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REVIEW

Clinical pharmacokinetics and pharmacodynamics of venetoclax, a selective B-cell lymphoma-2 inhibitor

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Abstract

Venetoclax, a highly potent BCL-2 inhibitor, is indicated for treatment of some hematologic malignancies as monotherapy, and/or in combination with other agents. Venetoclax pharmacokinetics has been extensively characterized in patients and healthy participants. After oral dosing, the median time to reach maximum plasma concentration ranged from 5 to 8 h and harmonic mean half-life ranged from 14 to 18 h. Food increases venetoclax bioavailability by 3–5-fold and venetoclax should be administered with food to ensure adequate and consistent bioavailability. Venetoclax is eliminated via cytochrome P450 (CYP)3A metabolism, and a negligible amount of unchanged drug is excreted in urine. Strong CYP3A/P-glycoprotein inhibitors increased venetoclax exposures (AUC) by 1.44- to 6.90-fold while a significant decrease (71%) has been observed when dosed with strong CYP3 inducers. Venetoclax does not inhibit or induce CYP enzymes or transporters. Venetoclax pharmacokinetics is not appreciably altered by age, weight, sex, but the exposure is up to twofold higher in participants from Asian countries. Mild-to-severe renal impairment or end-stage renal disease do not alter venetoclax exposures, and venetoclax is not cleared by dialysis. Although mild-to-moderate hepatic impairment does not affect venetoclax exposures, twofold higher exposure was observed in subjects with severe hepatic impairment. Venetoclax exposure is comparable across patients with different hematologic malignancies and healthy participants. Overall, venetoclax exposure is only affected by food and CYP3A modulators and is only higher in Asian subjects and subjects with severe hepatic impairment. Venetoclax exposure–response relationships are malignancy-dependent and can be different between monotherapy and combination therapy.

BACKGROUND AND MECHANISM OF ACTION

Overexpression of the anti-apoptotic protein BCL-2 allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins. Venetoclax (ABT-199, GDC-0199) is a selective, highly potent, first-in-class orally bioavailable, BH3 mimetic inhibitor of BCL-2. As shown in Figure 1, venetoclax binds selectively to BCL-2 freeing pro-apoptotic proteins that initiate programmed cell death or apoptosis.

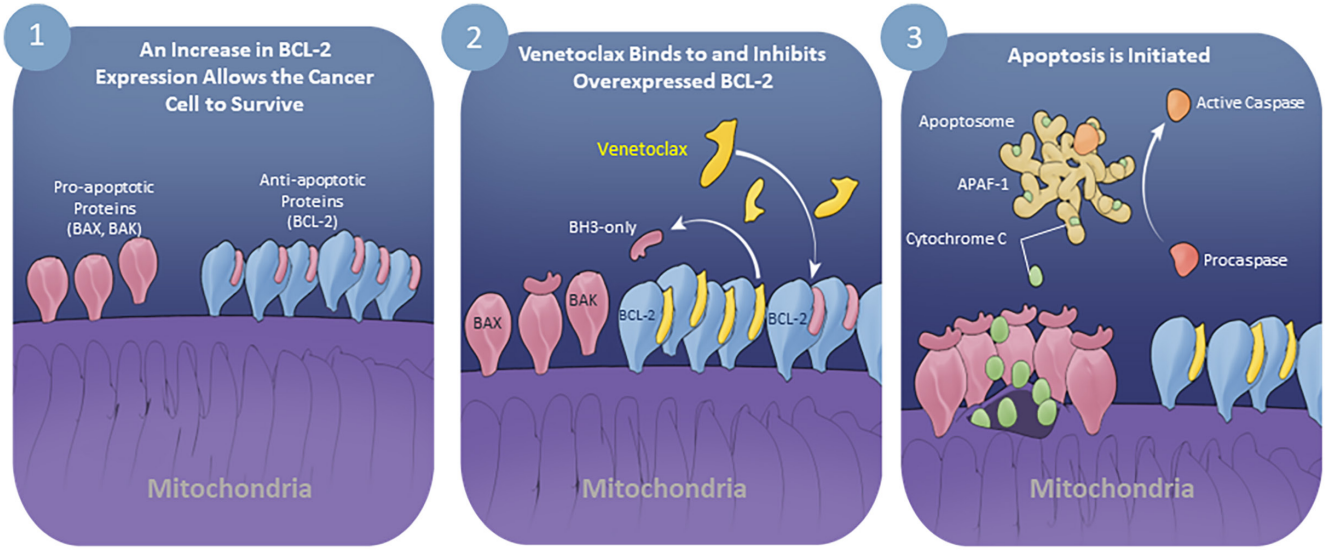

FIGURE 1 Mechanism of action of venetoclax.

During the time leading up to the discovery of venetoclax, the role of BCL-2 family members in tumor initiation and disease progression was well recognized[1]; however, the feasibility of disrupting protein–protein interactions as a druggable target had not been realized. In addition, the BH3 binding domain responsible for BCL-2 protein–protein interactions is highly similar to that of BCL-XL, which through early work on BCL-2 antagonism for the agents ABT-737 and navitoclax,[2–7] was known to be a key protein involved in platelet survival.[8] To overcome this challenge, navitoclax was re-engineered to form venetoclax, which has sub-nanomolar affinity for BCL-2 but much lower affinity for BCL-XL.[9] The development of venetoclax as an orally bioavailable, high-affinity inhibitor of a protein–protein interaction represented a breakthrough event in medicinal chemistry and apoptosis research that has opened the door for investigation in a wide range of hematological malignancies.

Venetoclax was initially approved in 2016 for the treatment of patients with relapsed/refractory chronic lymphocytic leukemia (CLL) with 17p deletion who had received at least one prior therapy.[10] Rituximab is an anti-CD20 monoclonal antibody that is commonly used in combination with chemotherapy in patients with CLL, and on the basis of results from the MURANO trial,[11] venetoclax is now approved for use in combination with rituximab in patients with CLL or small lymphocytic lymphoma (SLL) who have received at least 1 prior therapy and in combination with azacitidine, or decitabine, or low-dose cytarabine in adults 75 years or older, or who have comorbidities that prevent the use of intensive induction chemotherapy and are newly diagnosed with acute myeloid leukemia (AML). Venetoclax continues to have an active development program, which is being conducted in collaboration between AbbVie and Genentech, and is being developed for several other hematological malignancies, including multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL), and others. Venetoclax in combination with obinutuzumab was also approved as a first-line therapy for adult patients with CLL in the European Union (EU) and thus provides an alternative approach to first-line chemotherapy.[12]

Venetoclax was granted Breakthrough Therapy designation and accelerated approval by the FDA, and in the EU was given an Orphan Drug Designation for MM, diffuse B-cell lymphoma (DLBCL), and NHL. An important aspect of the venetoclax clinical development program was the robust clinical pharmacology and pharmacometrics approach that was used to characterize the properties of this first-in-class agent and support its accelerated approval. Below, we summarize the clinical pharmacokinetics and pharmacodynamics of venetoclax and highlight the drug–drug interactions (DDIs) and modeling aspects of the clinical pharmacology program.

PHYSICOCHEMICAL PROPERTIES AND ADME

Venetoclax has a high molecular weight (868 Da), with high hydrophobicity (logP = 8.1).[13] It has very poor aqueous solubility of 0.0023, 0.0004, 0.011, 0.010 mg/mL at pH 1, 7.4, fasted state simulated intestinal fluid, fed state simulated intestinal fluid, respectively. It also has low long-chain triglyceride (LCT) solubility of 2 mg/mL despite the high $\log D_{pH7.4}$ of 5.4. Venetoclax is an ionizable compound with two pKa values of physiological importance (3.4, acidic sulfonamide and 10.3, basic piperazine).

