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REVIEW ARTICLE

Clinical Pharmacology of Asciminib: A Review

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Abstract

Asciminib is a first-in-class allosteric inhibitor of the kinase activity of BCR::ABL1, specifically targeting the ABL myristoyl pocket (STAMP). This review focuses on the pharmacokinetic (PK) and pharmacodynamic data of asciminib, which is approved at a total daily dose of 80 mg for the treatment of adult patients with chronic myeloid leukemia in chronic phase who are either resistant or intolerant to ≥ 2 tyrosine kinase inhibitors or those harboring the T315I mutation (at a dose of 200 mg twice daily). Asciminib is predicted to be almost completely absorbed from the gut, with an absolute bioavailability (F) of approximately 73%. It should be administered in a fasted state, as food (particularly high-fat meals) reduces exposure. Asciminib displays a slightly greater than dose-proportional increase in exposure, with no time-dependent changes in PK observed following repeated dosing. This drug shows low clearance (6.31 L/h), with a moderate volume of distribution (111 L) and high human plasma protein binding (97.3%). The apparent terminal elimination half-life ($t_{1/2}$) across studies was estimated to be between 7 and 15 h. The PK of asciminib is not substantially affected by body weight, age, gender, race, or renal or hepatic impairment. Asciminib is primarily metabolized via CYP3A4-mediated oxidation (36.0%) and UGT2B7- and UGT2B17-mediated glucuronidation (13.3% and 7.8%, respectively); biliary secretion via breast cancer resistance protein contributes to about 31.1% to total systemic clearance, which is mainly through hepatic metabolism and biliary secretion through the fecal pathway, with renal excretion playing a minor role. The potential for PK drug interaction for asciminib both as a victim and a perpetrator has been summarized here based on clinical and predicted drug–drug interaction studies. Robust exposure–response models characterized asciminib exposure–efficacy and exposure–safety relationships. In patients without the T315I mutation, the exposure–efficacy analysis of the time course of *BCR::ABL1*^{IS} percentages highlighted the existence of a slightly positive, albeit not clinically significant, relationship. Higher exposure was required for efficacy in patients harboring the T315I mutation compared with those who did not. The exposure–safety relationship analysis showed no apparent association between exposure and adverse events of interest over the broad range of exposure or dose levels investigated. Asciminib has also been shown to have no clinically relevant effect on cardiac repolarization. Here, we review the clinical pharmacology data available to date for asciminib that supported its clinical development program and regulatory applications.

1 Introduction

Incorrect repair of a DNA double-strand break in a hematopoietic stem cell that results in a reciprocal chromosome translocation (t9,22), creating a shortened version of chromosome 22 (termed Philadelphia chromosome, Ph), and formation of the *BCR::ABL1* oncogene are the initiating events that lead to chronic myeloid leukemia (CML) [1]. Following the registration of imatinib (Gleevec®) in 2001, drugs that inhibit the Abelson (ABL1) tyrosine kinase activity of the BCR::ABL1 oncoprotein became established as efficacious therapies for CML [2]. The orthosteric ATP-binding site of protein kinases is highly conserved across the human

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Key Points

Asciminib has a unique mechanism of action (working by STAMP) and has shown very good efficacy in patients with chronic-phase CML even in the presence of *BCR::ABL1* mutations.

Asciminib has a predictable PK profile and a manageable drug-drug interaction risk. No clinically significant impact of body weight, age, sex, race, and hepatic or renal impairment on the pharmacokinetics of asciminib has been observed and no dose adjustments are needed.

The safety profile of asciminib is similar across all evaluated doses, showing good tolerability.

kinome, which comprises of > 500 members that mediate intracellular signal transduction in all tissues [3]. The first- (imatinib), second- (dasatinib, nilotinib, and bosutinib), and third-generation (ponatinib and olverembatinib) tyrosine kinase inhibitors (TKIs) currently approved for the treatment of CML target the orthosteric site of ABL1, either in a type-I or type-II binding mode, to engage the catalytically active or inactive conformation of the SH1 domain, respectively. Because they indiscriminately target this pocket, these drugs are not highly selective for the ABL kinases but inhibit multiple protein kinases [2], thereby eliciting off-target side-effects; these may result in adverse events that can lead to drug intolerance [4].

Asciminib was designed and developed to provide an improved treatment for CML, having a unique mechanism of action such that it maintains activity against forms of BCR::ABL1 carrying mutations known to confer resistance to ATP-binding site-targeting TKIs [5–7]. Asciminib binds to a specific allosteric site on the myristoyl-binding pocket of BCR::ABL1, rather than to the ATP-binding site targeted by other TKIs. By binding to this unique site, asciminib prevents the activation of the ABL kinase and subsequent downstream signaling: asciminib thus works by specifically targeting the ABL myristoyl pocket (STAMP). Asciminib (Scemblix®) is widely approved for the treatment of adult patients with CML in chronic phase (CP) who are either resistant or intolerant to ≥ 2 prior TKIs or those who harbor the gatekeeper *BCR::ABL1* Thr15Ile (T315I) mutation, which confers resistance to all approved ATP-binding TKIs except ponatinib and olverembatinib [7, 8].

The pharmacokinetics (PK) and absorption, distribution, metabolism, and excretion (ADME) properties of asciminib have been studied extensively in the preclinical setting using in vitro experiments and in vivo animal models, as well as in healthy volunteers and in patients with CML or Philadelphia chromosome-positive (Ph^+) acute lymphoblastic leukemia (ALL). The pharmacodynamics (PD) of asciminib have also been comprehensively characterized in patients with CML [9, 10]. The most important PD marker in CML is the percentage $BCR::ABL1^{IS}$ transcript level of a standardized reference baseline value, which is monitored to assess molecular response (MR) rate; a 3-log reduction in the *BCR::ABL1* mRNA transcript expression, designated as a major molecular response (MMR), is a primary clinical endpoint and treatment goal of TKI therapy [9, 10]. Integrated analysis of PK, efficacy and safety data, including PK/PD modeling of the relationship between asciminib concentration and $BCR::ABL1^{IS}$ levels, has been the cornerstone to establish the dose and dosing regimen for asciminib in patients with CML [6, 11, 12].

Asciminib has been evaluated over a wide dose range in the first-in-human study in patients with CML (10–200 mg twice daily [b.i.d.] and 80 to 200 mg once daily [q.d.]) and shown to be both efficacious and safe, including in patients harboring the T315I mutation [11]. Based upon the results of the Phase 1, first-in-human [NCT02081378] and phase 3 ASCEMBL [NCT03106779] studies [5, 6, 11], the recommended dose of asciminib was 40 mg b.i.d. for patients with CML not harboring the T315I mutation (later updated to a total daily dose of 80 mg in most countries including the USA) and 200 mg b.i.d. for patients with the mutation.

In the phase 3 study ASCEMBL, an asciminib dose of 40 mg b.i.d. was evaluated against bosutinib at 500 mg q.d. in 233 patients with CML who had failed or were intolerant to ≥ 2 prior TKIs. The results showed significantly superior MMR rates for asciminib at week 24 (25.5% versus 13.2% for bosutinib) and week 96 (37.6% versus 15.8%) [5, 6]. Based on extensive PK/PD relationship analyses and physiologically-based PK (PBPK) simulations, the FDA approved the asciminib 40 mg b.i.d. dose tested in ASCEMBL, as well as the more patient-centric dosing regimen of 80 mg q.d. [13, 14]. In addition, based upon results from the phase 1 study asciminib was approved for adults harboring the T315I mutation at a dose of 200 mg b.i.d. [11].

In this article we review the preclinical pharmacology of this drug and its PK and PD properties in humans.

2 Pharmacology

2.1 Asciminib In Vitro Studies

In an effort to find an improved drug, a high-throughput differential cytotoxicity screening was performed using BCR::ABL1-transformed and parental mouse hematopoietic 32D cells [15]. Whereas parental 32D cells require interleukin-3 (IL-3) for proliferation, the expression of BCR::ABL1 renders these cells growth factor-independent. This study

identified a prototype cytotoxic agent, GNF-2, which was selective for BCR::ABL1-dependent cells.

