1 Vital signs comprising blood pressure, pulse rate, and temperature will be recorded at every visit. Measurements of vital signs should be obtained after the subject has rested for at least 5 minutes in a quiet room at a comfortable temperature, with the subject's arm unconstrained by clothing or other material. Blood pressure measurements will be obtained with the appropriate cuff size, with the subject's arm supported at the level of the heart, while the subject is resting in a semi-supine position. It is acceptable to obtain a pulse rate from the blood

pressure or ECG machine.

9.6.2 Body Weight, Height, and Body Mass Index

9.6.2.1 Body weight will be recorded at all visits; height and BMI will be recorded at screening only. For determination of height and body weight, subjects should be clothed with shoes removed

9.6.3 Physical Examination

9.6.3.1 Subjects will undergo a physical examination at every visit. A full physical examination should be performed per normal site practice as part of the screening evaluation (e.g., genitourinary and breast examinations may be omitted when not required by normal site practice). A targeted (i.e., symptom driven) physical examination will be performed at subsequent study visits to assess for any changes from the previous examination, including, at a minimum, evaluation of new or worsening signs or symptoms.

9.6.4 Clinical Chemistry, Hematology, Urinalysis, and Other Laboratory Assessments

9.6.4.1 Blood and urine samples will be obtained per the schedule of assessments as specified in 7.2 for asciminib phase and 7.3 for TFR phase. All BCR/ABL RQ-PCR samples will be collected for the designated central laboratory, which will analyze all samples. However, local laboratories may be used in place of the central laboratory at the sponsor's request (e.g., for logistical reasons) or for analysis of samples collected for assessment of possible AEs (e.g., when emergent safety concerns require expedited turnaround times for safety laboratory assessments). The use of a local laboratory in this manner, and any differences in analyte panels between the central and local laboratories, based on the availability of testing at the local laboratory, will not be considered protocol deviations for the purposes of this protocol. All laboratory tests except for BCR/ABL1 RQ-PCR will be performed using the local laboratory. In the event of delays in transport to the designated central laboratory (e.g., due to COVID-19), the local laboratory should be utilized. Results from the laboratory values should be reviewed as received by the investigator. Evidence of this review should be provided in the source records and may include printing of the laboratory reports with a signature attesting to a review. For out-of-range laboratory findings, the interpretation of clinically significant or not clinically significant should be denoted in the source records. Clinically significant laboratory findings, as assessed by the investigator, should be recorded as AEs as described in the protocol (Section 10)

9.6.5 Menopause and Pregnancy Testing

9.6.5.1 FSH will be measured at screening in women declaring themselves postmenopausal ≤ 2 years to confirm non-

childbearing status if above the reference range. At screening, a serum pregnancy test should also be drawn if a female subject who is postmenopausal ≤ 2 years is found to be of childbearing potential. For all women of childbearing potential, a serum β-human chorionic gonadotropin (β-hCG) test will be performed at screening. Urine pregnancy tests will be assessed at all subsequent visits or as required per normal site practice. A serum pregnancy test should immediately be drawn and sent for analysis for any positive urine pregnancy test. For female participants who meet the criteria for postmenopausal status, an FSH can be measured during the study; pregnancy testing will continue until postmenopausal status by the above definition is met.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