Given such challenging physicochemical properties, venetoclax is a biopharmaceutics classification system (BCS) class IV compound that required the use of an amorphous solid dispersion formulation within the currently marketed tablets.[14] This improved the bioavailability but resulted in a relatively large tablet (physical size of the 100 mg tablet >1 g) because of low tablet drug loading. The high lipophilicity of the molecule could explain its oral absorption via lymphatic transport.[13]

In a mass balance study of a single-dose radiolabeled [^{14}C]venetoclax,[15] 100% of the total radioactive dose was recovered, almost entirely in feces. Urinary excretion was minimal (<0.1%). The extent of absorption was estimated to be at least 65%. Venetoclax was cleared primarily by hepatic metabolism (~66%). Unchanged venetoclax represented 72.8% of total plasma radioactivity. Metabolite M27, formed by CYP3A4, was identified as a major metabolite. The absolute bioavailability of venetoclax was estimated at 5.4% under fasting conditions[16] in a phase I study of 12 females using a stable labeled (^{13}C-labeled) intravenous microdose. This would translate to an absolute bioavailability in clinical practice of 18%–28% under fed conditions. Venetoclax is highly bound to human plasma protein with unbound fraction in plasma <0.01 across a concentration range of 1–30 μM (0.87–26 μg/mL).[10] The mean blood-to-plasma ratio was 0.57. The apparent volume of distribution (Vd_{ss}/F) of venetoclax ranged from 256 to 321 L in patients.[10]

Central nervous system penetration

Venetoclax can cross the blood–brain barrier as demonstrated in an open-label, phase I study in 46 pediatric patients with relapsed/refractory (R/R) AML, acute lymphoblastic leukemia (ALL), or other hematological malignancies. Venetoclax concentrations in cerebrospinal fluid (CSF) were between <0.1 and 26 ng/mL with a mean concentration of 3.6 ng/mL.[17] The mean plasma-to-CSF ratio was 385 with a range of 44–1559, the mean is more than fourfold higher than the blood-to-brain ratio observed preclinically in mice, which suggests that other anatomical and/or physiological factors are involved in venetoclax disposition to the CSF.[17]

SINGLE- AND MULTIPLE-DOSE PHARMACOKINETICS

The clinical pharmacokinetics of venetoclax has been investigated in several oncology patient populations and healthy participants. Studies in healthy participants were only conducted in females because venetoclax may compromise male fertility based on findings in animals.[10]

Single-dose pharmacokinetics

The single-dose pharmacokinetics of venetoclax was evaluated in the first-in-human study in patients with R/R CLL/SLL in addition to healthy participants, a summary is provided in Table 1.[18] The majority of patients (50/56) in this assessment received a single 50 mg dose while healthy participants received doses between 50 and 400 mg.

Venetoclax plasma concentrations peaked at approximately 6–8 h after a single dose in patients (Figure 2). The mean maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve from time zero to infinity (AUC_{∞}) values at the highest dose of 400 mg were 2.35 μg/mL and 41.0 μg*h/mL, respectively. The venetoclax harmonic mean half-life ranged from 14.1 to 18.2 h at different doses.

Multiple-dose pharmacokinetics

The multiple-dose pharmacokinetics of 150–1200 mg venetoclax was also evaluated in the first-in-human study in a pooled dataset of 222 patients with CLL/SLL or NHL, a summary of multiple-dose pharmacokinetics in patients is provided in Table 2.[19] This dataset included the patients from the single-dose pharmacokinetic evaluation.

Venetoclax showed minimal accumulation with accumulation ratio of 0.8–1.6 over the 100–800 mg once daily dose range.[19] At venetoclax dosing of 400 mg once daily with a meal, the mean (±SD) steady-state C_{max} value was 2.10 ± 1.11 μg/mL, and the AUC_{0-24} value was 32.8 ± 16.9 μg*h/mL. The C_{max} and AUC values were dose-proportional in this study across the dose range of 300–900 mg ($p \geq 0.124$) and somewhat less than dose-proportional at the 1200 mg dose. Steady-state concentrations were achieved by week 6 or 7 of venetoclax dosing.[19]

INFLUENCE OF INTRINSIC FACTORS ON VENETOCLAX PHARMACOKINETICS

Age, body weight, and sex

The effect of demographic variables (age, body weight, and sex) on venetoclax pharmacokinetics was evaluated using population PK (popPK) models developed using plasma concentration data from 51 healthy participants and 455 patients with R/R CLL/SLL or NHL enrolled in 8 clinical studies.[30] Ages ranged from 25 to 88 years and the median age of the population was 65 years. The majority of participants were older than 60 years of age, consistent with the typical demographics of patients with CLL/SLL or NHL.

TABLE 1 Summary of venetoclax pharmacokinetic parameters after a single dose in healthy participants and patients (Mean [%CV]).

Dose (mg)	*n*	Meal type	T_{max}[a] (h)	C_{max} (μg/mL)	$t_{1/2}$[b] (h)	AUC[c] (μg*h/mL)
Relapsed/refractory chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) patients[18]						
20	3	Low fat	6.0 (6.0–6.0)	0.07 (28.6)	16.9 (16.1, 17.7)[d]	2.0 (1.9, 2.1)[d]
50	50	Low fat	6.0 (2.0–18.2)	0.26 (46.1)	19.0 (33.7)[e]	5.2 (57.7)[e]
100	1	Low fat	8.0	1.19	22.5	35.8
200	2	Low fat	7.0 (6.0–8.0)	1.15 (0.73,1.57)	40.9 (30.9, 50.9)	49.5 (23.1, 76.0)
Non-Hodgkin lymphoma (NHL) patients[19]						
50[19]	4	High fat	8.0 (6.0–8.0)	0.34 (35.3)	15.3 (8.5)	6.8 (48.5)[c]
100	3	High fat	4.0 (4.0–22.9)	0.50 (62)	18.2 (17.1, 19.3)[d]	9.7 (5.4, 14.1)[c,d]
200	13	High fat	6.0 (3.0–24.0)	1.05 (39)	16.0 (20.6)[f]	20.4 (28.9)[c,f]
300	9	High fat	8.0 (4.0–23.0)	1.81 (50.8)	16.7 (47.9)[g]	38.0 (50.5)[c,g]
400	3	High fat	6.9 (6.0–7.2)	1.43 (51.0)	14.1 (17.7)	30.2 (36.1)[c]
50	3	Fasting	4.0 (4.0–6.0)	0.16 (68.8)	–	2.2 (77.3)[c]
100	4	Fasting	5.0 (4.0–8.0)	0.24 (54.2)	–	3.5 (51.4)[c]
200	13	Fasting	8.0 (4.0–24.0)	0.22 (45.5)	–	3.3 (45.5)[c]
300	9	Fasting	4.0 (4.0–8.0)	0.58 (93.1)	–	7.6 (90.8)[c]
400	2	Fasting	16 (8.0–24.0)	0.38 (0.31,0.46)	–	6.1 (4.8, 7.4)[c]
20	15	Low fat	6.0 (4.0–8.0)	0.09 (33.3)	–	1.2 (41.7)[c]
100	6	Low fat	6.0 (3.0–24.0)	0.45 (55.6)	–	5.3 (47.2)[c]
300	4	Low fat	8.0 (4.0–8.0)	1.15 (57.4)	–	12.3 (81.3)[c]
400	9	Low fat	8.0 (4.0–24.0)	1.05 (37.1)	–	15.2 (32.2)[c]
50[20]	11	Low fat	8 (4–12)	0.212 (39.2)	19.1 (50.8)	4.32 (51.2) (AUC_t) 4.52 (52.7) (AUC_{inf})
Acute myeloid leukemia (AML) patients						
400[21]	11		8.0 (4.0–24.0)	2.34 (83.3)	–	38.5 (97) (AUC_{24})
Healthy volunteers						
200[22]	12	Moderate fat	8.0 (6.0–10.0)	1.12 (41.1)	19.3 (20.2)	14.7 (42.2)
100[23]	12	Moderate fat	6.0 (4.0–8.0)	0.763 (24)	19.6 (4.34)	9.46 (24)
400[24]	3	Moderate fat	8.0 (8.0–10.0)	2.35 (23.4)	14.5 (11)	41.0 (37.8)
100[25]	24	Fasting	4.0 (4.0–6.0)	0.17 (59)	16.1 (50.9)	2.48 (60)
100[25]	24	Low fat	6.0 (4.0–10.0)	0.54 (38.9	18.0 (31.1)	7.79 (41.1)
100[25]	24	High fat	6.0 (4.0–14.0)	0.84 (41.7)	19.1 (18.3)	11.34 (37.1)
50 (film-coated)[25]	15	Moderate fat	4.0 (4.0–8.0)	0.40 (27.5)	17.2 (53.2)	4.46 (33.4)