The ABL proteins (ABL1 and ABL2) are post-translationally modified to carry an N-terminal myristoylated glycine residue, which is involved in the autoregulation of their kinase activity [16, 17]. By binding intramolecularly to a myristate-binding pocket in the C-lobe of the ABL1 SH1 domain, the myristoyl group induces an assembled inactive state in which the SH3 and SH2 domains dock against the catalytic SH1 domain to reduce its conformational flexibility. This inactive state conformation is different from the typical kinase inactive "DFG-out" conformation, where the Asp-Phe-Gly (DFG) motif located at the N-terminus of the activation loop is flipped "out" relative to its conformation in the active state; the Asp residue faces away from the ATP-binding site and prevents kinase activation. Type-II inhibitors directed at the ATP-binding site can bind directly to the DFG-out loop conformation and stabilize the inactive conformation of the kinase domain [18, 19]. This autoinhibitory mechanism in ABL1 is lost in the BCR::ABL1 fusion protein because the BCR fragment replaces the N-terminal region of ABL1 that contains the myristoylation site, thus leading to constitutive activation of tyrosine kinase activity [16].

Studies showed that the selectivity of GNF-2 was due to binding to the myristate-binding site [20]. Medicinal chemistry optimization of GNF-2 for biochemical and cellular potency as well as drug-like properties, guided by nuclear magnetic resonance studies and X-ray crystallography, culminated in the discovery of asciminib [19, 21]. Successful development of asciminib led to its approval by the FDA in 2021, as the first CML therapy to inhibit BCR::ABL1 by specifically targeting the ABL myristoyl pocket (STAMP).

In biochemical assays, asciminib inhibited tyrosine phosphorylation catalyzed by the $ABL1^{64\text{-}515}$ construct with mean preclinical 50% inhibitory concentration (IC_{50}) values of 2.6 nM (assessed by radiometric filter binding) and 0.5 nM (assessed by caliper electrophoresis mobility shift) [19, 22]. Because of the allosteric STAMP mechanism of action, asciminib only inhibits those kinases whose activity is regulated by the myristate binding site, namely the ABL1 and ABL2 kinases. This assertion is substantiated by biochemical studies, where asciminib did not inhibit the catalytic activity of 335 wild-type kinases [22], as well as by a Cancer Cell Line Encyclopedia (CCLE) study in which asciminib was evaluated for effects on the viability of 495 diverse human cancer cell lines and only substantially inhibited the proliferation of those dependent upon BCR::ABL1 (IC_{50} <25 μM) [7].

Protein *N*-myristoylation, mediated by *N*-myristoyl transferases which are expressed in most human tissues with reports of > 1000 substrates, is an important process whereby attachment of a myristoyl group is vital for the function of many proteins [23, 24]. The myristoyl groups function by interacting with either lipids or binding sites on proteins. However, structural analysis of myristate-bound human proteins showed that the myristate-binding pocket on ABL1 is substantially different to that of other kinases, and thus, asciminib is unlikely to bind to these proteins [7]. Although it has been suggested that cyclin-dependent kinase 2 (CDK2) has a binding site that could be engaged by asciminib [25], this appears to be speculative and is unlikely, since the viability of cell lines dependent upon CDK2 was not substantially sensitive to the effects of asciminib (e.g., breast HCC1569, IC_{50} 14.9 μM; gastric MKN1, IC_{50} 25 μM; ovarian Kuramochi, IC_{50} 27 μM) [7].

The absence of substantial off-target activity is further supported by studies assessing the effects of asciminib against G-protein coupled receptors, transporters, ion channels, nuclear receptors, and enzymes (for details of the panel and the methods see ref. [26]). Inhibitory effects of > 50% at ≤ 10 μM were only observed against 5-lipoxygenase (IC_{50} 3.3 μM), VMAT-2 vesicular monoamine transporter (IC_{50} 3.5 μM), and 5HT2B serotonin receptor in antagonist mode (IC_{50} 5.1 μM) [22]. Inhibitory effects were observed at concentrations > 10 μM, on the type-3 adenosine receptor Ad3 (IC_{50} 21 μM), on the 5HT2A receptor (IC_{50} 18 μM), and on the human norepinephrine transporter (NET) (IC_{50} 22 μM). With respect to the human ether-a-go-go-related gene (hERG) channel, the IC_{50} value was > 30 μM in the [^{3}H] dofetilide binding assay (performed with HEK293 cells) and 11.4 μM in the patch clamp assay [27]. Consequently, given the low levels of inhibition, it can be concluded that none of these targets are likely to lead to profound physiological off-target effects with asciminib when administered at doses ≤ 200 mg b.i.d.

An important feature of asciminib is that, because of its STAMP mechanism of action, it maintains activity against mutant forms of *BCR::ABL1* that confer resistance toward ATP-competitive drugs. Thus, it binds to the myristate pocket of the native form of ABL1 (residues 64-545) with an affinity (K_d) of 0.5 nM, similar to that for the T315I mutant form of ABL1 ($ABL1^{T315I}$), in which the Thr315 residue is mutated to Ile (K_d 0.5–0.8 nM) [7]. However, because various mutations affect the conformational dynamics of ABL kinases and the overall stability of the inactive conformation regulated by the myristate binding site, asciminib does not inhibit the kinase activity of ABL variants harboring these mutations with the same potency. Thus, it inhibits the proliferation of murine Ba/F3 hematopoietic cells transformed to be dependent upon BCR::ABL1 with a mean IC_{50} value of 0.61 nM, compared with a value of 7.64 nM for cells dependent upon $BCR::ABL1^{T315I}$ [7]. Hence, higher doses are required for patients harboring the drug resistance-driving T315I mutation. Cells can also acquire *BCR::ABL1* mutations that reduce or abrogate their sensitivity to

asciminib, such as Ala337Val (A337V), and these cells are not resistant to ATP-competitive drugs; in such cases drug combinations might be of value.[7, 28]

2.2 Asciminib In Vivo Studies

Preliminary PK studies with asciminib free-base in mice indicate that the drug was fairly rapidly absorbed following administration by oral gavage (time to maximum plasma concentration [t_{max}], 2 h; bioavailability [F], 21%) and displayed a plasma half-life ($t_{1/2}$) of 1.1 h when administered intravenously [19]. The effects of orally administered asciminib on the growth of subcutaneous leukemic cell xenografts were then studied in immunodeficient mice [21, 22]. Following administration of a single 30 mg/kg dose (delivering maximum plasma concentration [C_{max}] 7.13 ± 0.47 µM and area under the plasma concentration-time curve [$AUC_{0–20h}$] 23.5 µM × h), asciminib suppressed tumor levels of phosphorylated STAT5 (pSTAT5, a downstream biomarker of BCR::ABL1 inhibition) by 80% at the 16 h timepoint. This PK–PD relationship is consistent with neither of the major circulating metabolites of asciminib, M29.5 and M44 [29] contributing to the in vivo efficacy, which is in accordance with their substantially weaker ABL1 kinase inhibition potency [30]. In an initial efficacy study, when administered once daily to mice bearing tumors with an average volume of 151 mm^3 (range 139−176 mm^3, 7 days post-cell implantation), asciminib dose-dependently inhibited tumor growth, with tumor volume regressing by 33% after 11 days of treatment with a dose of 30 mg/kg [22].

Asciminib (30 mg/kg) and nilotinib (75 mg/kg), either as single agents or in combination, were compared in a longer term study, following twice-daily administration to mice bearing tumors with an average volume of 189 mm^3 (range 135−337 mm^3, 9 days post-KCL22 cell implantation) [21, 22]. On day 29, when vehicle-treated animals were euthanized upon reaching tumor size end points, asciminib- and nilotinib-treated animals showed 56% and 82% decreases in tumor volume, respectively. However, upon further treatment with asciminib or nilotinib as single agents, tumors relapsed with a median of 38 and 52 days, respectively, when resistant tumors reached the end point of 500 mm^3. In asciminib-relapsed tumors, the A337V mutation predominated, although the Pro223Ser (P223S) mutation was also found. In mice treated with nilotinib, only the T315I mutation was detected in relapsing tumors. However, daily combination treatment with asciminib and nilotinib resulted in complete and durable regression of KCL22 tumor xenografts, and after treatment was suspended (day 74), all animals remained tumor-free [21].

These efficacy studies employed KCL22 cells, derived from a patient undergoing blast crisis, which are genetically unstable and can be expected to behave quite differently to CML-CP cells. This is consistent with asciminib responses being quite durable in patients with CML-CP [5, 6]. Mouse studies showed that upon switching treatments, nilotinib was initially efficacious in the presence of mutations conferring resistance to asciminib, and asciminib was initially efficacious in the presence of mutations conferring resistance to nilotinib; despite this, in both cases the tumors eventually relapsed after initially regressing [21]. Importantly, a combination of the two drugs prevented the emergence of drug-resistant tumors. However, as with all cancers, tumors can develop drug resistance leading to relapse by additional mechanisms other than mutations in the target protein [31]. One such mechanism is the upregulation of transport proteins (e.g., ABCB1 and ABCG2) that can efflux the drug from cells, which has been observed in leukemic cells treated with asciminib [32, 33]. Such resistance could be combatted by either saturating the activity of the transporter by increasing the administered dose of substrate drug (in this case asciminib) or by adding a BCR::ABL1 inhibitor, which is not a substrate for the transporter protein, such as a suitable ATP-competitive TKI.