10.1 Adverse Event List(s) for asciminib

Asciminib Safety pool N=356 n (%)		
	All grades	**Grade >=3**
Preferred term	**n (%)**	**n (%)**
Number of subjects with at least one event	340 (95.5)	214 (60.1)
Thrombocytopenia	78 (21.9)	51 (14.3)
Headache	77 (21.6)	7 (2.0)
Fatigue	74 (20.8)	3 (0.8)
Nausea	70 (19.7)	3 (0.8)
Diarrhea	69 (19.4)	2 (0.6)
Arthralgia	66 (18.5)	3 (0.8)
Hypertension	61 (17.1)	31 (8.7)
Lipase increased	60 (16.9)	35 (9.8)
Vomiting	53 (14.9)	8 (2.2)
Neutropenia	52 (14.6)	40 (11.2)
Rash	52 (14.6)	0
Abdominal pain	44 (12.4)	4 (1.1)
Pain in extremity	44 (12.4)	2 (0.6)
Pruritus	43 (12.1)	1 (0.3)
Upper respiratory tract infection	42 (11.8)	1 (0.3)
Anemia	41 (11.5)	17 (4.8)
Back pain	40 (11.2)	4 (1.1)
Cough	39 (11.0)	0
Nasopharyngitis	39 (11.0)	0
Constipation	38 (10.7)	0
Dizziness	38 (10.7)	1 (0.3)
Amylase increased	36 (10.1)	8 (2.2)
Myalgia	33 (9.3)	2 (0.6)
Alanine aminotransferase increased	31 (8.7)	9 (2.5)
Oedema peripheral	30 (8.4)	2 (0.6)
Pyrexia	29 (8.1)	3 (0.8)
Abdominal pain upper	27 (7.6)	0
Dyspnea	27 (7.6)	2 (0.6)
Insomnia	27 (7.6)	2 (0.6)
Aspartate aminotransferase increased	26 (7.3)	5 (1.4)
Hyperuricemia	24 (6.7)	6 (1.7)
Decreased appetite	23 (6.5)	1 (0.3)
Hypertriglyceridemia	23 (6.5)	7 (2.0)
Dyspepsia	22 (6.2)	0
Muscle spasms	22 (6.2)	1 (0.3)

Non-cardiac chest pain	22 (6.2)	3 (0.8)
Anxiety	21 (5.9)	3 (0.8)
Bone pain	20 (5.6)	1 (0.3)
Hyperglycemia	20 (5.6)	6 (1.7)
Oropharyngeal pain	20 (5.6)	0
Blood creatinine increased	19 (5.3)	0
Gamma-glutamyl transferase increased	19 (5.3)	7 (2.0)
Platelet count decreased	19 (5.3)	14 (3.9)
Dry eye	18 (5.1)	0
Dry skin	18 (5.1)	0
Hyperhidrosis	18 (5.1)	0
Hypophosphatasemia	18 (5.1)	5 (1.4)

10.2 Adverse Event Characteristics

10.2.1 Definition of adverse event: an AE is any untoward medical occurrence in a patient administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a medical product whether considered related to the medical product.

10.2.2 CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

10.2.3 A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

10.2.3.1 Results in death,

10.2.3.2 Is life-threatening,

10.2.3.3 Requires inpatient hospitalization or prolongation of existing hospitalization,

10.2.3.4 Results in persistent or significant disability/incapacity,

10.2.3.5 Is a congenital anomaly/birth defect, or

10.2.3.6 Is an important medical event.

10.2.4 Attribution of the AE:

10.2.4.1 Definite – The AE *is clearly related* to the study treatment.

10.2.4.2 Probable – The AE *is likely related* to the study treatment.

10.2.4.3 Possible – The AE *may be related* to the study treatment.

10.2.4.4 Unlikely – The AE *is doubtfully related* to the study treatment.

10.2.4.5 Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 Pregnancy

10.3.1 Although not an adverse event in and of itself, pregnancy as well as its

outcome must be documented. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old.

10.4 Secondary Malignancy

10.4.1 A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation, or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

10.4.2 Three options are available to describe the event:

10.4.2.1 Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])

10.4.2.2 Myelodysplastic syndrome (MDS)

10.4.2.3 Treatment-related secondary malignancy

10.4.3 Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.5 Second Malignancy

10.5.1 A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

10.6 Adverse Event Reporting

10.6.1 All SAEs should be reported by the Treating Physician in the eCRF within 24 hours of awareness.

10.6.2 All SAEs must be reported with Treating Physician's assessment of the event's seriousness, severity, and relatedness to asciminib.

10.6.3 All AEs must be reported in routine study data submissions. Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial.

10.6.4 Collection by sponsor

10.6.4.1 All SAEs

10.6.4.2 All reports of drug exposure during pregnancy

10.6.4.3 All non-serious AEs

10.6.4.4 All reports of misuse and abuse of investigational drug, other medication errors and uses outside of what is foreseen in protocol (irrespective if a clinical event has occurred)

10.6.5 Transfer to Novartis within 15 days of awareness

10.6.5.1 All collected SAEs in subjects exposed to the Novartis investigational drug

10.6.5.2 All collected pregnancy reports in subjects exposed to the Novartis investigational drug

10.6.5.3 All collected reports of abuse and misuse of the Novartis

investigational drug

11. STATISTICAL CONSIDERATIONS

11.1 Study populations

11.1.1 Screen failures

11.1.1.1 Subjects who give informed written consent but are not eligible to study treatment and are noted as screen failures in the CRF are considered screen failures. Reasons for screen failure will be summarized using this population.