[a] T_{max} presented as median (range).

[b] Harmonic mean and pseudostandard deviation.

[c] $AUC = AUC_{\infty}$ on week 1 day −7 (0–72-h sampling) and AUC_{0-24} on week 1 day 1 (0–24-h sampling). For all healthy volunteers assessments, AUC reported is AUC_{inf}.

[d] $n = 2$.

[e] $n = 47$.

[f] $n = 12$.

[g] $n = 8$.

There was minimal to no relationship between individual participant estimated apparent oral clearance (CL/F) or apparent volume of distribution of the peripheral compartment after oral administration (V_2/F) and age. These findings were confirmed in a recent popPK analysis of over 3000 participants.[31] As venetoclax is predominantly metabolized by CYP3A, which has been shown to be unaffected by age in adults,[32,33] the lack of an age-related effect on venetoclax CL/F was expected.

Similarly, there was minimal to no relationship between individual participant estimated CL/F or V_2/F and bodyweight (range of 36.9–143.0 kg, median 78.6 kg),

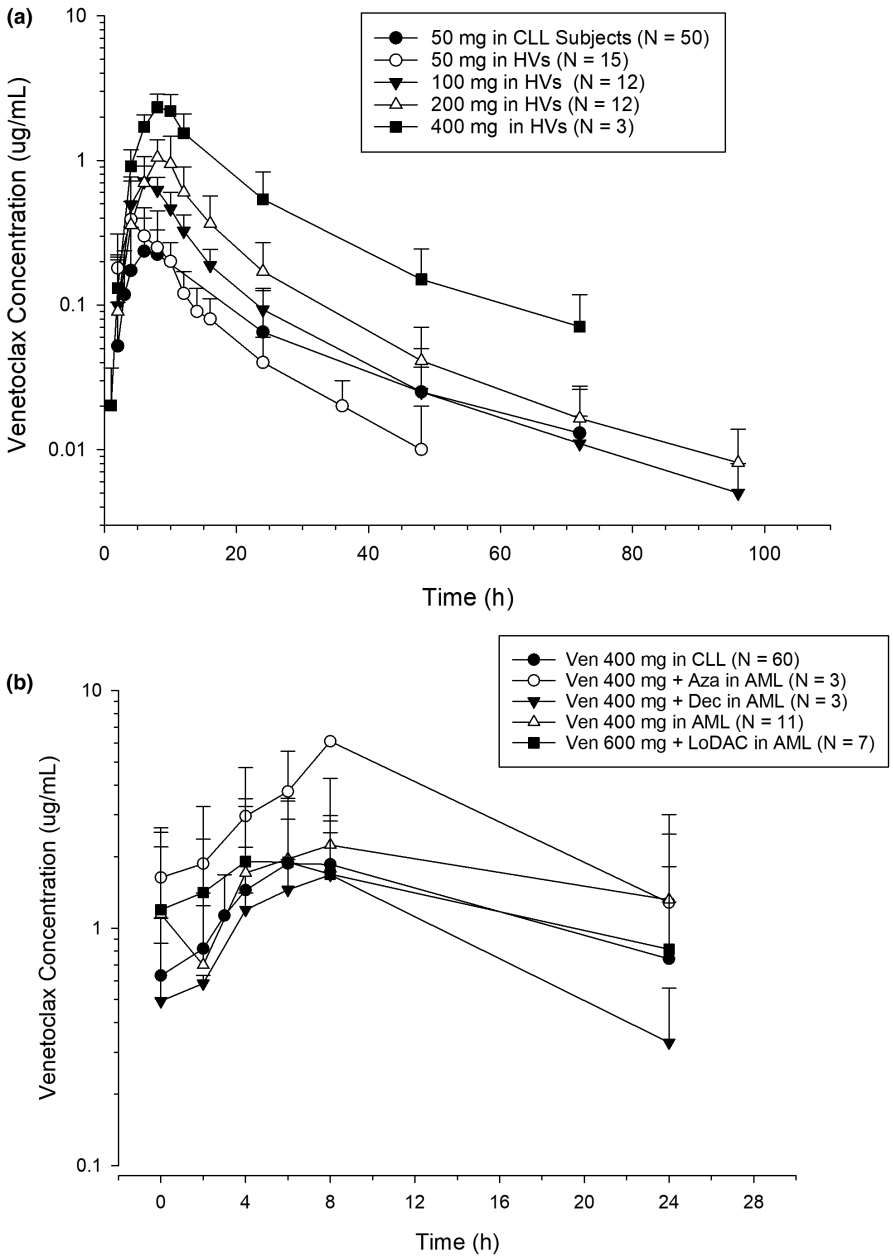

FIGURE 2 Venetoclax plasma concentration–time profiles after a single dose (a) and at steady-state (b). Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; CLL, chronic lymphocytic leukemia; Dec, decitabine; HVs, healthy volunteers; LoDAC, low dose cytarabine.

supporting a fixed-dosing regimen for venetoclax regardless of body weight. Venetoclax CL/F was similar between males and females; however, V_2/F was estimated to be 32% (95% CI = 23–41) lower in females. Sex did not have an effect on AUC, the main measure of exposure, suggesting that dose adjustments based on sex are not necessary despite the slightly lower V_2/F in females.

Pediatrics

Venetoclax pharmacokinetics have been evaluated in pediatrics, primarily with AML or ALL.[34–36] Utilizing the venetoclax popPK model, doses in pediatrics were selected based on weight (allometric scaling) for children ages ≥2 years old and based on weight and CYP3A ontogeny for children aged <2 years old using a CYP3A maturation function.[36] This dosing scheme achieved exposures in pediatric subgroups comparable to that expected in adults.

Race and ethnicity

Asian participants on average showed higher exposure than non-Asian participants. First-generation healthy Han Chinese participants residing in China had 94% higher mean C_{max} values and 66% higher mean AUC values than those observed historically in non-Asian participants receiving the same dose. However, the T_{max} and harmonic mean half-life values were similar and individual venetoclax concentrations in the majority of the 12 participants

TABLE 2 Venetoclax pharmacokinetic parameters after multiple doses in patients (Mean [%CV]).

