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APPLICATION NUMBER:

208573Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	208573
Submission Date(s):	10/29/2015
Brand Name: **Generic Name:**	VENCLEXTA® Venetoclax
Submission Type; Code: **PUDFA Date:**	Original NDA; 505(b)(1); NME Priority review 6/29/2016
Applicant:	AbbVie Inc.
Formulation; Strength(s):	Oral Tablets: 10 mg, 50 mg, 100 mg
Proposed Indication:	For the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, including those with 17p deletion (17p del)
OND Division:	Division of Hematology Products (DHP)
OCP Division:	Division of Clinical Pharmacology V (DCP V) Division of Pharmacometrics (DPM) Genomics and Targeted Therapy Group (GTTG)
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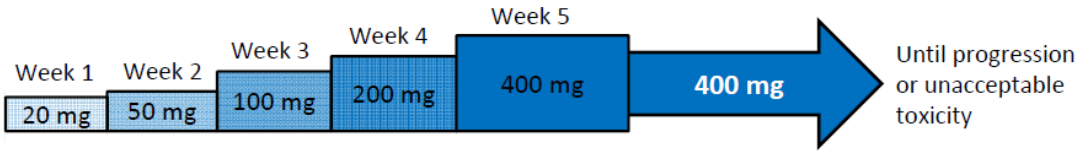
1 EXECUTIVE SUMMARY

Venetoclax is a small molecule inhibitor of anti-apoptotic protein B-cell lymphoma-2 (Bcl-2). The applicant is seeking approval of venetoclax for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, including those with 17p deletion. To manage the risk of tumor lysis syndrome (TLS) and achieve favorable benefit of venetoclax treatment, the applicant proposed the following ramp-up dosing regimen:



To support the proposed indication, the applicant conducted a single-arm, Phase 2 trial in patients with CLL (N=106) harboring 17p deletion with at least one prior therapy who were treated with the proposed venetoclax dosing regimen. The primary efficacy endpoint, overall response rate (ORR) assessed by an Independent Review Committee (IRC), was 80.2% with 95% CI of 71.3% to 87.3%. The most frequent serious adverse reactions (≥2%) were pneumonia, febrile neutropenia, pyrexia, anemia and tumor lysis syndrome (TLS). Overall, the efficacy and safety data indicate venetoclax has favorable benefit-risk properties in the Phase 2 trial population; as a result, the Agency is planning to approve venetoclax for the treatment of patients with CLL harboring 17p deletion who received at least one prior therapy.

The selected dose and dosing regimen is supported by exposure-response analyses based on pooled data from the pivotal Phase 2 trial and a key dose-finding Phase 1 trial. ORR appears to plateau at doses greater than 400 mg. The relationship between exposure and safety (grade 3/4 neutropenia and infection) is relatively flat and supports the selection of proposed dosing regimen.

After oral administration, venetoclax is metabolized by the liver and entirely excreted by the fecal route. Dose adjustment for patients with mild and moderate renal or hepatic impairment is not recommended based on population PK analyses; however, such patients should be closely monitored for toxicity during initiation and dose ramp-up phases due to a trend of increased adverse events in these patients.

Venetoclax is substrate of CYP3A4/5 and P-gp and inhibitor of P-gp. Concomitant use of strong CYP3A inhibitors should be avoided during dose ramp-up phase. For patients on stable dose of venetoclax who require treatment with concomitant moderate or strong CYP3A inhibitors, the dose of venetoclax should be reduced 2- and 4-fold, respectively. Concomitant use of strong and moderate inducers of CYP3A, P-gp inhibitors and narrow therapeutic index P-gp substrates should also be avoided.

1.1 Recommendation

NDA 208573 is acceptable for approval from a clinical pharmacology perspective provided that the applicant and the FDA come to an agreement regarding the labeling language.

Decision	Acceptable to OCP?			Comment
Overall	Yes ☒	No ☐	NA ☐	Approvable as a monotherapy based on ORR in patients with CLL harboring 17p deletion who received at least one prior therapy
Evidence of Effectiveness	Yes ☒	No ☐	NA ☐	1 pivotal Phase 2 trial and 1 key Phase 1 trial
Proposed dose for general population	Yes ☒	No ☐	NA ☐	400 mg daily following dose ramp-up schedule with initial dose of 20 mg
Proposed dose selection for others	Yes ☒	No ☐	NA ☐	No dose adjustment is recommended for patients with mild and moderate renal or hepatic impairment
Pivotal BE	Yes ☒	No ☐	NA ☐	Two relative BA trials were conducted, PK exposure were comparable between to-be-marketed formulation and formulation used in early studies.
Labeling	Yes ☐	No ☒	NA ☐	Revised labeling is proposed

1.2 Post Marketing Requirements

The applicant is required to conduct the following post-marketing requirement trials:

1. Conduct a pharmacokinetic trial to determine the appropriate dose of venetoclax in patients with varying degree of hepatic impairment in accordance with the FDA Guidance for Industry entitled "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf . Submit the final study report as PMR under the NDA.