11.1.2 Intent-to-treat population

11.1.2.1 The intent-to-treat (ITT) population is defined as all enrolled subjects, regardless of whether study treatment was administered. This population will be the primary population for efficacy analyses.

11.1.3 Safety population

11.1.3.1 The safety population is defined as all subjects who receive at least 1 dose of study drug. This population will be used for all analyses of accountability, demographics, and safety. Data will be analyzed according to the actual treatment received at first dose for all subjects.

11.1.4 Per protocol population

11.1.4.1 The per-protocol (PP) population is defined as all subjects who did not violate key protocol inclusion or exclusion criteria, received the study drug, and did not have any protocol deviations or violations that would affect analysis. This population will be used for a sensitivity analysis of the primary efficacy analysis.

11.1.5 Completers population

11.1.5.1 The subset of subjects in the ITT population who complete the study. This population will be used for a sensitivity analysis of the primary efficacy analysis.

11.2 General consideration for data analysis

11.2.1 In general, descriptive summaries will include n, mean, standard deviation, median, minimum, and maximum for continuous variables and n and percent for categorical variables. Summaries will be presented by treatment and study visit. All individual subject data will be listed as measured.

11.3 Subject Demographic and Disposition Data

11.3.1 Demographic data and baseline characteristics including age, gender, race or ethnicity, height, body weight, BMI, and CML history will be summarized by treatment and overall. The following baseline measures will be summarized using descriptive statistics: dose, type, and duration of TKIs. Subject disposition will be presented by treatment and overall. The number of subjects who completed the study and those that discontinued from the study will be provided. The

reasons for early discontinuation will be presented. A tabulation of the number of subjects exposed to study drug and duration of exposure will also be presented for each treatment and overall. Treatment adherence, dose interruptions, and reason for dose interruptions will be provided as summaries or listed as appropriate.

11.4 Analysis of Efficacy Variables

11.4.1 The efficacy analyses will be based on the ITT population. The analyses of the PP population and completers population will be used to support the primary efficacy analyses.

11.5 Sample Size Calculation

11.5.1 The sample size is calculated based on Simon's exact single-stage phase II design assuming that P0=0.25; P1=0.4; α-error=0.05 (one-sided); β-error=0.2.

11.5.2 The final number of patients required will be 69 with consideration of 10% of drop-out rate.

11.6 Statistical analysis

11.6.1 Molecular response

	MMR	MR^4	$MR^{4.5}$	MR^5
Minimum sum of reference gene transcripts	10,000 ABL1[a] 24,000 GUSB[a]	10,000 ABL1 24,000 GUSB	32,000 ABL1 77,000 GUSB	100,000 ABL1 240,000 GUSB
BCR-ABL1 transcript level on the IS[b]	≤0.1%	≤0.01%	≤0.0032%	≤0.001%
[a]Minimal sensitivity for accurate quantification. [b]International Scale, IS.				

11.6.2 The cumulative incidence of MR3.0 or less continuously up to one year of TKI and TKI suspension is defined as the cumulative incidence of MR3.0 maintained for one year from the first day of suspension of administration of Aciminib and TKI.

11.6.3 The rate of re-achievement of MR4.5 for adding an assiminib to a TKI is defined as the rate at which MR4.5 is re-acquired after adding an assiminib.

11.6.4 The time to MR3.0/4.0/4.5 disappearance is calculated from the first day of discontinuation of administration of Aciminib and TKIs, respectively, when MR3.0/4.0/4.5 disappearance is confirmed.

11.6.5 The molecular relapse free survival (MRFS) will be calculated from day 1 of stopping asciminib and TKIs till reoccurrence of BCR/ABL1 RQ PCR.