Dose (mg)	*n*	T_{max}[a] (h)	C_{max} (μg/mL)	AUC_{24} (μg*h/mL)
Relapsed/refractory chronic lymphocytic leukemia (CLL)[18]				
100[i,u]	2	5.0 (4.0, 6.0)	1.58 (1.36, 1.80)	22.0 (20.2, 23.8)
150[i,u]	9	6.0 (3.0–23.5)	0.91 (27.5)	12.7 (37.8)[o]
200[i,u]	7	8.0 (4.0–8.0)	1.44 (44.4)	24.3 (44.4)[v]
300[i,u]	6	5.0 (3.0–8.0)	1.16 (52.6)	16.1 (50.3)[x]
400[i,u]	8	7.0 (4.0–11.2)	2.18 (49.5)	35.5 (57.2)[w]
600[i,u]	12	8.0 (4.0–24.0)	2.73 (54.2)	46.0 (52)[x]
800[i,u]	7	8.0 (6.0–8.0)	2.99 (36.8)	45.7 (31.5)
400[i,y]	60	6.0 (2.0–24.7)	2.07 (51.7)	31.8 (48.7)[z]
Non-Hodgkin lymphoma (NHL)				
50[b,26]	4	5 (4–6)	0.43 (91)	5.83 (86)
100[b,26]	4	7 (6–8)	0.70 (18)	10.0 (30)
100[c]	4	6 (4–8)	0.39 (74)	4.4 (43)
200[c]	3	8 (6–8)	0.82 (98)	11.5 (93)
400[c]	4	6.6 (6–7.5)	1.32 (68)	19.4 (65)
100[d]	2	6, 6	0.63 (0.60–0.66)[e]	7.79, 9.74[e]
200[d]	1	4	0.55	7.74
400[d]	6	6 (1.5–6.0)	1.55 (51)	20.3 (44)[f]
600[d]	7	8 (0–8)	1.83 (55)	29.0, 59
800[d]	3	8 (3–8)	3.23 (14)	39.5, 50.8[e,g]
1200[d]	7	6 (0–8)	5.26 (84)	89.9 (85)
200[h,i,27]	3	6.0 (4.0–6.0)	1.11 (27.9)	16.3 (28.2)
300[h,i]	5	6.0 (4.0–8.0)	1.94 (38.7)	31.5 (35.2)
400[h,i]	15	6.0 (4.0–8.0)	2.24 (58.5)	36.9 (61)[j]
600[h,i]	12	6.0 (2.2–8.0)	2.70 (65.9)	45.3 (81)
800[h,i]	6	6.0 (4.0–8.0)	3.96 (58.6)	53.0 (57.4)[k]
900[h,i]	6	7.7 (6.0–8.0)	2.93 (22.9)	45.2 (14.2)
1200[h,i]	10	8.0 (4.0–8.0)	4.60 (41.1)	72.1 (39.4)
1200[h,i]	22[l]	8.0 (4.0–24.0)	3.53 (48.7)	58.1 (47.2)[l]
1200[i,m]	32	8.0 (4.0–24.0)	3.87 (47)	62.8 (44.6)[n]
Combined Non-Hodgkin lymphoma or chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL)[19]				
100[e,i]	2	5.0 (4.0, 6.0)	1.58 (1.36, 1.80)	22 (20.2, 23.9)
150[i]	9	6.0 (3.0–23.5)	0.91 (27.5)	12.7 (37.8)[o]
200[i]	10	7.0 (4.0–8.0)	1.34 (42.5)	21.6 (44.9)[p]
300[i]	11	6.0 (3.0–8.0)	1.51 (50.3)	23.8 (51.3)[q]
400[i]	75	6.0 (2.0–24.7)	2.10 (52.9)	32.8 (51.5)[r]
600[i]	24	6.0 (2.2–24.0)	2.71 (59)	45.6 (67.1)[s]
800[i]	13	6.0 (4.0–8.0)	3.43 (51.3)	48.8 (44.1)[t]
900[i]	6	7.7 (6.0–8.0)	2.93 (22.9)	45.2 (14.2)
1200[i]	32	8.0 (4.0–24.0)	3.87 (47)	62.8 (44.6)[n]
Acute myeloid leukemia (AML)[28]				
800	13	6 (4–8)	3.74 (48.4)	61.6 (69.3)
Multiple myeloma (MM)[29]				
300	6	5 (2–8)	0.897 (66)	13.4 (64)

TABLE 2 (Continued)

Dose (mg)	*n*	T_{max}[a] (h)	C_{max} (μg/mL)	AUC_{24} (μg*h/mL)
600	5	8 (2.7–8)	2.56 (69)	38.2 (66)
900	4	6 (4–8)	1.850 (70)	26.3 (77)[aa]
1200	12	6.1 (4–8)	4.16 (37)	71.5 (50)[ab]

Abbreviation: ND, not determined.

[a]T_{max} presented as median (range).

[b]Arm A: venetoclax daily × 3 days per a 28-day cycle (3/28-day dosing).

[c]Arm B: venetoclax daily × 7 days per a 28-day cycle (7/28-day dosing).

[d]Arm C: venetoclax daily × 28 days per a 28-day cycle (28/28-day dosing).

[e]Presented as mean (individual values).

[f]$n = 5$.

[g]$n = 2$.

[h]Steady-state: Week 6/7 Day 1 data.

[i]Low-fat meal.

[j]$n = 13$.

[k]$n = 5$.

[l]$n = 20$.

[m]Steady-state combined data at 1200 mg from Week 6/7 Day 1 dose-escalation and safety-expansion cohorts.

[n]$n = 30$.

[o]$n = 8$.

[p]$n = 9$.

[q]$n = 10$.

[r]$n = 69$.

[s]$n = 23$.

[t]$n = 12$.

[u]Steady-state: combined data from Week 3 Day 1 (Cohort 1) and Week 6 Day 1 (subsequent cohorts) in the dose-escalation cohorts.

[v]$n = 6$.

[w]$n = 5$.

[x]$n = 11$.

[y]Steady-state combined data at 400 mg from Week 6/7 Day 1 dose escalation and safety expansion cohorts.

[z]$n = 56$.

[aa]$n = 3$.

[ab]$n = 9$.

in the study were within the range observed for non-Asian participants.[37]

For Japanese patients with R/R CLL/SLL ($n = 10$), the mean C_{max} and $AUC_{0–24}$ at the 400 mg dose were 2.08 μg/mL and 31.0 μg*h/mL, respectively, which is similar to that observed in non-Asian patients.[38] In patients with AML, Asian patients had 67% higher mean relative bioavailability than non-Asian patients; however, the range of exposures was similar between Asian and non-Asian patients.[39] A recent popPK analysis in more than 3000 participants estimated a 61% higher bioavailability in Asian participants.[31]

The higher venetoclax exposure in Asian participants is likely attributed to a difference in bioavailability rather than clearance of venetoclax. This is supported by similarity in terminal half-life between Asian and non-Asian participants.[37] The bioavailability difference could be the result of variability in CYP3A expression and differences in activity/expression of transport proteins in the gastrointestinal tract, because function-altering genetic variants in the CYP3A4 gene are extremely rare.