2. Conduct a pharmacokinetic trial to evaluate the effect of venetoclax co-administration on pharmacokinetics of a probe substrate of P-gp to determine dose recommendations for co-administration of narrow therapeutic index P-gp substrates with venetoclax in accordance with the FDA Guidance for Industry entitled "*Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf . Submit the final study report as PMR under the NDA.

1.3 Post Marketing Commitment

None.

Signatures:

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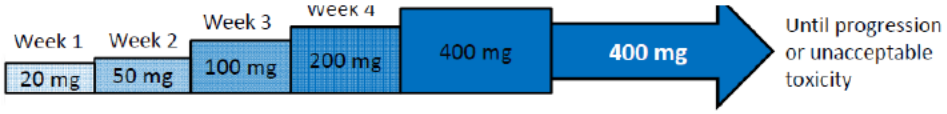
GTTG Reviewer – **S Dorff**; GTTG TL – **R Charlab Orbach**
DDD – **B Booth**; DD – **A Rahman**

1.4 Summary of Important Clinical Pharmacology Findings

Venetoclax is an orally bioavailable, small molecule inhibitor of anti-apoptotic protein B-cell lymphoma-2 (Bcl-2). The proposed indication of venetoclax is for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, including those with 17p deletion (17p del).

The proposed dosing regimen of venetoclax is shown in **Figure 1**. Venetoclax tablets should be taken orally once daily with a meal and water.

Figure 1: Venetoclax ramp-up dosing regimen in patients with CLL



Dose Selection

In the first-in-human Phase 1 trial M12-175, to manage the risk of TLS, the applicant titrated venetoclax dosing regimen utilizing a ramp-up dosing schedule along with TLS management and prophylaxis (receiving uric acid reducing agents and hydration). A total of 56 patients with R/R CLL with or without 17p del were treated with venetoclax at 6 dose levels from 150 to 1200 mg QD following the dose ramp-up schedule in the dose escalation cohorts. Based on preliminary efficacy, PK and safety results from the dose escalation cohorts, the sponsor selected 400 mg QD regimen for the safety expansion cohorts (N=60) since the ORR plateaued at doses greater than 400 mg. (b) (4)

(b) (4)

As shown in **Table 1**, there was higher ORR at dose of 400 mg compared to lower doses. Dose higher than 400 mg did not show higher ORR. The results of complete remission (CR) rates suggested an increase of CR at doses higher than 400 mg. In addition, treatment-emergent

adverse event (TEAE) rates did not increase with increasing dose within the tested dose range of 150 to 1200 mg.

Based on the safety and efficacy results of Phase 1 trial M12-175, the applicant evaluated the efficacy and safety of venetoclax at 400 mg QD following ramp-up schedule in 106 patients with R/R CLL harboring 17p del who were enrolled in the main cohort of pivotal Phase 2 trial (M13-982). The primary efficacy endpoint of ORR as assessed by IRC was 80.2% and the investigator assessed ORR was 74.5%, consistent with the efficacy results observed in Phase 1 trial M12-175. In pivotal trial M13-982, the IRC assessed complete remission (CR) rate was 7.5% and the investigator assessed CR rate was 16.0%.

Exposure – Response (E-R) relationship
Exposure-response relationship for ORR was generally flat beyond 400 mg dose, indicating that increase in venetoclax exposure will not result in additional increase of ORR. For CR, there was a trend showing increasing probability of CR with higher exposure, suggesting potential increase in remission might be gained by dose higher than 400 mg. However, the exposure-response analyses (dose ranges from 150 to 1200 mg) were based on the INV data, while the IRC data for CR was only available for 400 mg. Considering the observed discrepancy between the IRC and INV assessed CR rates in the pivotal Phase 2 trial M13-982, the potential increase in CR with higher doses is inconclusive. In addition, based on discussion with the clinical review team, ORR is the most relevant efficacy endpoint for the indicated population (CLL patients with 17p del), thus making the proposed 400 mg dose acceptable. No apparent exposure-response relationship was identified for adverse events, including grade 3/4 infection and grade 3/4 neutropenia.

ADME
Venetoclax PK is linear over the dose range of 150 to 800 mg. Exposure of venetoclax increased by 3- to 5-fold when it was administered with low- or high-fat meals. After oral administration, the median time to reach C_{max} was 5 to 8 hours. Venetoclax is highly bound to plasma protein (f_{ub}<0.01) independent of concentrations. *In vitro* studies indicated that venetoclax is predominantly metabolized by CYP3A4/5 to form a major metabolite M27, which is considered pharmacologically inactive. The half-life of venetoclax is estimated to be 26 hours. In the human mass balance study M13-363, approximately 100% of administered radioactive dose was recovered in the feces, with 21% as unchanged venetoclax.

Hepatic and Renal Impairment
The applicant has not conducted specific studies to evaluate the effect of organ (hepatic and renal) impairment on venetoclax PK.

Based on the population PK (popPK) analyses, no dose-adjustment is needed for patients with mild or moderate hepatic or renal impairment. However, due to the trend of increased incidence of TEAEs in these patients, tighter safety monitoring and dose-modification based on toxicity during the dose ramp-up period may be needed.