With respect to combinations of asciminib with ATP-competitive TKIs, there is some controversy in the literature. Manley and colleagues have presented biophysical and cellular data that are consistent with asciminib being able to bind BCR::ABL1 concomitantly with ATP-competitive drugs to form a ternary complex, although in doing so, the combination does not lead to synergy [34]. However, Soellner and co-workers interpret their findings in cell-based studies as showing that combinations of asciminib with ATP-competitive drugs are antagonistic, and that the biophysical data published by Manley and co-workers is not physiologically relevant [35, 36]. Although the controversy is not completely resolved, studies from Friedman and colleagues have shown that asciminib enhances the anti-proliferative effects of nilotinib, one such ATP-competitive TKI, in CML cell lines [37]. Ongoing studies with asciminib in combination are described in the Sect. 6.1.2.

3 Product Description

3.1 Pharmacokinetic Assay

The plasma concentration of asciminib can be determined by a validated liquid chromatography–tandem mass spectrometric (LC–MS/MS) method with a dynamic range of 1.00–5000 ng/mL [38, 39]. Briefly, aliquots of 25 µL plasma are extracted with 200 µL of protein precipitant, acetonitrile; deuterated (D_5) asciminib is then added as the internal standard. After vortex-mixing, filtration,

and evaporation, 10 µL of sample extract reconstituted in 80% aqueous acetonitrile (v/v) with 0.1% formic acid are injected onto the LC–MS/MS system for analysis [38]. This system consists of Shimadzu LC-20AD pumps, a CBM-20A controller, a CTO-20A column oven, a SIL-30 ACMP autosampler, a DGU-20A5 online degasser (Shimadzu, Columbia, MD) and an API4000 tandem mass spectrometer (Sciex, Concord, ON, Canada). An optimal chromatographic separation of asciminib and internal standard is achieved with gradient elution on a MAC-MOD ACE 5 C8 column (50 mm × 2.1 mm, 5 µm). Mobile phases contain water with 0.1% formic acid (mobile phase A) and acetonitrile with 0.1% formic acid (mobile phase B). The following MS transitions are monitored: *m/z* 450 → 239 for asciminib and m/z 455 → 244 for the internal standard [38, 39].

The method was validated following health authority guidance. The accuracy and precision for the lower limits of quantification (LLOQs, 1.00 ng/ml) were within ± 5.0% bias and ≤ 8.0% coefficient of variation (CV), respectively. From the intraday and interday evaluations, the precision of the other quality control samples ranged from 2.8% to 6.2% CV and the accuracy (percent bias) from −2.0% to 5.3%, respectively. A linear $1/x^2$ weighted regression model provided the best fit for asciminib (1.00−5000 ng/mL) in human plasma [38, 39].

Asciminib was demonstrated to be stable in human plasma for at least 24 h at room temperature, after 5 freeze–thaw cycles with storage temperature at ≤ −15 °C and ≤ −60 °C, for at least 188 days following storage at ≤ −15 °C and for at least 1191 days following storage at ≤ −60 °C. Asciminib was stable in human plasma sample extracts for at least 7 days stored in the autosampler set at 10 °C and was demonstrated to be stable in human whole blood for at least 2 h at room temperature [38, 39].

3.2 Pharmacodynamic Assay

BCR::ABL1 and ABL1 transcripts are quantified using the approved MRDx BCR-ABL Test (K173492, MolecularMD). This assay is an in vitro diagnostic test intended for the quantitation of *BCR::ABL1* transcripts (e13a2/b2a2 and/or e14a2/b3a2) [40] and the *ABL1* endogenous control mRNA in peripheral blood specimens from patients previously diagnosed with Ph^+ CML. The test utilizes quantitative, real-time reverse transcription polymerase chain reaction (RT–qPCR) performed on the Applied Biosystems 7500 Fast Dx instrument (ThermoFisher Scientific), and the ratio of *BCR::ABL1* to *ABL1* is calculated and reported on the WHO International Scale (IS). To perform this test, blood samples are collected in PAXgene Blood RNA tubes processed by a manual extraction procedure using the PAXgene Blood RNA Kit (Qiagen). Total RNA is then extracted from peripheral blood cells and serves as a template for RT-qPCR. *BCR::ABL1* and *ABL1* amplicons are generated and detected in real-time using TaqMan® MGB probes. *BCR::ABL1* transcript levels are measured in relation to the *ABL1* transcript as an endogenous reference; the calculated *BCR::ABL1* : *ABL1* ratio is then converted to the IS. MMR corresponds to a 3-log reduction in *BCR::ABL1* transcripts below the standardized baseline (≤0.1% $BCR::ABL1^{IS}$). The MolecularMD MRDx BCR-ABL Test has been validated in terms of precision (repeatability and reproducibility), linearity, detection limit (limit of blank, limit of detection [LoD], and limit of quantitation [LoQ]), and specificity and was evaluated for clinical performance in two separate clinical studies (ENESTop [NCT01698905] and ENESTfreedom [NCT01784068]). The final LoD was determined to be 0.00029% $BCR::ABL1^{IS}$ ($MR^{5.5}$) for EDTA blood collection tubes and 0.00039% $BCR::ABL1^{IS}$ ($MR^{5.4}$) for PAXgene Blood RNA Tubes for both transcripts. The LoQ for PAXgene Blood RNA Tubes was 0.0025% $BCR::ABL1^{IS}$ ($MR^{4.6}$). The MRDx BCR-ABL Test Software limits the LoQ and quantitated results to 0.0032% $BCR::ABL1^{IS}$ ($MR^{4.5}$) for both blood tube types.

4 Pharmacokinetics

4.1 General PK and ADME Properties

Asciminib is a low molecular weight (MW: 449.8 g/mol), lipophilic drug with a log*P* value of 3.9. Consistent with it possessing a weak basic center (pKa 4.0), asciminib showed decreasing thermodynamic solubility with increasing pH [19]. Apparent passive permeability across a Madin–Darby Canine Kidney (MDCK) cell monolayer was high [22]. Asciminib was identified to be a low-affinity substrate of P-glycoprotein (P-gp): no K_m value could be determined [32]. For breast cancer resistance protein (BCRP), the apparent asciminib K_m value was low (1.83 µM) and considered saturated in the intestine at levels achieved with oral doses of asciminib of 40−200 mg. Consequently, asciminib was classified as a Biopharmaceutics Classification System (BCS) class 2 compound due to its limited solubility and high permeability. However, Scemblix® tablets contain the crystalline hydrochloride salt of asciminib, which showed a pronounced supersaturation effect resulting in no solubility limitations across the established dose range from 40 to 200 mg. Thus, asciminib can be classified as a pseudo BCS class 1 compound in this dose range. Established PBPK models have predicted almost complete absorption of asciminib across the established dose range [27]; however, the absolute bioavailability of asciminib has not been evaluated clinically in humans. Based on PBPK modeling, the estimated

absolute bioavailability was 73%, which is in accordance with values observed using solid dispersion formulations in monkey (76%) and dog (66%) [27].

The plasma protein binding of asciminib was high across species with fractions unbound (f_u) of 96.2, 94.5, 98.0, 95.9, and 97.3% for mouse, rat, dog, monkey, and human, respectively [22]. The blood to plasma ratios of 1.02, 0.94, 0.93, 0.88, and 0.80 for mouse, rat, dog, monkey, and human indicate that asciminib is more distributed to plasma than to blood cells across species. No apparent concentration dependency was observed for plasma f_u or blood–plasma ratios. In human plasma, asciminib preferentially bound to human serum albumin [22].

The high permeability of asciminib allows for fast distribution to all body compartments except the brain, where penetration was limited by the efflux transporters P-gp and BCRP [30]. Thus, asciminib showed almost no brain exposure in a rat autoradiography study. Following oral administration to rats, the highest exposure of [^{14}C]-radiolabeled material was observed in gastro-intestinal tissue, liver, and kidneys. In general, total radioactivity showed rapid elimination indicated by time of last measurable concentration (t_{last}) values of 48 h.

Asciminib blood clearance was low across species (mouse: 11.5 mL/min/kg, rat: 13.6 mL/min/kg, dog: 6.5 mL/min/kg, monkey: 1.8−7.3 mL/min/kg) [27]. In the human ADME study, apparent plasma clearance (CL/F) was estimated to be 1.03 mL/min/kg [29].