Despite the higher exposure in Asian participants, the dose typically used in non-Asian patients was deemed appropriate for Asian subjects based on the established venetoclax exposure–response relationship.[38,39]

Hepatic or renal impairment

In the hepatic impairment study,[40] venetoclax C_{max} and AUC values in participants with mild ($n = 6$) or moderate ($n = 6$) hepatic impairment were similar to those in participants with normal hepatic function ($n = 6$; central value ratios [90% CI] of 1.08 [0.73–1.6] and 1.26 [0.81–1.97], respectively, in mild hepatic impairment and 0.88 [0.58–1.33] and 1.40 [0.87–2.23], respectively, in moderate hepatic impairment). These results confirmed those obtained using popPK analysis.[30,31] The venetoclax C_{max}

value in participants with severe hepatic impairment ($n=5$) was also similar to that in participants with normal hepatic function (central value ratio [90% CI] of 0.95 [0.61–1.48]), but the AUC value was substantially higher (2.7 [1.63–4.49]) and the half-life was considerably longer (35 vs. 17 h). No significant adverse events were reported. A twofold reduction in dose is recommended for patients with severe hepatic impairment while no adjustment is needed for patients with mild or moderate hepatic impairment.[10]

Mild, moderate, and severe renal impairment were also found not to affect venetoclax pharmacokinetics.[31,39] The lack of relationship between venetoclax exposure and renal function is consistent with the observation that venetoclax is not eliminated in the urine.[15] No dose adjustment of venetoclax is recommended for patients with mild, moderate, or severe renal impairment.

A study to assess how end-stage renal disease (ESRD) might affect the pharmacokinetics of venetoclax was also conducted in participants with ESRD undergoing hemodialysis (eGFR < 15 mL/min).[41] There was no difference in plasma venetoclax concentrations between arterial and venous samples, suggesting that hemodialysis did not affect the pharmacokinetics of venetoclax. The fraction unbound (fu) of venetoclax increased approximately twofold for participants with ESRD compared with participants with normal renal function. The unbound C_{max} and AUC from time 0 to 48 h were comparable between ESRD and normal function groups indicating that no dose adjustment is needed for patients with renal insufficiency based on pharmacokinetics. The mean half-life in subjects with ESRD was also comparable to subjects with normal renal function demonstrating that ESRD did not affect the half-life of venetoclax.

Venetoclax PK across patient populations

A summary of venetoclax PK across patient populations is presented in Tables 1 and 2. Evaluation of venetoclax pharmacokinetics in different populations (healthy, $n=51$; CLL/SLL, $n=336$; and NHL, $n=118$) indicated no relationship between CL/F and population, and a 79% higher (95% CI = 35–123) V_2/F in patients with CLL/SLL or NHL compared with healthy participants.[30] This corresponds to a point-estimate of V_2/F of 118 L in healthy male participants and 202 L in CLL/SLL/NHL male patients. The larger V_2/F in patients with CLL/SLL and NHL is due to a lower C_{max} value, which is likely a reflection of less frequent pharmacokinetic sampling and therefore less precise estimates of C_{max} in the cancer patients that were studied compared with the healthy participants. Among cancer patients, there were no statistically significant differences ($p > 0.01$) in parameters between those with CLL/SLL versus those with NHL, indicating similar pharmacokinetics in both populations.[27,30] Likewise, among CLL patients, there were no differences in venetoclax pharmacokinetics between patients with the 17p deletion compared with the overall CLL population.[42] Thus, the same venetoclax doses can be used among these patient populations.

Evaluation of venetoclax pharmacokinetics in patients with MM and AML following multiple-dose administrations at 1200 mg (mean C_{max} [%CV] 3.74 μg/mL[43] and AUC_{0-24} 59 μg*h/mL[44]) and 800 mg (mean C_{max} 3.74 μg/mL[23] and AUC_{0-24} 61.6 μg*h/mL[45]), respectively, were consistent with those observed in patients with CLL or NHL.[28,29]

Influence of food on venetoclax bioavailability

The effect of food on venetoclax pharmacokinetics was evaluated in two separate studies, one in healthy participants and one in patients with NHL,[19,25] and in popPK analyses conducted across studies in healthy participants and patients.[30,31]

In the study in healthy participants, the median T_{max} of venetoclax was delayed by approximately 2 h when administered with food (T_{max} of 4 h without food and 6 h with food), and the C_{max} and AUC increased by approximately 3.4-fold when venetoclax was administered after a low-fat breakfast versus an overnight fast. A high-fat meal increased venetoclax C_{max} and AUC by approximately 50% relative to a low-fat meal.

Similar results were observed in the study in patients with NHL: C_{max} and AUC_{∞} values increased by 3.68-fold (90% CI = 3.01–4.50) and 4.42-fold (90% CI = 3.37–5.79), respectively, after a high-fat meal relative to fasting conditions and the AUC_{0-24} value increased by 4.27-fold (90% CI = 2.98–6.12) after a low-fat meal relative to fasting conditions.[19]

In the popPK analysis of pooled data from these two studies plus six additional studies in which the effect of food was assessed (7483 venetoclax plasma concentrations from a total of 505 patients and participants), the bioavailability of venetoclax was predicted to increase by 2.99-fold (95% CI = 2.94–3.05) after a low-fat meal, 3.71-fold (95% CI = 3.39–4.03) after any meal, without regard to fat content, 3.77-fold (95% CI = 3.15–4.39) after a moderate-fat meal, and 4.25-fold (95% CI = 4.15–4.36) after a high-fat meal when compared with the fasting state.[30] A lower food effect was observed with a venetoclax prodrug.[46]

Given the increase in bioavailability with food, venetoclax is recommended to be taken with food but without specific recommendations for fat content, to ensure adequate and consistent bioavailability.[10]

DRUG–DRUG INTERACTIONS

Venetoclax and its major metabolite in plasma, M27, are predominantly metabolized by CYP3A4 in vitro. In addition, both venetoclax and M27 are substrates for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Active uptake of venetoclax or M27 was not observed in cells overexpressing OATP1B1, OATP1B3, or OCT1.[10]

In vitro studies indicated that venetoclax is not an inhibitor or inducer for CYP enzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4) at clinically relevant concentrations. Additionally, venetoclax is not an inhibitor of most UGT (1A4, 1A6, 1A9, and 2B7) enzymes. Venetoclax is a weak inhibitor of UGT1A1 in vitro, but it is not predicted to cause clinically relevant inhibition of UGT1A1. Venetoclax is a P-gp and BCRP inhibitor and a weak OATP1B1 inhibitor in vitro. Based on in vitro data, venetoclax is not expected to inhibit OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2K at clinically relevant concentrations.[10]

Based on the in vitro data, dedicated clinical DDI studies were conducted to determine the effect of strong CYP3A, P-gp inhibitors and CYP3A inducers on venetoclax. The potential of venetoclax to impact CYP2C9 and P-gp substrates was also evaluated. In addition, the effect of various co-medications on venetoclax was evaluated using popPK.

Effect of CYP3A inhibitors on venetoclax

The potential for DDIs between venetoclax and CYP3A inhibitors was investigated in dedicated DDI studies with ketoconazole and posaconazole in patients with NHL or AML, respectively,[20,21] and ritonavir in healthy participants,[47] several analyses of patients who received CYP3A inhibitors during the course of venetoclax treatment,[19,30,31] as well as by physiologically-based pharmacokinetic (PBPK).[48] Coadministration of ketoconazole with venetoclax in a study in 11 patients resulted in a 2.3-fold increase in venetoclax C_{max} and a 6.4-fold increase in AUC_{∞} and a corresponding decrease in metabolite M27 C_{max} and AUC_t, consistent with inhibition of CYP3A-mediated metabolism of venetoclax.[20] Inhibition of P-gp and BCRP may have also contributed to the increase in venetoclax exposure, as ketoconazole has inhibitory effects on P-gp and BCRP and venetoclax is a P-gp and BCRP substrate.