The recommended dose for patients with severe hepatic or renal impairment has not been determined.

Drug-Drug Interactions (DDIs)

Venetoclax is predominantly metabolized by CYP3A4/5, and a substrate of efflux transporters P-gp and BCRP. Co-administration of ketoconazole (a strong CYP3A, P-gp and BCRP inhibitor) increased venetoclax C_{max} and AUC_{∞} by 2.3- and 6.4-fold, respectively. Co-administration of moderate CYP3A4/5 inhibitors showed a smaller effect on venetoclax exposure (40 to 60% increase in C_{max} and AUC_{0-24}). Venetoclax exposure also increased (C_{max} ↑ 106%, AUC_{∞} ↑ 78%) after co-administration of single dose of rifampin, presumably due to the inhibition of P-gp by rifampin. However, venetoclax C_{max} and AUC_{∞} were reduced by 42% and 71%, respectively, after multiple doses of rifampin due to the predominant effect of CYP3A4/5 induction. Based on these results, the applicant's proposed dose recommendations for patients taking CYP3A modulators are considered acceptable and shown in **Table 2**. In addition, co-administration of P-gp inhibitors should also be avoided during the ramp-up phase and requires 2-fold reduction of venetoclax dose during the stable dose phase.

Table 2: Dose recommendations for patients taking CYP3A modulators

(b) (4)

As a perpetrator, venetoclax increased CYP2C9 substrate warfarin exposure by 18% for C_{max} and 28% for AUC_{∞}. As an inhibitor of P-gp, venetoclax also have DDI potential with P-gp substrates in the gut at therapeutic dose levels.

Cardiac Electrophysiology

Venetoclax had no large effect on QTc interval (i.e., > 20 ms) and there was no relationship between venetoclax exposure and change in QTc interval.

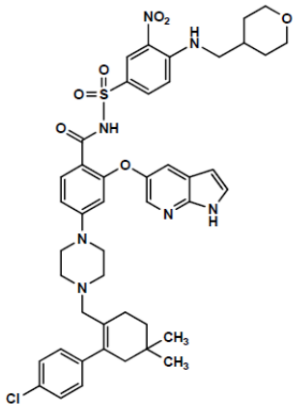
2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Venetoclax has the following physical and chemical characteristics, and chemical structure shown in **Figure 2**.

Figure 2: Venetoclax Structure



Source: Applicant's Quality Overall Summary (Drug Substance)

Established Name:	Venetoclax
Molecular Weight:	868.44 Da (b) (4)
Molecular Formula:	$C_{45}H_{50}ClN_7O_7S$
Chemical Name:	4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino] phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide
Description:	Light yellow to (b) (4) dark yellow powder
Chirality:	NA
Solubility:	As a function of pH in aqueous buffer, aqueous solubility is <0.0042 µg/mL at pH 7.4
Log P:	5.5
pKa-Values:	3.4 and 10.3

The solubility of venetoclax was measured in various media and the data are presented in **Table 3**.

Table 3: Solubility of venetoclax in various media

Solvent	Solubility (mg/mL)	Descriptive Term (Per USP)
1% Sodium dodecyl sulfate (w/v aq)	2.79	Slightly Soluble
1% polysorbate 80 (w/v aq)	0.30	Very Slightly Soluble
1% polysorbate 20 (w/v aq)	0.08 [a]	Practically Insoluble
1% Poloxamer 124 (w/v aq)	< 0.0006	Practically Insoluble
Vinylpyrrolidone dimer	> 200	Very Soluble
Methanol	0.44	Very Slightly Soluble
Methylene chloride	20 to 25	Very Soluble
Ethyl Acetate	< 8.8	Sparingly Soluble

a. A different residual x-ray powder diffraction pattern was observed for only polysorbate 20.

The solubility of venetoclax drug substance in aqueous buffers as a function of pH is shown in **Table 4**.

Table 4: Solubility of venetoclax as a function of pH at 25 °C

Final pH after dissolution	Solubility (µg/mL)
	(b) (4)

Venetoclax is available as film-coated tablets (10, 50, or 100 mg per tablet).

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Venetoclax is a small-molecule inhibitor of anti-apoptotic protein Bcl-2. Overexpression of Bcl-2 has been demonstrated in various hematologic and solid tumor malignancies. Venetoclax helps to restore the process of apoptosis by binding directly to the Bcl-2 protein, displacing pro-apoptotic proteins like BIM, triggering mitochondrial outer membrane permeabilization and the activation of caspases.

The applicant's proposed indication is for the treatment of patients with CLL who have received at least one prior therapy, including those with 17p del. However, the Agency is planning to limit the indication to patients with CLL harboring 17p del who have received at least one prior therapy. The Agency's planned indication is reflective of the Phase 2 trial population.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Initiating therapy with venetoclax at 20 mg once daily for 7 days, followed by a weekly ramp-up dosing schedule (through 50, 100 and 200 mg) to the recommended daily dose of 400 mg by week 5, then 400 mg QD until disease progression or unacceptable toxicity is observed. Venetoclax tablets should be taken orally once daily with a meal and water. Do not chew, crush, or break tablets.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A list of relevant clinical pharmacology and clinical studies included in venetoclax NDA application is shown in **Table 5**.