Cytochrome P450 (CYP450) enzyme phenotyping identified CYP3A4 as major contributor to asciminib oxidative metabolism [29]. Several UGTs (UGT2B7, UGT2B17, UGT1A3, and rUGT1A4) were shown to contribute to asciminib glucuronidation. Asciminib showed no active uptake into hepatocytes. Details of the fractional contribution to systemic clearance are specified in the "Drug–Drug Interaction" section.

4.2 Clinical Pharmacokinetic Properties of Asciminib

4.2.1 General PK

Asciminib is administered as either a b.i.d. or q.d. dosing regimen. The PK of asciminib is characterized by a rapid absorption, with plasma concentrations of asciminib generally declining in a bi-phasic manner. The median t_{max} of asciminib is 2–3 h, independently of dose (Table 1) [11, 29]. No time-dependent PK was observed. Systemic exposure to asciminib after oral administration of a single dose and multiple doses, as measured by C_{max} and AUC, increased in a slightly greater than dose-proportional manner for the b.i.d. dosing regimens [22]. Steady state was reached after three days of dosing [22]. The apparent terminal $t_{1/2}$ across studies was estimated to be between 7 and 15 h, whereas the apparent CL/F of asciminib was 4.34 L/h (based on non-compartmental PK analysis of a single dose of 80 mg in the human ADME study in healthy subjects) [11, 29, 39, 41]. The geometric mean average accumulation ratio 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.) [22]. Generally, the variability of exposure was low to moderate with intersubject variability (CV percent) ranging from approximately 17–69% for AUC_{last} and from 14–74% for C_{max} [22]. The PK in patients with CML was consistent between studies; there were no apparent differences in the PK of healthy subjects compared with patients with CML [11, 38, 42]. An integrated analysis of PK data in patients was conducted using population modeling which is reported in the "Effect of Demographic Characteristics and Extrinsic Factors on Asciminib Pharmacokinetics" section.

4.2.2 Human ADME

Following a single oral dose of 80 mg [^{14}C]-labeled asciminib, feces were identified as the main excretion pathway for asciminib and its metabolites, with 80% of radioactivity excreted in fecal matter in the human ADME study [29]. Renally eliminated radioactivity accounted for 11%, with 2.5% of unchanged asciminib, underlining the low relevance of this clearance pathway.

Asciminib was the major component in feces (56.7%), followed by M39 (oxidation with subsequent pyrrolidine ring-opening, 7.8%), M43.3 (decarboxylation of M39, 4.6%),

Table 1 Summary of asciminib pharmacokinetic parameters

Steady state[a] asciminib exposure at recommended dosages			
Asciminib dosage	C_{max} (ng/mL)[b]	AUC_{tau} (ng × h/mL)[b,c]	Accumulation ratio
80 mg once daily	1781 (23%)	15,112 (28%)	1.30
40 mg twice daily	793 (49%)	5262 (48%)	1.65
200 mg twice daily	5642 (40%)	37,547 (41%)	1.92
General PK values			
t_{max} (h)		2−3	
$t_{1/2}$ (h)		7−15	
CL/F (L/h)[d]		4.34	

[a]Steady state is achieved within 3 days

[b]Parameters are presented as geometric means (GeoCV %)

[c]AUC_{tau} represents $AUC_{0–12h}$ for twice daily dosing and $AUC_{0–24h}$ for once daily dosing

[d]Based on noncompartmental PK analysis of a single dose of 80 mg in the human ADME study in healthy subjects, presented as geometric mean

M37 (oxidation with subsequent pyrrolidine ring-opening, 2.2%), and M45 (oxidation, 2.2%) and four more metabolites contributing, all with less than 2% of the total [29]. The low amount of glucuronides observed in feces could be attributed to back-conversion to asciminib by intestinal bacteria. This instability was confirmed by in vitro incubation of the direct glucuronide metabolite M30.5 in feces, which was completely converted to asciminib within 24 h. In urine, the direct glucuronide M30.5 accounted for 7.0% of the dose; seven more metabolites were detected, all contributing to less than 1% of the dose [29].

The most abundant component in plasma was unchanged asciminib, representing 92.7% of the total drug-related AUC [29]. In human plasma, three metabolites were observed: M30.5 (direct glucuronide), M44 (oxidation), and M29.5 (oxidation with subsequent pyrrolidine ring-opening). No major circulating metabolite was identified, and each one contributed to plasma presence of asciminib with less than 5% of total drug-related AUC.

4.2.3 Relative Bioavailability

Asciminib was first developed as a hard-gelatin capsule and later as a film-coated tablet (FCT) formulation (asciminib free-base of drug substance). In addition, asciminib–HCl salt form drug substance was developed in FCT formulation. After extensive polymorphism evaluation and two relative bioavailability studies (study A2101 and study A2104) [38, 43], the asciminib–HCl salt form drug substance was selected for the final market image (FMI) tablet formulation, which was further used in clinical studies. It was established that no dose adjustment was needed for the switch from hard-gelatin capsule formulation to the FMI tablet formulation, which was used in all relevant clinical studies.

In addition, a pediatric formulation of asciminib was developed (1-mg film-coated minitablets with a diameter of 2 mm). Under fasting conditions, asciminib exposure for the minitablets versus the FMI tablet was shown to be comparable [44].

4.2.4 Food Effect

The absorption of asciminib is affected by food, and therefore, asciminib should be taken in the fasted state at all doses.

In the initial food effect study with two tablet variants (asciminib free-form and asciminib–HCl salt), the AUC from time zero to infinity (AUC_{∞}) and C_{max} of asciminib HCl salt tablet were decreased by 30% and 29% when administered with a low-fat meal and by 64% and 71% with a high-fat meal, when compared with fasting conditions. With the asciminib free form tablet, the AUC_{∞} and C_{max} were decreased by 31% and 36% when administered with a low-fat meal and by 63% and 71% with a high-fat meal when compared with fasting conditions [43].

The food effect of the FMI tablet was assessed in another study that revealed comparable effects of food on the PK of asciminib. Low-fat and high-fat meals decreased the exposure (AUC_{∞}) of asciminib by 30% and 62.3%, respectively [38]. This was accompanied by a prolonged t_{max} of asciminib, which was longer when asciminib was administered with a high-fat meal (4.01 h [range 1.00−8.00]) or low-fat meal (3.00 hr [range 0.997−5.00]), compared with the fasted state (2.01 h [range 1.00−5.00]) [38].

This negative food effect is believed to be caused by sequestration of asciminib with bile acids when present at high levels in the gastrointestinal tract in vivo.

4.2.5 Impact of Acid-Reducing Agents

In a DDI study, the bioavailability of asciminib (40 mg) at steady state did not appear to be affected by the co-administration of the proton pump inhibitor rabeprazole [42].

The geometric mean ratio (GMR) for AUC_{∞}, AUC_{last}, and C_{max} was 0.986 (90% CI [confidence interval], 0.959 to 1.01), 0.985 (0.957 to 1.01), and 0.908 (0.849 to 0.972), respectively. The median t_{max} remained unchanged when asciminib was administered with rabeprazole as compared with asciminib alone. The C_{max} of asciminib was decreased by 9% when administered with rabeprazole [42].

Since rabeprazole is considered the most potent compound in terms of acid-reducing/pH-increasing effects among currently available proton pump inhibitors, these results can be extrapolated to other acid-reducing agents. PBPK predictive modeling showed limited effects of elevated gastric pH on the rate and extent of asciminib absorption, in line with clinical results [42]. These data suggest that asciminib hydrochloride salt fully dissolves in the stomach due to its high solubility and does not precipitate in intestinal medium, as it forms a supersaturated solution in basic conditions. The amount of soluble drug substance available for absorption is, therefore, higher than that predicted by the low saturation solubility values within the pH range of 4.5–6.8. These results show that asciminib can be administered with acid-reducing agents.

4.2.6 Impact of Cyclodextrin

In a DDI study of asciminib with itraconazole (a strong CYP3A4 inhibitor) oral solution, an unexpected decrease in asciminib exposure was observed, most apparent in the decreased C_{max} [42]. The asciminib plasma elimination rate was similar between the two treatments, and t_{max} was unchanged. Following multiple doses of itraconazole, given as an oral solution, the geometric mean AUC_{∞}, AUC_{last}, and

C_{max} decreased by 40.2%, 41.2%, and 50.1%; however, this effect was not seen when itraconazole was given in capsule formulation. Further investigations of this unexpected result suggested that the most plausible explanation was a presystemic effect, potentially a complex formation with hydroxypropyl-beta-cyclodextrin, an excipient in the itraconazole solution; the hydroxypropyl-beta-cyclodextrin concentration was 40× the concentration of itraconazole in the oral solution (8 g cyclodextrin per 200 mg itraconazole dose). It has been hypothesized that hydroxypropyl-beta-cyclodextrin could have sequestered asciminib and, therefore, decreased the free asciminib concentration available for absorption in the gut. This was supported by flux experiments (performed under same conditions as in this study), which showed that the flux of 40 mg asciminib through a parallel artificial membrane permeability assay (PAMPA) in fasted state simulated intestinal fluid (FaSSIF) media containing 8 g of hydroxypropyl-beta-cyclodextrin was approximately 4.6-fold reduced compared with flux in FaSSIF media without hydroxypropyl-beta-cyclodextrin [42].