11.6.6 The treatment-free survival (TFS) will be calculated from day 1 of stopping asciminib and TKIs till loss of MR3.0 and subsequent restart of CML treatment.

11.6.7 Overall survival will be calculated from day 1 of stopping asciminib and TKIs till death due to any causes.

11.6.8 The survival curves will be constructed using the Kaplan-Meier method.

11.6.9 The univariate analysis will be performed using Pearson's chi-square,

Fisher's exact test, or the log-rank test for survival curves.

12. STUDY ADMINISTRATION

12.1 Study Monitoring

12.1.1 During study conduct, clinical research organization (CRO) or its designee will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practice (GCP) are being followed. The monitor(s) will review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow the representative(s) of CRO or its designee direct access to source documents to perform this verification.

12.1.2 It is important that the investigator(s) and relevant personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.1.3 During the study, a representative(s) from CRO or its designee will have regular contacts with the investigational site personnel for the following:

12.1.3.1 Provide information and support to the investigator(s)

12.1.3.2 Confirm that facilities remain acceptable

12.1.3.3 Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs, and that investigational product accountability checks are being performed

12.1.3.4 Perform source data verification. This includes a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).

12.1.3.5 Record and report any protocol deviations not previously sent to CRO or its designee

12.1.3.6 Confirm AEs and SAEs have been properly documented on the CRFs and confirm any SAEs have been forwarded to BioCryst or its designee and those SAEs that met criteria for reporting have been forwarded to the ethics committee

12.1.4 The representative(s) of CRO or its designee will be available between visits if the investigator(s) or other staff needs information or advice.

12.2 Audits and Inspections

12.2.1 Authorized representatives of CRO or its designee, Korean Food and Drug Administration (KFDA) and other regulatory authorities, and/or ethics committee may visit the site to perform audits or inspections, including source data verification.

12.2.2 The purpose of CRO audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, standard operating procedures, ICH GCP guidelines, and any

applicable regulatory requirements.

12.2.3 The investigator should contact CRO immediately if contacted by a regulatory agency about an inspection.

12.2.4 It is important that the investigator and relevant personnel are available during the possible audits or inspections and that sufficient time is devoted to the process.

12.3 Institutional review board (IRB)

12.3.1 The investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB committee, including the ICF and any recruitment materials, must be maintained by the investigator and made available for inspection.

12.4 Serious Breaches of GCP

12.4.1 It is the responsibility of the PI to notify the competent authority of any serious breach of GCP that is likely to affect, to a significant degree, the safety or mental integrity of the subjects of the study or the scientific value of the study.

12.4.2 All serious breaches will be notified to the relevant competent authority in accordance with locally applicable regulations.

12.4.3 The reporting to the PI will be performed by the party who suspects the serious breach.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Quality control

13.1.1 During study conduct, CRO or its designee will conduct periodic monitoring visits to ensure that the protocol and GCP are being followed as described in Section 12.1.

13.2 Quality assurance

13.2.1 To ensure compliance with GCP and all applicable regulatory requirements, CRO or its designee may conduct a quality assurance audit. Please see Section 12.2 for more details regarding the audit process. The investigator agrees to allow the auditors to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

14. IRB

14.1 IRB Review

14.1.1 The final study protocol and the final version of the ICF must be approved or given a favorable opinion in writing by IRB committee, as appropriate.

14.1.2 The investigator must submit written approval from the IRB committee to CRO before he or she can enroll any subject into the study. The IRB committee will be informed of any amendment to the protocol in accordance with local requirements. In addition, the IRB committee must approve any advertising used to recruit subjects for the study.

14.1.3 The protocol must be re-approved by the IRB committee upon receipt of amendments and annually, as local regulations require. The IRB committee will be provided with reports of any reportable serious

adverse drug reactions from any other study conducted with the investigational product, in accordance with local regulations.

14.1.4 CRO will provide this information to the investigator. Progress reports and notifications of serious adverse drug reactions will be provided to the ethics committee according to local regulations and guidelines.

14.2 Ethical Conduct of the Study

14.2.1 The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP, applicable regulatory requirements.

14.3 Written Informed Consent

14.3.1 In accordance with applicable national or local law, and current institutional practice, written informed consent to participate in the study will be obtained from each subject prior to conducting any study-related assessments/procedures.