Table 5: Summary of venetoclax clinical pharmacology and clinical studies

Study	Assessment	Design	Population	Dosing Regimen
Clinical Pharmacology Studies				
M13-363	Mass balance/ADME	Phase 1, open-label	Healthy female subjects (N=4)	**[^{14}C] venetoclax**: single oral dose 200 mg active (100 μCi) solution, within 30 min after a moderate-fat breakfast
M14-253	Relative bioavailability (coated vs. uncoated tablets)	Phase 1, open-label, randomized, 2-period crossover study	Healthy female subjects (N=15)	-**Regimen** A: Single oral dose of venetoclax 50 mg tablet (uncoated) -**Regimen B:** Single oral dose of venetoclax 50 mg tablet (coated) Both were administered ~30 min after a standard breakfast
M15-101	Relative bioavailability (manufacturing site change) and food effect	Phase 1, open-label, randomized, 4-period crossover study	Healthy female subjects (N=24)	-**Regimen** A: Single oral dose of venetoclax 100 mg tablet (manufactured in Ireland) under fasting condition -**Regimen B:** Single oral dose of venetoclax 100 mg tablet (manufactured in Ireland) administered ~30 min after a low-fat meal -**Regimen C:** Single oral dose of venetoclax 100 mg tablet (manufactured in Ireland) administered ~30 min after a high-fat meal -**Regimen D:** Single oral dose of venetoclax 100 mg tablet (manufactured in USA) administered ~30 min after a low-fat meal
M13-364	DDI (ketoconazole)	Phase 1, open-label	Patients with R/R NHL (N=15)	**Venetoclax:** single 50 mg oral dose on Day 1 and Day 8 with a standard low-fat meal **Ketoconazole:** oral 400 mg QD from Days 5 to 11
M14-497	DDI (Rifampin)	Phase 1, open-label, 2-period	Healthy female subjects (N=12)	-**Period 1**: Venetoclax: Single oral dose of 200 mg ~ 30 min after a moderate-fat meal on Day 1

				-**Period 2 (after 8 days wash-out)**: Venetoclax: Single oral dose of 200 mg ~ 30 min after a moderate-fat meal on Day 1 and Day 14 Rifampin: 600 mg single dose on Day 1, and 600 mg QD dose from Days 5 to 17
M15-065	DDI (Warfarin)	Phase 1, open-label, 2-period	Healthy female subjects (N=8)	-**Period 1**: Warfarin: Single oral dose of 5 mg ~ 30 min after a moderate-fat meal on Day 1 -**Period 2 (after 14 days wash-out)**: Warfarin: Single oral dose of 5 mg ~ 30 min after a moderate-fat meal on Day 1 Venetoclax: Single oral dose of 400 mg ~ 30 min after a moderate-fat meal on Day 1 (at the same time as warfarin dose)
Clinical Studies				
M12-175	First-in-human, safety, tolerability (MTD), PK and efficacy	Phase 1, open-label, two arms	Patients with R/R CLL/SLL (N=116) and NHL (N=106)	-**Arm A in R/R CLL/SLL**: 1. Dose-escalation cohorts: Venetoclax alone: initial single dose 50 mg, followed by dose ramp-up schedule to 150, 200, 300, 400, 600, 800 and 1200 mg cohorts 2. Safety expansion cohort: Venetoclax alone: 400 mg daily following dose ramp-up schedule with initial dose of 20 mg -**Arm B in NHL**: 1. Dose-escalation cohorts: Venetoclax alone: initial single dose 20-400 mg, then dose ramp-up to 200 to 1200 mg daily 2. Safety expansion cohort: Venetoclax alone: 1200 mg daily following dose ramp-up schedule with initial dose of 400 mg
M13-982	Pivotal study, efficacy, safety and PK	Phase 2, open-label, single arm	Patients with CLL harboring 17p del (N=144)	-**Main cohort (N=106)**: Venetoclax alone: 400 mg daily following dose ramp-up schedule with initial dose of 20 mg -**Safety expansion cohort (N=38)**: Venetoclax dosing: same as above
M14-032	Efficacy, safety and PK	Phase 2, open-label, non-randomized, two arms	Patients with CLL relapsed after or refractory to treatment with B-cell receptor inhibitors (N=28)	-**Arm A: patients R/R after ibrutinib (N=22)**: Venetoclax alone: 400 mg daily following dose ramp-up schedule with initial dose of 20 mg - **Arm B: patients R/R after idelalisib (N=6)**: Venetoclax dosing: same as above
M13-365	Efficacy, safety, tolerability (MTD) and PK in combination with rituximab	Phase 1b, open-label, two stages	Patients with R/R CLL/SLL (N=49)	- **Dose-escalation cohorts (N=41)**: Venetoclax: targeting 200, 300, 400, 500 or 600 mg daily following dose ramp-up schedule with initial dose of 20 mg