4.3 Recommended Doses

Results from in vitro studies in human-derived leukemic cells expressing wild-type *BCR::ABL1* and mouse xenograft models, coupled with PK/PD model–based predictions, indicated that a dose of 40 mg b.i.d. would maintain 100% of patients with CML-CP without a T315I mutation above the preclinical 90% inhibitory concentration (IC_{90}) for pSTAT5 inhibition [7, 21, 22]. Preclinical data showed that the asciminib concentration required to achieve inhibition of T315I-mutated BCR::ABL1 was 5–10 times higher than to achieve inhibition of wild-type BCR::ABL1 [11, 21].

As previously mentioned, asciminib efficacy and safety have been tested across a wide dose range in patients with CML (10–200 mg b.i.d. and 80–200 mg q.d.). Based on the results of preclinical studies plus those from the first-in-human study, the recommended asciminib doses were established as 40 mg b.i.d. for patients not harboring the T315I mutation and 200 mg b.i.d. for patients with the T315I mutation; the latter was based on results from the first-in-human study, showing that the majority of responding patients harboring the T315I mutation had received asciminib at doses equal or greater than 150 mg b.i.d. [7, 11, 21]. In addition, asciminib was also tested up to doses of 280 mg b.i.d. in patients with Ph^+ ALL [11].

The pivotal ASCEMBL trial assessed an asciminib dose regimen of 40 mg b.i.d. Administration of asciminib twice daily while fasting may pose a challenge for patients with regards to adherence and long-term compliance to therapy. A more patient-centric dose of 80 mg q.d. was then proposed for approval as an alternative regimen to improve ease of use and adherence.

Based on the minimum plasma concentration (C_{min}) values being above the target of IC_{90} for pSTAT-5 inhibition, asciminib doses of 40 mg b.i.d. or 80 mg q.d. were predicted to achieve efficacious concentrations in plasma [11]. Exposure-efficacy models showed that the efficacy of asciminib 80 mg q.d. was predicted to be similar to that of 40 mg b.i.d. [13]. An asciminib dose of 80 mg q.d. has been shown to be efficacious and safe in the first-in-human study [11], without any apparent differences compared with the asciminib dose of 40 mg b.i.d. and higher doses. With this dosing regimen, MMR was achieved by 53/86 (61.6%) patients at any time during the study [45]. The 80 mg q.d. dosing regimen has now been approved in several countries including the USA.

5 Effect of Demographic Characteristics and Extrinsic Factors on Asciminib Pharmacokinetics

5.1 Race

No dose adjustment is required based on race (Asian, white, or African American), since no clinically significant differences in the PK of asciminib were observed based on race or ethnicity [22].

5.2 Population Pharmacokinetics

Using the data from the phase 1, first-in-human and phase 3 (third-line therapy) studies, the population pharmacokinetic (PopPK) analysis of asciminib was conducted using a two-compartment model with delayed first-order absorption and elimination [14]. The parameter values and covariate relationships are listed in Supplementary Table 1. A typical individual with a body weight of 70 kg and a 90.4 mL/min actual glomerular filtration rate taking a total daily dose of 80 mg (i.e., 40 mg b.i.d.) has a CL/F of 6.31 L/h and an apparent steady-state volume of distribution of 111 L ($V_c/F + V_p/F$).

The exposure (AUC) of asciminib over 24 h was comparable for 80 mg per day, whether it is taken once a day (q.d.) or divided into twice-daily (b.i.d.) [14]. The over-proportionality in asciminib exposure with respect to dose was tested on the relative bioavailability and apparent clearance. Dose effect on apparent clearance mitigated the correlation between total daily dose and the interindividual variability in clearance to a greater extent than having the dose effect on the relative bioavailability. As described in the "Drug–Drug Interaction" section, saturation of hepatic BCRP transport is the likely driver of this effect. Given the negative exponent associated with the dose covariate normalized to the total daily dose of 80 mg, higher doses are expected to result in lower clearance and consequently higher exposure. The

asciminib clearance of 200 mg b.i.d. is estimated to be approximately 42% lower than that of 40 mg b.i.d.

5.3 Age and Body Weight

The impact of age and body weight on the PK of asciminib was evaluated with a PopPK approach. Body weight has a significant influence on the clearance and central volume of asciminib. The power model centered on 70 kg: $(BW/70)^{\theta}$, wherein the exponents were estimated by the model and an allometric scaled model (θ fixed to 0.75 and 1 for clearance and volumes of distribution) was evaluated; both models described the data equally well. Allometric principles were incorporated in the relationship between the model parameters and body weight as the PK data were primarily from adult patients; extrapolation to pediatric population using allometric scaled model often results in a more precise estimation of exposure in the lower body weight group. For a fixed dose of 40 mg b.i.d., the difference in PK exposure for individuals with 67 and 88 kg, representing the 25th and 75th percentiles of body weight distribution, versus a typical individual weighing 70 kg is expected to be less than 20%. No age effect was detected in the covariate screening [14].

5.4 Renal and Hepatic Function

The PK profile of a single dose of asciminib was evaluated in individuals with varying degrees of hepatic and renal impairment (based on the Child–Pugh classification and absolute glomerular filtration rate [aGFR], respectively) [39]. Among individuals with mild and severe hepatic impairment, asciminib AUC was 21−22% and 55−66% higher, respectively, while the C_{max} was 26% and 29% higher compared with those with normal hepatic function; this suggests no clinically meaningful changes in exposure associated with hepatic impairment. When compared with healthy volunteers with normal renal function, patients without cancer with severe renal impairment had similar C_{max} (+8%), higher AUC_{∞} (+56%; GMR [90% CI], 1.56 [1.05. 2.30]), higher AUC_{last} (+49%; GMR [90% CI], 1.49 [1.01, 2.20]) and lower CL/F (-36%; GMR [90% CI], 0.643 [0.434, 0.952]) [39]. Based on these findings in severe renal impairment, the PK of asciminib in individuals with mild or moderate renal impairment was not assessed.

Renal excretion was identified as a negligible excretion pathway for asciminib, with 2.5% of the dose excreted via urine as unchanged drug [29]. However, it is well established that renal impairment can have an effect on the PK of drugs that are predominantly cleared by nonrenal mechanisms. This alteration in metabolism may result from uremic toxins that accumulate in subjects with renal impairment leading to down regulation of CYP3A4 gene expression and in turn to increased asciminib exposure [46].

Based on the covariate screening process, renal function was measured by baseline aGFR and was defined as normal (aGFR ≥ 90 mL/min), mildly (90 mL/min > aGFR ≥ 60 mL/min), or moderately impaired (aGFR <60 mL/min) [14]. In terms of renal function, using the PopPK model, simulation showed an increase in asciminib median steady-state $AUC_{0–24h}$ by 11.5% in subjects with mild-to-moderate renal impairment compared with patients with normal renal function.

Based on these data, no dose adjustment is required in subjects with mild, moderate, or severe renal impairment at all recommended doses.

5.5 Gender

After considering the effect of body weight, there was no apparent difference in the PK of asciminib in female compared with male patients [14].

5.6 Patient Population

There were no apparent differences in the PK of asciminib in patients with CML or Ph^+ ALL compared with healthy subjects [11, 22]. In line with these observations, based on PBPK modeling there were no apparent differences in the simulated PK of asciminib in patients with cancer (CML or Ph^+ ALL) compared with healthy subjects [22].

5.7 Drug–Drug Interactions

Enzyme phenotyping studies indicate that asciminib is metabolized mainly via CYP3A4, UGT2B7, UGT2B17, and UGT1A3/4 [29]. The observed slight over-proportional increase in exposure with increasing doses of asciminib is most likely caused by saturation of a clearance mechanism. Transport mediated by BCRP had the lowest K_m value compared with other enzymes and transporters (0.14 µM versus 9.41−15.7 µM) [27]. Therefore, canalicular efflux via BCRP was included in the PBPK model and its fractional contribution (31%) to total systemic clearance was optimized to match the observed over-proportional exposure increase. In consequence, the fractional contribution of the metabolizing enzymes was calculated to be 35.1%, 13.1%, 7.6%, and 6.6% for CYP3A4, UGT2B7, UGT2B17, and UGT1A3/4, respectively [27].