14.3.2 A signed ICF must be obtained from each subject prior to performing any study-related procedures. Each subject should be given both oral and written information describing the nature, purpose, and duration of the study. Subjects will be informed that they are free not to participate in the study and that they may withdraw consent to participate at any time. They will be told that refusal to participate in the study will not prejudice future treatment. They will also be told that their records may be examined by competent authorities and authorized persons, but that personal information will be treated as strictly confidential and will not be publicly available. The informed consent process should take place under conditions where the subject has adequate time to consider the risks and benefits associated with participation in the study.

14.3.3 Subjects must be given the opportunity to ask questions. Subjects will not be screened or treated until the subject has signed an approved ICF written in a language in which the subject is fluent.

14.3.4 The ICF that is used must be approved by the governing IRB committee. The ICF should be in accordance with the current revision of the Declaration of Helsinki, current ICH and GCP guidelines. The investigator shall maintain a log of all subjects for whom consent was signed and indicate if the subject was enrolled into the study or reason for non-enrollment.

14.3.5 The subject should receive a signed and dated copy of the ICF. The original signed ICF should be retained in the study files.

15. DATA HANDLING AND RECORDKEEPING

15.1 Inspection of Records

15.1.1 CRO or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts, and study source documents, and other

records relative to study conduct.

15.2 Retention of Records

15.2.1 To enable evaluations and/or audits from regulatory authorities or CRO, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eCRFs, and medical/hospital records), all original signed ICFs, all eCRFs, and detailed records of study drug accountability and treatment disposition. The records should be retained by the investigator according to local regulations or as specified in the Clinical Study Agreement, whichever is longer.

15.2.2 If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator, another institution, or to BioCryst. The investigator must obtain CRO's written permission before disposing of any records and must notify CRO before transferring any records to another facility. All correspondence related to records retention, destruction, or transfer of study documents, should be sent directly to CRO study personnel.

15.3 Confidentiality of Information and Data

15.3.1 PI affirms the subject's right to protection against invasion of privacy and secure maintenance of the confidential nature of his/her personal data. Only a subject identification number and subject identifiers permitted by local regulation will identify subject data retrieved by CRO. However, in compliance with Korean regulations, CRO requires the investigator to permit CRO's representatives and, when necessary, representatives of the KFDA or other regulatory authorities to review and/or copy any medical records relevant to the study, maintaining pseudo-anonymity.

15.3.2 All parties will abide by all applicable laws and regulations regarding subject privacy and confidentiality, where this rule is applicable. A valid authorization and consent must meet the specifications of the applicable laws and regulations relating to such personal data and health information.

15.3.3 It is the responsibility of the investigator and institution to obtain such waiver/authorization in writing from the appropriate individual.

16. PUBLICATION POLICY

16.1 General policy

16.1.1 All data generated from this study are the property of PI and shall be held in strict confidence along with all information furnished by PI.

16.1.2 Except as provided through written agreement between PI, independent analysis and/or publication of these data by the investigator or any member of his/her staff is not permitted without prior written consent of PI.

16.1.3 Such consent will not be withheld unreasonably.

16.1.4 PI is in agreement with the principle of full disclosure of clinical study

results.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. 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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

Formulas to estimate renal function using serum creatinine provided by the NCI's Investigational Drug Steering Committee (IDSC) Pharmacological Task Force in table below.

1. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey *et al.*, 2009).

Formulae:

Race and Sex	Serum Creatinine (SCr), *µmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$

SCr in mg/dL; Output is in mL/min/1.73 m^2 and needs no further conversions.

2. eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al.*, 2006).

$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if black)
Output is in mL/min/1.73 m^2 and needs no further conversions.

3. Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg\ /\ dL)} \{\times 0.85\ for\ female\ patients\}$$

Followed by conversion to a value normalized to 1.73 m^2 with the patient's body surface area (BSA).

References

1. Levey, A.S., L.A. Stevens, C.H. Schmid, *et al*. (2009). A new equation to

estimate glomerular filtration rate. *Ann Inter Med*. 150:604-612.
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3. Cockcroft, D.W. and M.H. Gault. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*. 16:31-41.