				Rituximab: After a week at the designated cohort dose of venetoclax, 375 mg/m^2 on Month 1/Day 1 and 500 mg/m^2 from Month 2 to Month 6 -**Safety expansion cohort (N=8)**: Venetoclax: 400 mg daily following dose ramp-up schedule with initial dose of 20 mg Rituximab: same as above
GP28331	Safety, tolerability (MTD), PK and efficacy in combination with obinutuzumab	Phase 1b, open-label, two stages	Patients with R/R CLL or previously untreated CLL	-**Dose-escalation cohorts (N=20)**: Venetoclax: targeting 100, 200, or 400 mg daily following dose ramp-up schedule with initial dose of 20 mg Obinutuzumab: given based on different schedules shown blow, IV infusion 100 mg on Cycle 1/Day1, 900 mg on Cycle 1/Day2, 1000 mg on Cycle 1/Day 8 and Cycle 1/Day 18, then 1000 mg on Day 1 of each subsequent cycle (28 days) up to 6 cycles • Dosing Schedule A: venetoclax introduced before obinutuzumab, initiated first and provide recommendation for schedule B • Dosing Schedule B: venetoclax introduced after obinutuzumab -**Safety expansion cohort (N=0)**: Not available
GO28440	Safety, tolerability (MTD), PK and efficacy in combination with bendamustine/rituximab (BR)	Phase 1b, open-label, two stages	Patients with R/R CLL or previously untreated CLL	-**Dose-escalation cohorts (N=19)**: Venetoclax: targeting 100, 200, 400 or 600 mg daily following dose ramp-up schedule with initial dose of 20 mg Bendamustine/rituximab (BR): given based on different schedules shown blow. Bendamustine: 70 mg/m^2 in R/R patients and 90 mg/m^2 in untreated patients, given on Days 1 and 2 of a 28-cycle • Dosing Schedule A: venetoclax introduced before BR, initiated first and provide recommendation for schedule B • Dosing Schedule B: venetoclax introduced after BR -**Safety expansion cohort (N=0)**: Not available

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint in the pivotal Phase 2 study M13-982 was overall response rate (ORR), defined as the proportion of subjects with an overall response (CR + CRi + nPR + PR) per the NCI-WG guidelines as assessed by the IRC in patients enrolled in the main cohort.

Additional secondary efficacy endpoints measured in this study included complete response (CR) rate, partial response (PR) rate, duration of response (DOR), progress-free survival (PFS), event-free survival (EFS), time to progression (TTP), time to 50% reduction in ALC, overall survival (OS) and percent of patients who moved on to stem cell transplant. Minimal residual disease (MRD) response rate was evaluated as an exploratory endpoint.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, venetoclax is the major active moiety in the plasma after oral administration and it was appropriately identified and measured to assess PK and exposure-response relationship. The major metabolite, M27, is not considered pharmacologically active because its inhibitory activity against Bcl-2 was at least 58-fold lower than venetoclax *in vitro*.

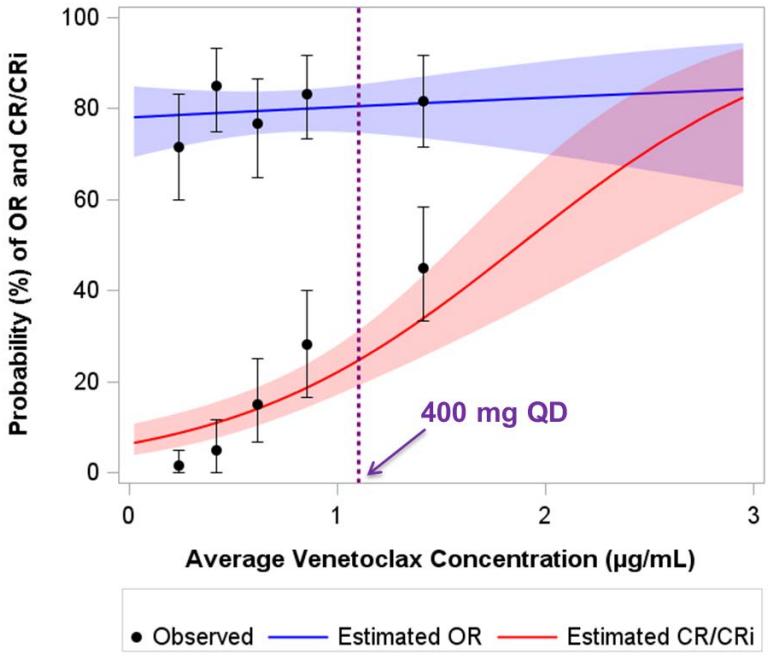
2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The exposure-response relationship for ORR and CR was conducted using logistic regression analysis, based on pooled data from 2 studies (studies M13-982, M12-175). The exposure metric was average venetoclax concentration up to the first time of the response (e.g., ORR or CR), calculated as the cumulative AUC (derived from the final popPK model) across dosing intervals up to the first time of the respective response, divided by the time (i.e., from the first dose administration until the time of the response). The average concentration across the entire treatment period was utilized for subjects who did not achieve the response under consideration. See Pharmacometrics Review for more details.