The effect of UGT2B7 genetic variants (polymorphisms) on the PK of asciminib (specifically trough concentration, C_{trough}) was analyzed in patient samples from the asciminib phase 3 study ASCEMBL, based on 123 patients for whom pharmacogenomic data was available [27]. There were four major UGT2B7 phenotypes observed: extensive metabolizer (34/123, 27.6%), ultrarapid metabolizer (32/123, 26.0%), ultra-rapid or extensive metabolizer (44/123, 35.8%), and

unknown (13/123, 10.6%). Among the different UGT2B7 phenotypes, no statistically significant differences in C_{trough} were observed. Of note, no poor metabolizers have been identified for UGT2B7 with the assay used in these studies [27]. The data for UGT2B17 were inconclusive. However, based on the low fractional contribution of UGT2B17 to the total clearance (7.8%), a clinically relevant impact on the PK of asciminib is unlikely.

The DDI potential of asciminib as a victim was investigated in clinical studies using a single dose of 40 mg with the perpetrators clarithromycin (strong CYP3A4 inhibitor), itraconazole (strong CYP3A4 inhibitor), and rifampicin (strong CYP3A4 inducer) (Table 2) [27, 42]. Altogether, these results show that asciminib has low sensitivity toward strong CYP3A4 perpetrators; based on its wide therapeutic range, no asciminib dose adjustments are required when comedicating with such perpetrators.

The DDI potential of asciminib as a perpetrator was investigated in a clinical study following 5 days of administration of asciminib 40 mg b.i.d. with a substrate cocktail of midazolam (sensitive CYP3A4 substrate), S-warfarin (sensitive CYP2C9 substrate), and R-warfarin; asciminib was observed to be a weak inhibitor of CYP3A and CYP2C9, with no significant effect on CYP2C8 (Table 3) [27, 47]. In a separate study arm, following 3 days of treatment with asciminib 40 mg b.i.d., the AUC increase of repaglinide (CYP2C8, CYP3A4, and OATP1B substrate) was 8%. PBPK simulations at steady-state conditions of the substrates midazolam, S-warfarin, and repaglinide showed that asciminib up to 200 mg b.i.d. is a weak CYP3A4 inhibitor, whereas it is a weak CYP2C9 inhibitor for daily doses of 80 mg and a moderate CYP2C9 inhibitor at 200 mg b.i.d. (Table 3) [27]. Sensitivity toward CYP2C8 and CYP3A4 was explored by repaglinide DDI simulations. Asciminib 200 mg b.i.d. was predicted not to inhibit CYP2C8 to a clinically relevant extent, with a repaglinide AUC increase of 1.10 when only using the asciminib CYP2C8 Ki value in the simulation. When using only the asciminib CYP3A4 Ki value in the DDI simulation, a repaglinide AUC ratio of 1.16 was predicted for the 200 mg b.i.d. dose of asciminib. In conclusion, the predicted net DDI effect of asciminib 200 mg b.i.d. on repaglinide of 1.42 appears to be driven by inhibition of both enzymes, CYP2C8 and CYP3A4, with a larger contribution from CYP3A4 [27]. In vitro data suggested that asciminib may inhibit OATP1B1, OATP1B3, P-gp, and BCRP [27].

Table 2 Summary of drug–drug interaction predictions (AUC ratios) for asciminib as victim.

Drug–drug interaction with CYP3A4 perpetrators		Geometric mean AUC[a] ratio	Geometric mean C_{max} ratio
Clarithromycin (CYP3A4 inhibitor)			
Asciminib 40 mg	Observed	1.36	1.19
Asciminib 40 mg BID	Predicted	1.32	1.05
Asciminib 80 mg QD	Predicted	1.40	1.05
Asciminib 200 mg BID	Predicted	1.50	1.05
Itraconazole (CYP3A4 inhibitor)			
Asciminib 40 mg	Observed	1.04	1.04
Asciminib 40 mg BID	Predicted	1.24	1.05
Asciminib 80 mg QD	Predicted	1.28	1.05
Asciminib 200 mg BID	Predicted	1.34	1.05
Rifampicin (CYP3A4 inducer)			
Asciminib 40 mg	Observed	0.851	1.09
Asciminib 40 mg BID	Predicted	0.566	0.838
Asciminib 80 mg QD	Predicted	0.531	0.837
Asciminib 200 mg BID	Predicted	0.492	0.838

Summary of all DDI predictions using PBPK-derived simulations. Prediction is a model-based simulation and also indicates cases in which parameters were obtained with a dose of 40 mg for asciminib as a victim

[a]AUC_{∞} for single dose or AUC_{tau} for multiple doses

AUC, area under the curve; AUC_{∞}, AUC from time zero to infinity; AUC_{tau}, AUC during a dosage interval (tau); BID, twice daily; C_{max}, maximum concentration; CYP, cytochrome P450; DDI, drug–drug interaction; PBPK, physiologically-based pharmacokinetics; QD, once daily

6 Pharmacodynamics

6.1 Clinical Efficacy of Asciminib

6.1.1 Asciminib Monotherapy

In the asciminib first-in-human study, asciminib demonstrated efficacy in patients with Ph^+ CML-CP resistant to or intolerant of ≥ 2 prior TKIs; patients harboring the T315I mutation were eligible after ≥ 1 prior TKI. The subset of patients with CML-CP not harboring the T315I mutation received asciminib ranging from 10 to 200 mg b.i.d. and 80 to 200 mg q.d. In addition, asciminib was also tested up to doses of 280 mg b.i.d. in patients with Ph^+ ALL and patients with CML in blast crisis [48]. In this study, MMR rates by 6 and 12 months were 37% and 48% in patients not harboring the T315I mutation and 25% and 28% in patients with the T315I mutation, respectively [11]. After an approximately 4-year exposure to asciminib, 61.6% of patients without the T315I mutation had achieved MMR [45]. Asciminib was well tolerated and the safety profile did not appear to change

Table 3 Summary of drug–drug interaction predictions (AUC ratios) for asciminib as perpetrator

AUC ratio by interacting drug		
S-Warfarin (CYP2C9 substrate)		
Asciminib 40 mg BID	Observed	1.41
Asciminib 40 mg BID	Predicted	1.40
Asciminib 80 mg QD	Predicted	1.52
Asciminib 200 mg BID	Predicted	4.14
Midazolam (CYP3A4 substrate)		
Asciminib 40 mg BID	Observed	1.28
Asciminib 40 mg BID	Predicted	1.23
Asciminib 80 mg QD	Predicted	1.24
Asciminib 200 mg BID	Predicted	1.88
Repaglinide (CYP2C8, CYP3A4, OATP1B1 substrate)		
Asciminib 40 mg BID	Observed	1.08
Asciminib 40 mg BID	Predicted	1.10
Asciminib 80 mg QD	Predicted	1.12
Asciminib 200 mg BID	Predicted	1.42

Summary of all DDI predictions using PBPK-derived simulations. Prediction is a model-based simulation and also indicates cases in which parameters were obtained with a dose of 40 mg BID for asciminib as a perpetrator

AUC, area under the curve; BID, twice daily; CYP, cytochrome P450; DDI, drug–drug interaction; PBPK, physiologically-based pharmacokinetics; QD, once daily

with increasing dose; this was confirmed in exposure-safety analyses ("Exposure–Response for Safety" section).

In the pivotal phase 3 ASCEMBL study in patients with Ph^+ CML-CP resistant to or intolerant of ≥ 2 prior TKIs, treatment with asciminib 40 mg b.i.d. led to a twofold improvement in MMR rate at week 24 compared with bosutinib in this heavily pretreated patient population (25.5% in the asciminib arm compared with 13.2% in the bosutinib arm), with a between-arm difference of 12.2% ($P = 0.029$) [5]. MMR rates continued to increase at week 48 (29.3% versus 13.2%, respectively, with a between-arm difference of 16.1%) [49] and week 96 (37.6% versus 15.8%, respectively, with a between-arm difference of 21.7%) [6]. Efficacy was observed in both ponatinib-pretreated and ponatinib-naive patients [8]. A matching-adjusted indirect comparison (MAIC) conducted in patients with CML-CP receiving third- or later-line treatment found favorable efficacy outcomes for asciminib compared with dasatinib, nilotinib, and ponatinib. [50]

In newly diagnosed patients with CML, the pivotal phase 3 ASC4FIRST study (NCT04971226) assessed asciminib 80 mg q.d. versus investigator-selected TKI (imatinib, dasatinib, nilotinib, and bosutinib), with randomization stratified by European Treatment and Outcome Study long-term survival score category (low, intermediate, or high risk) and by TKI selected by investigators before randomization (including imatinib and second-generation TKIs) [51]. MMR rates at week 48 were significantly higher in the asciminib group among all patients (67.7% versus 49.0% in the investigator-selected TKI group; adjusted two-sided $P < 0.001$]) and also among patients within the imatinib treatment stratum (69.3% versus 40.2% in the imatinib group; adjusted two-sided $P < 0.001$). Among patients within the second-generation TKI stratum, MMR rates at week 48 were 66.0% with asciminib and 57.8% with investigator-selected second-generation TKIs.