Similarly, coadministration of posaconazole, a strong CYP3A inhibitor and commonly used antifungal agent, with venetoclax in a study in 12 patients resulted in a 53% increase in venetoclax C_{max} and a 76% increase in venetoclax AUC_{24} for a 50 mg dose of venetoclax and a 93% increase in C_{max} and 155% increase in AUC for a 100 mg dose of venetoclax, both of which were evaluated to determine the magnitude of dose reduction that would be needed in patients who require antifungal prophylaxis with posaconazole.[21] The effect of higher doses of posaconazole on venetoclax was assessed using a PBPK model and showed similar effects similar to the 300 mg once daily dose with delayed release tablets that were assessed in the clinic.[49]

In healthy participants, single doses of ritonavir 50 or 100 mg increased venetoclax C_{max} 2.3–2.4-fold and AUC 6.1- and 8.1-fold, respectively. Once daily doses of ritonavir 50 mg increased venetoclax C_{max} and AUC 2.4- and 7.9-fold, respectively, and completely inhibited the formation of the major venetoclax metabolite M27.[47]

In the popPK analysis, moderate and strong CYP3A inhibitors were estimated to decrease venetoclax CL/F by 19% (95% CI = 13–26) and 84% (95% CI = 82–86), respectively.[30] In addition, in an analysis of 31 patients who received moderate CYP3A inhibitors during venetoclax treatment in the first-in human study, venetoclax C_{max} and AUC_{0-24} values were 40%–60% higher in the presence of moderate CYP3A inhibitors but similar in the presence of weak CYP3A inhibitors.[19]

In a PBPK model, estimates of venetoclax exposures (AUC_{∞}) were 100%–385% higher in the presence of moderate CYP3A inhibitors and 480%–680% higher in the presence of strong CYP3A inhibitors.[48] In this model, the label recommended venetoclax dose reductions of at least 50% and 75% when coadministered with moderate and strong CYP3A inhibitors, respectively,[10] maintained venetoclax exposures between therapeutic and maximally achieved safe doses, similar to the result observed in a semi-mechanistic model.[43]

A common issue with patients with hematological malignancies is the need for multiple therapies to address comorbidities or side effects from cancer treatments. Using PBPK and popPK to investigate whether additional dose adjustments were needed in patients taking multiple strong CYP3A inhibitors concomitantly, it was found that venetoclax exposures were similar to that of just taking one strong CYP3A inhibitor.[31,50] This supports that the recommended dose adjustment of venetoclax when administered in combination with more than one strong CYP3A inhibitor should be identical to that prescribed for a single strong CYP3A inhibitor.[50]

Effect of CYP3A inducers on venetoclax

The effects of single and multiple doses of the strong CYP3A inducer, rifampin, on venetoclax pharmacokinetics were evaluated in a study in 10 healthy female participants of nonchildbearing potential.[22] Coadministration of multiple doses of rifampin to maximally induce CYP3A caused a 42% (90% CI = 31–52) decrease in venetoclax C_{max} and a 71% (90% CI = 66–76) decrease in venetoclax AUC_{∞}

compared with the C_{max} and AUC observed with venetoclax alone. A comparison of the single- and multiple-dose effects of rifampin to isolate the net effect of chronic CYP3A induction showed that CYP3A induction decreased venetoclax C_{max} by 72% and AUC by 84%. This result is consistent with CYP3A-mediated metabolism of venetoclax. During the studies included in the popPK analysis,[30] no patients or participants received moderate CYP3A inducers and only 1 participant received a strong CYP3A inducer during administration of venetoclax; therefore, CYP3A inducers were not able to be evaluated as covariates in the model. However, weak CYP3A inducers did not have a statistically significant effect on venetoclax CL/F in the model.[30] Results from simulations based on the PBPK model of CYP3A modulators demonstrated that both moderate and strong CYP3A inducers are estimated to decrease venetoclax exposures.[48] Collectively, the results support the recommendation that moderate and strong CYP3A inducers should be avoided during treatment with venetoclax.[10]

Effect of P-gp inhibitors on venetoclax

Venetoclax is also a substrate of P-gp, and the effect of azithromycin, a commonly used antibiotic in cancer patients, and an inhibitor of P-gp on the pharmacokinetics of venetoclax was evaluated in 12 healthy participants. Multiple doses of azithromycin reduced venetoclax C_{max} and AUC by 25% and 35% (Figure 3), but had no effect on venetoclax half-life or T_{max}.[23] The reason for the decrease is not clear as an increase in exposures would have been expected. These modest changes, however, suggest that venetoclax can be coadministered with drugs that inhibit P-gp, and that azithromycin can be used as an alternative to other antimicrobial agents in patients being treated with venetoclax. In contrast to the study with azithromycin, in a study evaluating the effects of coadministration of a single dose of rifampin, which has acute inhibitory effects on drug transporters, such as P-gp, venetoclax C_{max} was increased by 106% (90% CI = 73–145) and AUC_{∞} by 78% (90% CI = 50–111).[22] The increase in venetoclax exposures after a single dose of rifampin suggest that venetoclax is a P-gp substrate and coadministration with a P-gp inhibitor could increase venetoclax-associated toxicities.[10]

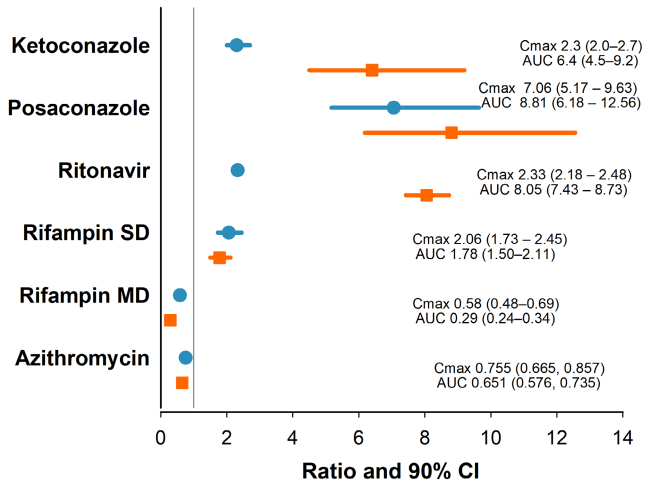

FIGURE 3 Forest plots of drugs that affect venetoclax C_{max} and AUC. Abbreviations: AUC, area under the plasma-concentration time curve; CI, confidence interval; C_{max}, maximum plasma concentration; MD, multiple dose; SD, single dose.