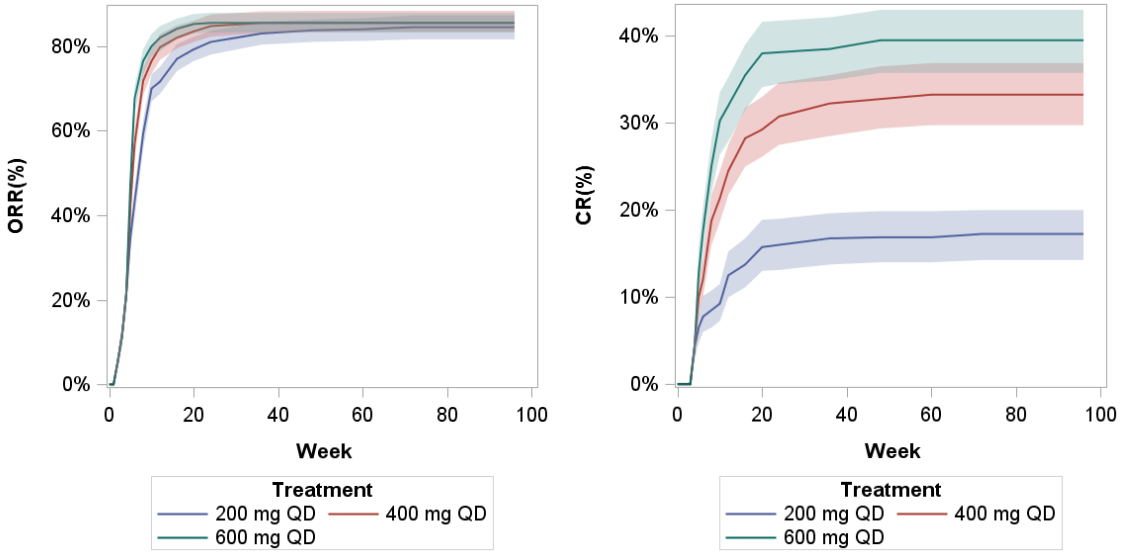
The analysis results were generally consistent with the observed dose-response in study M12-175. No evident exposure-response relationship was identified for probability of ORR (**Figure 3**). A dose of 400 mg QD, associated with an average concentration of 1.10 μg/mL, is in the plateau part of the exposure-response curve. There appears to be a clear trend for CR, showing increasing probability of CR with higher exposure of venetoclax, which suggests potential benefit in remission might be gained by administering doses higher than 400 mg. This trend is consistent with or without adjusting for baseline lymphocytes and tumor size, which were identified as significant covariates for CR based on multivariate analysis. In addition, 17p del mutation status was not identified as a significant covariate for ORR or CR, thus these relationships are not expected to be different between patients with 17p del and those without 17p del, given similar response rates in these two patient populations.

Figure 3: Increase in probability of achieving ORR and CR with increasing venetoclax exposure (Study M12-175 and M13-982)



A population PK/PD model for lymphocytes and tumor size response was developed by applicant to further refine the exposure-response relationship. The final population PK/PD models were subsequently used to simulate ORR and CR at various dosing regimens. Simulated ORR and CR time profiles by the designated dosage regimen (including ramp-up doses) of 200, 400, and 600 mg QD are shown in **Figure 4**.

Figure 4: Time courses of simulated ORR (left) and CR (right) on the 200, 400 and 600 mg QD target dosing regimens



Note: ORR was defined as a decrease in lymphocytes of ≥ 50% from baseline and a decrease in tumor size of ≥ 50%; CR was defined as lymphocyte levels below 4000/µL and tumor size smaller than 1.5 cm.

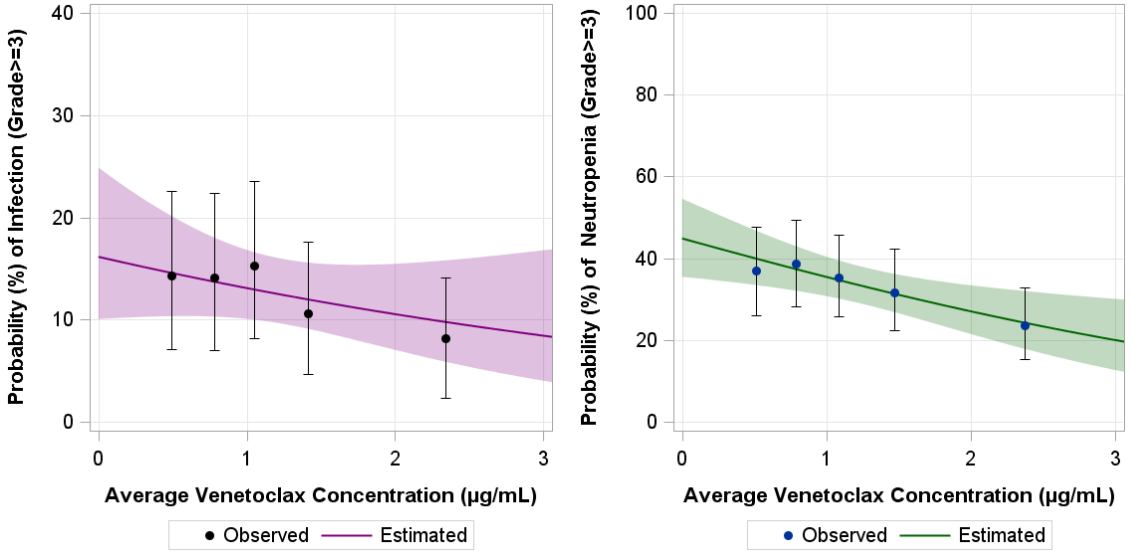
Simulation results indicated that by 6 months of venetoclax treatment, the ORR reached 80.9%, 84.8% and 85.5% at the 200, 400 and 600 mg dosage regimens, respectively. The model predicted a separation in ORR between the 400 mg and 600 mg doses at early time points; however, the difference diminished after 24 weeks of treatment. The CR at end of 6 months was 17.2%, 33.2%, 39.5% for the 200, 400 and 600 mg dosage regimens, with 6.3% difference between 400 and 600 mg dosing regimen.