6.1.2 Asciminib in Combination

In the first-in-human phase 1 study, 25 patients with CML-CP pre-treated with ≥ 2 TKIs received asciminib at different doses (40 mg q.d., 60 mg q.d., 80 mg q.d., or 40 mg b.i.d.) in combination with imatinib 400 mg q.d. [52] MMR was achieved by week 48 by 8/19 (42%) of evaluable patients. Dose-limiting toxicities for each asciminib dose level were reported for one patient each (decreased neutrophil count for 40 mg q.d., abdominal pain and nausea for 60 mg q.d., pancreatitis and increased lipase for 80 mg q.d., and pancreatitis for 40 mg b.i.d.). Asciminib exposure (AUC and C_{max}) was increased by concomitant administration of imatinib, whereas the PK of imatinib was not affected by asciminib. Asciminib 40 mg q.d. and 60 mg q.d. provided comparable exposure in combination with imatinib as that obtained with asciminib alone at 40 mg b.i.d.

The ASC4MORE study (NCT03578367) is evaluating the efficacy, safety and PK of asciminib 40 mg q.d. plus imatinib 400 mg q.d. or asciminib 60 mg q.d. plus imatinib 400 mg q.d. versus continued imatinib treatment, switch to nilotinib treatment (300 mg b.i.d.) or asciminib treatment at 80 mg q.d. in patients with CML-CP pre-treated with imatinib [53]. An interim analysis of the 84 recruited patients showed $MR^{4.5}$ rates at week 48 of 19.0% and 28.6% in the 40-mg and 60-mg asciminib add-on arms, respectively (versus 0% and 4.8% in the imatinib and nilotinib monotherapy arms, respectively). Patients treated with asciminib plus imatinib experienced higher rates of adverse events (AEs), serious AEs, and treatment discontinuation than those treated with imatinib alone; however, these rates were lower than those of patients treated with nilotinib monotherapy.

The Frontline Asciminib in Combination (FASCINATION) investigator-initiated trial (NCT03906292) is a multicenter, prospective, open-label, interventional phase 2 trial evaluating the efficacy and tolerability of asciminib as first-line treatment in combination with nilotinib, dasatinib, or imatinib [54]. The dose of asciminib used in combination with each TKI was derived from PK data from the combination cohorts in the first-in-human trial. An interim analysis of the 125 patients who received combination therapy

showed that the MR^4 rate at 12 months was 37.7%. However, 17% of patients discontinued the combination therapy within the first 12 months due to toxicity, highlighting the decreased tolerability of asciminib when used in combination [54].

6.2 Clinical Safety of Asciminib

Because of its specificity, asciminib has no known off-target effects arising from the inhibition of kinases other than ABL1 or ABL2. In the first-in-human asciminib study, the most common AEs reported in patients who were treated with increasing doses of oral asciminib monotherapy (10 mg to 200 mg b.i.d. or 80 mg to 200 mg q.d. on a continuous schedule) were fatigue, headache, arthralgia, hypertension, and thrombocytopenia [11]. The maximum tolerated dose (MTD) for asciminib monotherapy in patients with CML-CP was not achieved in this study, suggesting a large therapeutic window for asciminib.

The phase 3 study ASCEMBL confirmed that asciminib 40 mg b.i.d. had a manageable safety profile [5]. Treatment discontinuation was reported for 45.9% of the patients in the asciminib arm versus 80.3% in the bosutinib arm at week 96. The rate of discontinuation due to AEs was 5.1% in the asciminib arm and 21.1% in the bosutinib arm. These results were obtained despite the median duration of exposure to study treatment being much longer for asciminib than for bosutinib (43.4 weeks versus 29.2 weeks, respectively, from start of treatment to last treatment as per data cutff date of 25 May 2020) [5]. The most common Grade ≥ 3 AEs reported following long-term treatment with asciminib in ASCEMBL were thrombocytopenia (in 22.4% of patients) and neutropenia (18.6%) [6].

In the ASC4FIRST study, asciminib 80 mg q.d. led to lower rates of grade ≥ 3 AEs than imatinib or second-generation TKIs (38.0%, 44.4%, and 54.9%, respectively) at week 48; similar results were observed for AEs leading to discontinuation (4.5%, 11.1%, and 9.8%, respectively) [51]. The most common grade ≥ 3 AEs observed with asciminib were hematological (thrombocytopenia: 13.0% versus 6.1% with imatinib and 13.7% with second-generation TKIs; neutropenia: 10.0%, 17.2%, and 17.6%, respectively; leukopenia: 2.0%, 10.1%, and 4.9%, respectively).

In summary, asciminib has been shown to be well-tolerated and efficacious over a wide range of doses and treatment lines, with the MTD not reached.

6.2.1 Cardiac Toxicity Assessments

Review of non-clinical data showed that the IC_{50} for asciminib in the hERG patch clamp assay was 11.4 µM, which translates into a clinical safety margin of > 200-fold, > 100-fold, and > 30-fold when compared with free exposure in patients at doses of 40 mg b.i.d., 80 mg q.d., and 200 mg b.i.d., respectively [22].

A linear mixed-effects model was used to analyze the change from baseline corrected QT interval by Fridericia's formula (QTcF) versus time-matched plasma asciminib concentrations, with baseline QTcF as covariate and patient as random effect. This model was used to estimate the changes in ECG parameter values at relevant concentration levels achieved at doses including 40 mg b.i.d., 80 mg q.d., and up to twice the highest clinically relevant exposure (HCRE, i.e., 1.59-fold exposure expected at 200 mg b.i.d. when administered with imatinib based on data from clinical DDI study E2101, assuming same extent of interaction at 200 mg b.i.d. as at 40 mg b.i.d.) [22].

Overall, the concentration-effect analysis demonstrated that therapeutic doses of asciminib in patients with CML-CP who have received at least 2 prior TKIs (i.e., 40 mg b.i.d. and 80 mg q.d.) do not have a clinically relevant effect on cardiac repolarization. This is evidenced by the estimated mean and upper bound of the 90% CIs mean change in QTcF (ΔQTcF) at 40 mg b.i.d., 80 mg q.d., 200 mg b.i.d., and at the HCRE (which is considered the worst-case scenario for C_{max} at 200 mg b.i.d.) being below the regulatory threshold of 10 ms. These findings indicate a low proarrhythmic risk in patients with CML treated with asciminib as a single agent at all clinical doses [22].

7 Exposure–Response Analyses

7.1 Exposure–Response for Efficacy

An MTD for asciminib was not reached in the phase 1 study that tested asciminib up to a dose of 280 mg b.i.d [11]. Exposure–response models were then used to quantify the longitudinal effect of asciminib on *BCR::ABL1*^{IS} percentage and safety variables from a large dose range of asciminib tested in patients. In this model-informed dose optimization, the molecular biology of the disease and the mechanism of action of the drug were considered to select a dose appropriate for the disease genotype [13].

Fassoni and coworkers studied the influence of different dosing regimens of imatinib in patients with CML on treatment outcomes and described the longitudinal *BCR::ABL1*^{IS} percentage using a two-compartment model in linear series without incorporating the subpopulation of patients experiencing resistance to treatment [55]. The limitation with this model was that it only described monophasic and biphasic patterns (i.e., either growth or decline) but not complex patterns, for example, those showing an initial decline followed by a rebound. Modeling longitudinal disease progression

incorporating resistance mechanisms allowed for a more reasonable prediction of response to therapy, including a rebound or relapse pattern [13]. The definition of resistance was based on the following assumptions: (1) a subpopulation of cells is not affected by therapy; (2) the resistant subpopulation follows the same growth and capacity limitations as the susceptible subpopulation; and (3) over time, therapeutic pressure will decrease the susceptible subpopulation and allow the resistant subpopulation to proliferate. Without the drug effect, *BCR::ABL1*^{IS} percentage was assumed to increase in a sigmoidal manner, with a faster exponential growth at low leukemic burdens subsequently approaching a plateau with slower growth rates as leukemic cells reach a larger population size; this pattern was described by a logistic growth model which was incorporated to both the proliferating bone marrow (P) and the resistant cell (R) populations. Both populations of cells started from the same source of quiescent leukemic stem cells. The carrying capacity was limited to 100-fold or 2-log unit increase from the combined baseline P and R populations, where $\text{total}_{\max} = 100 \times \left(P_{t=0} + R_{t=0}\right)$ [13].