Gastric acid-reducing agents

Venetoclax has low solubility in aqueous solutions across a pH range of 1–12.9; thus, gastric acid-reducing agents (e.g., proton pump inhibitors, H2-receptor antagonists, antacids, etc.) were not expected to affect its bioavailability or rate of absorption. To confirm the lack of effect, use of gastric acid-reducing agents was evaluated in a popPK analysis of venetoclax pharmacokinetics in patients across 8 studies.[30] A total of 241 patients, or 47.7% of the analysis population, received acid-reducing agents at some point during a study. Coadministration of a gastric acid-reducing agent was tested as a covariate on the rate (Ka) and extent (F1) of venetoclax absorption in the stepwise model building procedure, but it did not reach statistical significance during the forward inclusion process. Therefore, coadministration of gastric acid-reducing agents does not appear to affect the rate or extent of venetoclax absorption.[30]

Venetoclax effect on other drugs

Warfarin

In vitro data suggested that venetoclax is a weak inhibitor of CYP2C9,[10] making it a potential perpetrator of drug interactions in patients taking concomitant medications during treatment with venetoclax. This is particularly true for cancer patients who develop coagulation disorders due to cancer, in whom treatment with CYP2C9 substrate warfarin is common. However, in a drug interaction study in healthy participants,[24] the C_{max} and AUC_{∞} values for R- and S-warfarin increased by only 18%–28% in the presence of venetoclax and the half-lives (80–88 h) remained unchanged. Given that similar increases in exposure were observed for both the R- and S- enantiomers, even though CYP2C9 is involved in the metabolism of only the S-enantiomer, and the half-life of both enantiomers

remained the same, the interaction does not appear to be mediated via CYP2C9. These results together with the fact that venetoclax is highly protein bound suggest that venetoclax is unlikely to cause clinically significant drug interactions with CYP2C9 substrates in cancer patients.

Digoxin

Venetoclax is an inhibitor of P-gp with an in vitro half-maximal inhibitory concentration (IC_{50}) of 0.67 mM.[44] The effect of a single dose of venetoclax on the pharmacokinetics of a single dose of digoxin, a P-gp probe substrate, was evaluated in 10 healthy participants.[51] Coadministration of digoxin and venetoclax increased digoxin C_{max} by 35% and AUC by 9%, with little effect on digoxin half-life, renal clearance, or the fraction of drug excreted unchanged in urine. Based on a semi-mechanistic model, administration of digoxin at least 2 h before administration of venetoclax will minimize drug interactions for this narrow therapeutic index P-gp substrate.[43]

Coadministration with anticancer agents

A number of studies have evaluated the potential for two-way drug interactions between venetoclax and other anticancer agents, including bendamustine,[26] bortezomib and dexamethasone,[52] rituximab,[53] azacitidine,[54] decitabine,[54] obinutuzumab,[55] cytarabine,[56] ibrutinib,[57] and navitoclax.[34] The pharmacokinetic parameters for venetoclax when administered with these anticancer agents are described in Table 3. With the exception of ibrutinib, neither venetoclax nor concomitant anticancer agents pharmacokinetics was affected upon coadministration.

Upon coadministration, venetoclax did not affect ibrutinib pharmacokinetics.[57] Venetoclax plasma levels, on the other hand, were higher when coadministered with ibrutinib than those reported for venetoclax monotherapy at 400 mg dose.[57] However, those levels were within the exposure range observed at other venetoclax doses. In addition, exposure-safety analyses showed no association between exposure and safety events.[57]

Potential two-way drug interactions between venetoclax and rituximab were evaluated in a phase Ib open-label study in 49 patients with relapsed CLL/SLL (NCT01682616).[53] Coadministration of venetoclax with rituximab had no statistically significant effect on venetoclax single-dose C_{max} or $AUC_{0–24}$. In a popPK analysis of the patients from this study plus four additional patients, rituximab was estimated to increase venetoclax CL/F by 21% (545 vs. 447 L/day) and decrease venetoclax dose-normalized mean $AUC_{0–24}$ by 14%.[30] These differences are not expected to be clinically meaningful. Likewise, different doses of venetoclax did not have any statistically significant effect on rituximab mean concentrations prior to and immediately after infusion at each combination therapy visit. Thus, no dose adjustment is needed for venetoclax when coadministered with rituximab.[10]

VENETOCLAX FORMULATIONS AND BIOPHARMACEUTICS

The effect of venetoclax tablet formulation (film-coated vs. uncoated) on venetoclax bioavailability was evaluated in 15 healthy participants in a single dose, crossover study, where in Period 1, the participants received venetoclax 50 mg uncoated tablet and in Period 2, the participants received venetoclax 50 mg film-coated tablet under nonfasting conditions.[25] The plasma concentrations of venetoclax were similar between the two formulations, and the T_{max} was 4 h for both formulations. The venetoclax film-coated tablet was found to be bioequivalent to the venetoclax uncoated tablet as the 90% CIs of the geometric mean ratios for C_{max} and AUC_{∞} were contained within the 0.80–1.25 range.

Three different strengths of venetoclax were used in clinical studies and have been commercialized – 10, 50 and 100 mg. The 10 and 50 mg are predominantly used during ramp-up. The three strengths were evaluated in a phase I bioavailability study and were bioequivalent at the 100 mg dose.[14]

The impact of crushing or grinding venetoclax tablets on its bioavailability was recently evaluated in a three-way, crossover study in 15 healthy adult females.[58] Crushed and finely ground venetoclax tablets had similar bioavailability to the intact venetoclax tablets as the venetoclax AUC for both regimens met the bioequivalence criteria. The slightly lower C_{max} observed with the altered regimens are not considered clinically significant. Therefore, crushing or grinding venetoclax tablets as alternative methods of administration is a viable option for patients who have difficulty swallowing whole venetoclax tablets.

A venetoclax powder formulation is under development for oral administration in pediatric patients at two different strengths. The two oral powder formulations (7.2% and 0.72% strengths) were bioequivalent to the currently marketed tablet with respect to AUC, but the lower bound of the 90% CI of C_{max} extended slightly below 0.80. The lower C_{max} is not expected to affect venetoclax efficacy and exposure–response analyses demonstrated the lack of significant relationships between venetoclax C_{max} and clinical efficacy in AML and CLL. Clinical responses to venetoclax have been shown to correlate with AUC_{ss} or C_{avg}, for which the oral powder formulation meets the

TABLE 3 Venetoclax pharmacokinetic parameters after multiple doses in combination with other cancer drugs in patients (Mean [%CV]).