Overall, both the logistic regression analyses and the PK/PD model simulations suggested minimal differences between the 400 or 600 mg QD dose in ORR, while a potential increase in CR with the higher dose. However, it was noted that IRC data for CR was only available for 400 mg, and the exposure-response analyses (dose ranges from 150 to 1200 mg) were based on INV assessment data. Considering the observed discrepancy between the IRC assessed CR rate (7.5%) and the INV assessed CR rate (16.0%) in the pivotal Phase 2 study M13-982, the potential increase in CR with higher doses is inconclusive. Further, based on discussion with the clinical review team, ORR is the most relevant efficacy endpoint for the indicated population (CLL patients with 17p del), thus 400 mg dose is acceptable for the flat exposure-response for ORR.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

Exposure-response relationship for venetoclax TEAEs (grade 3/4 neutropenia and infection) were evaluated based on studies M12-175, M13-982, M13-365 and M14-032.

Figure 5: Sensitive analyses of logistic regression model of the probability of grade 3/4 infection (left) and grade 3/4 neutropenia (right) vs. average venetoclax concentration - excluded the 30 days lead-in period



Logistic regression analyses, similar to that used for the exposure-efficacy analyses, were employed. The sensitivity analysis after removing the confounding dose ramp-up phase data

showed that increase of venetoclax exposure was not associated the occurrence of these AEs (**Figure 5**). See Pharmacometrics Review for more details.

This is consistent with the summary of observed serious TEAEs in CLL patients from studies M13-982, M12-175 Arm A, and M14-032, by dose cohorts (**Table 6).** The safety profile of venetoclax is generally comparable across the dose groups, although there was limited sample size per dose cohort (sample size of 5 -15 subjects), except for the 400 mg dose group.

Table 6: Serious TEAEs reported in ≥ 1% of all subjects or the 400 mg dose group (all treated subjects in CLL venetoclax monotherapy studies by assigned dosage – 90-Day Safety Update)

	Number (%) of Subjects[a]							
System Organ Class Preferred Term (MedDRA v17.1)	**150 mg N = 6**	**200 mg N = 9**	**300 mg N = 7**	**400 mg N = 279**	**600 mg N = 15**	**800 mg N = 7**	**1200 mg N = 5**	**Total N = 328**
Any SAE	4 (66.7)	7 (77.8)	3 (42.9)	123 (44.1)	9 (60.0)	2 (28.6)	3 (60.0)	151 (46.0)
Blood and lymphatic system disorders	1 (16.7)	4 (44.4)	1 (14.3)	33 (11.8)	0	1 (14.3)	0	40 (12.2)
Anaemia	0	0	0	5 (1.8)	0	0	0	5 (1.5)
Autoimmune haemolytic anaemia	0	0	0	8 (2.9)	0	0	0	8 (2.4)
Febrile neutropenia	1 (16.7)	2 (22.2)	1 (14.3)	13 (4.7)	0	1 (14.3)	0	18 (5.5)
Immune thrombocytopenic purpura	1 (16.7)	1 (11.1)	0	2 (0.7)	0	0	0	4 (1.2)
Neutropenia	0	0	0	5 (1.8)	0	0	0	5 (1.5)
Thrombocytopenia	0	0	0	5 (1.8)	0	0	0	5 (1.5)
Cardiac disorders	0	0	1 (14.3)	9 (3.2)	1 (6.7)	0	0	11 (3.4)
Atrial fibrillation	0	0	0	4 (1.4)	0	0	0	4 (1.2)
Gastrointestinal disorders	1 (16.7)	1 (11.1)	0	16 (5.7)	3 (20.0)	1 (14.3)	0	22 (6.7)
Small intestinal obstruction	0	0	0	3 (1.1)	0	0	0	3 (0.9)
General disorders and administration site conditions	1 (16.7)	2 (22.2)	0	21 (7.5)	1 (6.7)	0	1 (20.0)	26 (7.9)
Multi-organ failure	0	1 (11.1)	0	3 (1.1)	0	0	0	4 (1.2)
Pyrexia	1 (16.7)	0	0	9 (3.2)	0	0	0	10 (3.0)