The model assumed that the action of asciminib only affected P but had no effect on R [13]. The relapse pattern was characterized such that the P compartment dies out over time due to drug effect, while the R compartment proliferates until it reaches the carrying capacity; the model also assumed that with a strong drug effect such as a sufficiently large dose, the R compartment transformed into the P compartment. The drug effect was characterized by either a power model or a maximum drug effect ($E_{\max}$) model for the overall population and the T315I populations, respectively, with the daily input PK metric of either AUC, $C_{\max}$, or $C_{\min}$. The PopPK model was used to simulate these individual daily exposure metrics. The longitudinal *BCR::ABL1*^{IS} percentage data from patients with CML-CP in the phase 1 and phase 3 studies were used to develop the model to provide a very large dose range.

The model for the overall population estimated that the average resistant population was in 10^{-7} units, whereas quiescent and proliferating populations were in 10^{-2} units. The relative magnitude of the two populations indicates that most patients responded to the initial therapy. Natural growth has a doubling time of about 9 days. The transformation rate constant from quiescent to resistant cells was smaller than that for the natural growth, so that cells do not become dominated by the resistant population. In some patients who had a prolonged drug holiday, their rebound is rapid and reapplication of therapy will put their *BCR::ABL1*^{IS} percentage back in control. In patients who were resistant to therapy, the drug initially controlled the disease but later relapsed even when patients adhered to their medication [13].

Several factors influencing *BCR::ABL1*^{IS} percentage response to asciminib had a biological basis related to resistance mechanisms. Baseline *BCR::ABL1*^{IS} percentage levels are known to affect MMR rates, with higher baseline *BCR::ABL1*^{IS} percentages associated with worse outcome. As expected, patients exposed to a higher number of different TKI treatments before asciminib were less responsive to asciminib treatment [13].

7.1.1 Dosing in Non-T315I Patients (40 mg b.i.d. and 80 mg q.d.)

The exposure-efficacy model of asciminib was a key component in the approval of the 80 mg q.d. dosing regimen in patients with CML-CP not harboring the T315I mutation, as well as 200 mg b.i.d. in patients with CML-CP and T315I; neither regimen was studied in the pivotal phase 3 trial [5, 13]. Further direct comparison between the 40 mg b.i.d. and 80 mg q.d. doses indicated similar efficacy between the two dosing regimens. The model predicted similar MMR rates for the two dosing regimens at 24 weeks post-treatment (27.6 ± 4.5% and 24.8 ± 4.2%, respectively, versus 25.5% in ASCEMBL), and the PK differences between the two dosing regimens were not expected to be of clinical relevance [12].

7.1.2 Dosing in T315I Patients (200 mg b.i.d.)

Preclinical data had demonstrated that different mutant forms of *BCR::ABL1* had different sensitivity toward asciminib ("Asciminib In Vitro Studies" section) [7]. The IC_{50} to inhibit the proliferation of murine Ba/F3 hematopoietic cells dependent on BCL::ABL1^{T315I} was 12.5-fold that of those reliant on wild-type BCR::ABL1 [20]. In patients harboring the T315I mutation, efficacy was observed in the cohorts that were administered higher doses of at least 150 mg b.i.d. in the phase 1 study. However, the sample size was small for each dosing cohort, except for 200 mg b.i.d. ($n = 51$) [11]. Modeling of the longitudinal *BCR::ABL1*^{IS} in patients harboring the T315I mutation was used to predict a robust MMR rate of over 20% for the dosing regimen of 200 mg b.i.d. after 24 weeks of treatment [13]. Simulations of asciminib exposure at a dose of 200 mg b.i.d. indicated that exposure (AUC) was predicted to be above the effective concentration 90% (EC_{90}) of the PK/PD model for more than 95% of patients.

This analysis was instrumental in providing scientific justification for the differential dosing regimen in CML-CP based on the underlying genetic variation (i.e., T315I mutation) that is responsible for the molecular pathology of the disease.

7.2 Exposure–Response for Safety

Safety parameters evaluated in the exposure-safety assessment included laboratory abnormalities, vital signs for

hypertension, and AEs of fatigue/asthenia at any time during treatment [56]. In the exposure-safety analysis, the pool of patients was larger than for exposure–efficacy because disease types other than CML-CP (such as Ph^+ ALL) were included in the analyses, whereas the exposure–efficacy analysis was based only on patients with CML-CP.

In the safety analysis, regression coefficients were plotted for various AEs associated with laboratory parameters. The majority of the coefficients were close to 0 for the regression coefficient of the log odds ratio, and those that were significant had negative regression coefficients, suggesting no increase in the risk of laboratory events with increased asciminib exposure [56]. Exposure-metric regression coefficients were positive for several laboratory abnormalities including lipase increase, hemoglobin decrease and bilirubin increase but were not statistically significant. Only an aspartate aminotransferase (AST) increase of grade ≥ 2 showed a significant positive estimate for the exposure metric AUC, which was regarded as not clinically relevant given that the frequency of grade ≥ 3 AST increase events was very low in the phase 3 study for asciminib 40 mg b.i.d. (0.6% versus 6.6% for bosutinib) [5]. For the 200 mg b.i.d. dose, the predicted probability of experiencing an event increased from 0.3% to 0.9% in the phase 1 study, which highlights the rarity of these events [56].

8 Conclusions

Asciminib has a unique mechanism of action (working by STAMP) and was designed to address resistance and intolerance issues observed with ATP-binding TKIs: by binding to a specific site on the myristoyl-binding pocket of BCR::ABL1, asciminib can maintain activity against mutated *BCR::ABL1* forms while reducing off-target effects on other kinases. In clinical trials, asciminib has shown very good efficacy and a tolerable safety profile in patients with Ph^+ CML-CP treated with ≥ 2 previous TKIs.

Asciminib exhibited a predictable PK profile, with no major deviation from linearity over a large dose range and low to moderate interindividual variability. Asciminib absorption can be reduced by food (particularly high-fat meals) and the presence of the excipient cyclodextrin; in both cases, this appears to be related to drug sequestration. The slightly greater than dose-proportional increase in exposure is likely due to the clearance mechanism, with saturation of transporters (most likely BCRP).

Overall, asciminib has a manageable DDI risk, with most interactions with other drugs having a weak effect on the PK of asciminib at all recommended doses.

Asciminib should be taken under fasted conditions due to the effect of food in reducing its absorption. Adhering to this restriction twice daily may be challenging for some patients. The robust exposure–response analyses detailed here showed a large therapeutic window for asciminib, as well as no relevant differences in efficacy or toxicity between the 40 mg b.i.d. dose (which was tested in the pivotal ASCEMBL study) and the 80 mg q.d. dose. Based on these analyses, the US FDA and several other countries approved, in addition to the 40 mg b.i.d. dose, the more patient-centric alternative dose of 80 mg q.d., without the need for a phase 3 study.

For patients with the T315I mutation, a higher dose of asciminib is required to provide sufficient BCR::ABL1 inhibition; a 200 mg b.i.d. dosing regimen has shown efficacy and a manageable safety profile in patients harboring the T315I mutation, and this dosing regimen was also validated by PopPK exposure–response analyses as both effective and safe.

Asciminib has shown effectiveness in combination with ATP-competitive TKIs; the results from clinical trials to date do not suggest an antagonistic effect of asciminib in combination.

Given that body weight, age, sex, race, and hepatic or renal impairment do not appear to have a clinically significant impact on the PK of asciminib, dose adjustments are not needed.

Asciminib has a favorable safety profile, which was similar across all dose regimens evaluated. Exposure-safety analyses suggest that increased exposure to asciminib has no clinically relevant association with increased risk of any of the assessed toxicities, including QTc prolongation.

In conclusion, asciminib is a unique novel compound belonging to a new class of TKIs that has shown a favorable PK/PD profile and remains efficacious for the treatment of CML in the presence of *BCR::ABL1* mutations.

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Declarations

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Competing interests All authors are employees of Novartis. M.H., F.P.C., and A.C. are also Novartis stockholders.

Author contributions M.H. conceived the article. All authors performed the literature search, drafted, and/or critically revised the work.

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