Venetoclax dose (mg)	*n*	T_{max}[a] (h)	C_{max} (μg/mL)	AUC_{0-24} (μg*h/mL)
Non-Hodgkin lymphoma (NHL) patients: venetoclax with bendamustine[26]				
50[b]	4	6 (6–6)	0.29 (5)	3. 49 (3)
100[b]	4	6 (6–8)	0.66 (12)	7.70 (23)
100[c]	4	8 (6–8)	0.31 (41)	4.02 (43)
200[c]	4	8 (4–8)	0.52 (83)	7.50 (74)
400[c]	5	8 (4–8)	1.10 (44)	15.6 (42)[d]
Multiple Myeloma (MM) patients: venetoclax with bortezomib and dexamethasone[52]				
50	3	6.0 (4–6)	0.194 (53)	2.90 (60)
100	4[e]	6.0 (4–8)	0.508 (65)	6.1 (64)
200	5	8.0 (6–24)	0.733 (42)	12.9 (49)
300	7	6.0 (4–24)	1.07 (39)	14.3 (32)
400	5	6.0 (4–7)	2.04 (40)	31.6 (53)
500	7	6.0 (4–7.2)	1.29 (29)	19.7 (32)
600	5	6.0 (4–8)	1.11 (50)	15.6 (41)
800	3	7.1 (4–26.9)	2.85 (45)	45.0 (60)
1000	3	6.0 (6–8)	3.29 (54)	45.4 (52)
1200	9	6 (1.7–24)	4.40 (59)	68.6 (71)
Acute myeloid leukemia (AML) patients: venetoclax with azacitidine[54]				
400	3	6.6 (4.0–8.0)	1.77 (39)	25.7 (43)
800	11	6.6 (0–8.0)	2.77 (52)	44.2 (52)[f]
1200	3	6.8 (6.0–8.0)	2.79 (73)	58.6 (22.2, 95.1)[g]
AML patients: venetoclax with decitabine				
400	3	4 (3.3–8.0)	3.36 (73)	57.1 (70)
800	12	6 (4.0–8.0)	3.13 (56)	41.2 (58)[h]
1200	4	7.0 (4.0–8.0)	5.66 (48)	99.7 (73)[i]
AML patients: venetoclax with low-dose cytarabine[56]				
600	7	7.0 (3.5–8.0)	2.92 (73)	51.8 (71)[j]
800	10	6.6 (4.0–8.0)	2.36 (51)	35.4 (56)[k]
Chronic lymphocytic leukemia (CLL) patients: venetoclax with rituximab in relapsed CLL[53]				
200[53]	5	6.0 (6.0–8.0)	1.35 (66)	19.9 (62.3)[l]
300	8	7.5 (4.0–8.0)	1.60 (36.9)	24.1 (39.1)
400	5	6.0 (4.0–8.0)	1.93 (35.8)	32.7 (37.6)[l]
500	7	6.0 (6.0–8.0)	3.74 (45.7)	56.9 (65.7)[m]
600	7	4.0 (0.0–8.0)	3.16 (72.8)	55.1 (74.4)
CLL patients: venetoclax with obinutuzumab in relapsed CLL				
100	3	6.0 (4–8)	0.701 (64.8)	8.01 (60.5)[n]
200	7	6.0 (4–10)	0.841 (53.3)	8.42 (62.6)[n]
400	4	7.0 (4–8)	2.12 (32.1)	20.9 (31.8)[n]
CLL patients: venetoclax with bendamustine/rituximab in relapsed CLL				
100	2	7.0 (6–8)	0.492 (55)	3.95 (56.2)
200	2	5.0 (4–6)	0.858 (31.7)	7.21 (35.1)
400	5	6.0 (4–10)	1.09 (42.7)	12.2 (54.1)

[a] T_{max} presented as median (range).

[b] Arm A: venetoclax daily × 3 days per a 28-day cycle (3/28-day dosing).

[c] Arm B: venetoclax daily × 7 days per a 28-day cycle (7/28-day dosing).

[d] $n = 4$.

[e] One subject excluded due to at least two consecutive samples not reported.

[f] $n = 9$.

[g] $n = 2$; reported as mean (individual values).

[h] $n = 8$.

[i] $n = 3$.

[j] $n = 6$.

[k] $n = 9$.

[l] $n = 4$.

[m] $n = 6$.

[n] AUC_{0-24} was determined using the 0-h as the 24-h concentration value in Cycle 1 Day 3.

bioequivalence criteria.[14] The effect of different dosing vehicles (water, apple juice, apple sauce, and yogurt) on the bioavailability of the oral powder formulations at a dosage of 100 mg once daily was also evaluated in a phase I bioavailability study. Pharmacokinetic analysis showed that compared with the oral powder formulation in water, the C_{max}, AUC_t, and AUC_∞ of both oral powder formulations in apple juice, apple sauce, and yogurt met the bioequivalence criteria.[14]

PHARMACODYNAMICS AND EXPOSURE–RESPONSE ANALYSES

Several pharmacodynamic biomarkers, such as lymphocytes count, tumor size, M-protein, undetectable minimal residual disease (uMRD) rates and QT prolongation have been linked to venetoclax concentrations.[59–63] An average steady-state venetoclax concentration of 0.00863 μg/mL would decrease lymphocyte counts in patients with R/R CLL and NHL by 50%. The average steady-state venetoclax concentration that would decrease lymph nodes tumor size by 50% is 0.146 μg/mL; approximately 17-fold higher than that for circulating lymphocyte counts.

The relationship between venetoclax exposure and efficacy/safety outcomes have been extensively investigated in patients with CLL,[59,64,65] AML,[39,66] NHL,[67] DLBCL[45] and MM.[68–71] The relationship, and hence selected dose, can vary among the different malignancies and with different combinations. In general, the probability of achieving partial responses or better was close to maximum at the 400 mg dose. However, the probability of achieving "higher bar" responses such as complete response/remission can increase at doses higher than the 400 mg dose.

With regards to safety, the relationship between venetoclax exposures and adverse events rates are generally flat for venetoclax monotherapy.[65,72] On the other hand, when venetoclax is combined with other agents that can cause bone marrow suppression, venetoclax can potentiate this effect and a positive association is observed between venetoclax exposures and rates of adverse events such as neutropenia and infections (e.g., AML with HMA agents).[39,66,68] Venetoclax exposure–response relationships were not found to vary by age, sex, ethnicity, and liver or kidney function.

For R/R CLL patients, the relationship between venetoclax monotherapy dose and the probability of achieving partial response (PR) or complete remission (CR) is shown in Figure 4. This relationship reflects a significant association of venetoclax exposure and the probability of achieving PR or CR. On the other hand, there was a non-significant association between venetoclax exposure and the rates of serious treatment emergent adverse events (Figure 4). This analysis excludes the initial treatment period to account for the confounding effect of the lower venetoclax concentrations during the venetoclax dose ramp-up.[72]

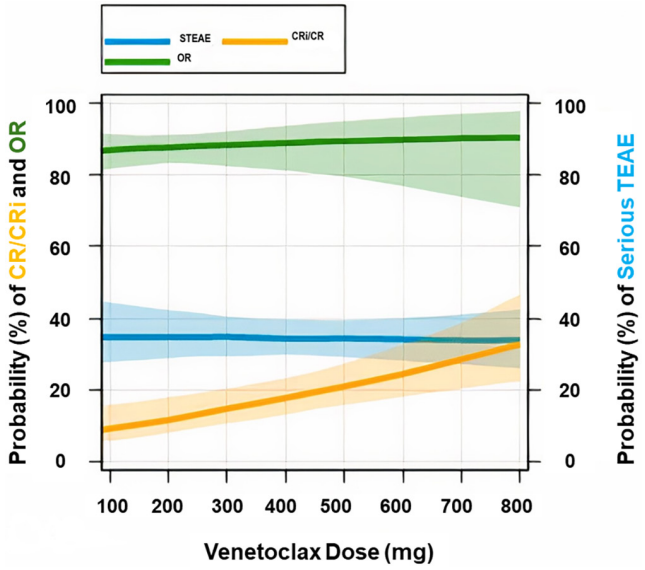

FIGURE 4 Probability of OR, CR or serious TEAEs versus venetoclax monotherapy dose in R/R CLL patients. Shaded regions indicate the predicted 95% CI, and points with vertical bars indicate the observed proportions with 95% binomial CI at the observed concentration quintiles for the indicated doses. CI, confidence interval; CR, complete remission; OR, objective response; TEAE, treatment emergent adverse events.

CONCLUSIONS

Venetoclax pharmacokinetics has been extensively characterized across multiple populations and with various concomitant medications required by patients with hematological malignancies after single- and multiple-dose administrations. The pharmacokinetic results support once daily dosing with food. Two factors have been found to require venetoclax dosing modifications, strong CYP3A inhibitors and severe hepatic impairment, thus prescribers should reference the prescribing information for appropriate modifications.

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CONFLICT OF INTEREST STATEMENT

AHS and RMM are employees of AbbVie and may hold AbbVie stock.

DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select "Home."

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