Source: Applicant's response to FDA information request, January 27, 2016

2.2.4.3 Does this drug prolong the QT or QTc interval?

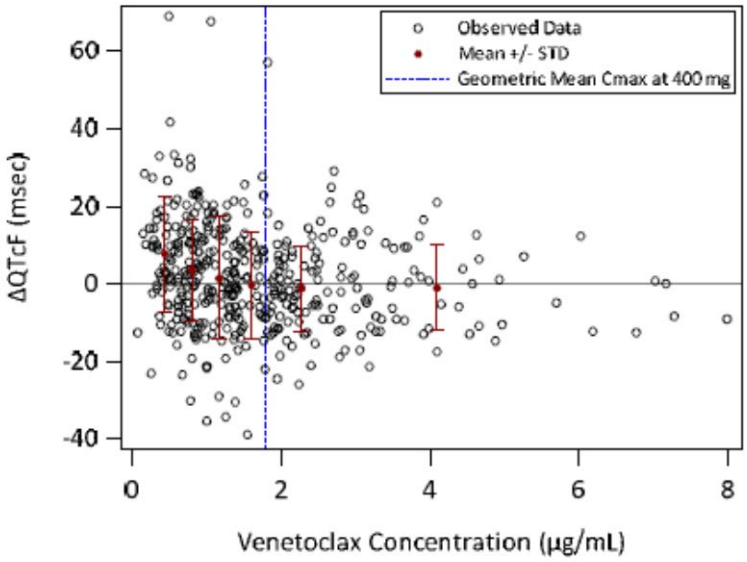
No large effect on QTc interval (i.e., > 20 ms) was detected (**Table 7**) and no concentration-ΔQTcF relationship (**Figure 6**) was observed in patients administered venetoclax doses ranged from 150 to 1200 mg. The QT/QTc assessment were determined in study M12-175 where electrocardiogram (ECG) measurements were collected in triplicate at baseline and at steady state dose of venetoclax ranged from 150 to 1200 mg in subjects with R/R CLL and NHL.

Table 7: The point estimates and the 90% CIs corresponding to the largest upper bounds at steady state for venetoclax once-daily (150 mg to 1200 mg)

		QTcF (ms)		ΔQTcF (ms)	
Dose Group	**Time (Hour)**	**N**	**Mean (SE)**	**Mean (SE)**	**90% CI**
< 400 mg	2	29	417.9 (4.9)	1.8 (3.2)	(-3.7, 7.2)
400 mg	2	50	420.9 (3.1)	3.8 (2.4)	(-0.2, 7.9)
> 400 mg	6	50	424.3 (2.3)	2.0 (1.8)	(-1.1, 5.0)
Overall	4	133	423.0 (1.8)	2.6 (1.1)	(0.8, 4.4)

Source: Reviewer's independent analysis

Figure 6: ΔQTcF versus venetoclax plasma concentrations in patients



Refer to QT-IRT review for details.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes, the proposed regimen of 400 mg QD following dose ramp-up schedule is acceptable based on ORR in patients with CLL harboring 17p del, who had at least one prior therapy.

In the dose-escalation phase of first-in-human, Phase 1 study (study M12-175), ORR was evaluated in 56 patients with R/R CLL with or without 17p del after escalating to the designated venetoclax steady state dose from 150 to 1200 mg QD. Based on preliminary ORR and safety data from the dose escalation cohorts, additional 60 patients were enrolled in the safety expansion cohort and treated with venetoclax dose of 400 mg QD. As shown in **Table 1**, the ORRs were (b) (4) in patients treated with venetoclax doses <400 mg, 400 mg, and >400 mg, respectively. The pooled dose-efficacy analyses indicated ORR plateaued at dose greater than 400 mg. Treatment-related adverse events were slightly higher at doses higher than 400 mg.

Based on the results of Phase 1 study M12-175, the efficacy and safety of venetoclax at 400 mg QD was evaluated in the pivotal Phase 2 study M13-982 (N=106) in patients with R/R CLL harboring 17p del and having received at least one prior therapy. The primary endpoint, ORR as assessed by IRC, was 80.2% with 95% CI of 71.3% to 87.3%. The safety profile of venetoclax at 400 mg in the pivotal study appears to be acceptable; the associated risk of TLS was manageable by the dose ramp-up schedule and a prophylactic regimen of hydration and uric acid reducers, along with close laboratory monitoring.

The proposed 400 mg daily dosing regimen is also supported by the flat dose-concentration-response relationship for ORR around 400 mg in the pooled exposure-response analyses, and acceptable safety risk comparing to lower dose levels in the exposure-safety analyses on Grade 3/4 neutropenia and infection.

(b) (4)

However the clinical relevance of CR rate in CLL patients with 17p del is still not clear based on available data.

There is no unresolved dosing or administration issue.

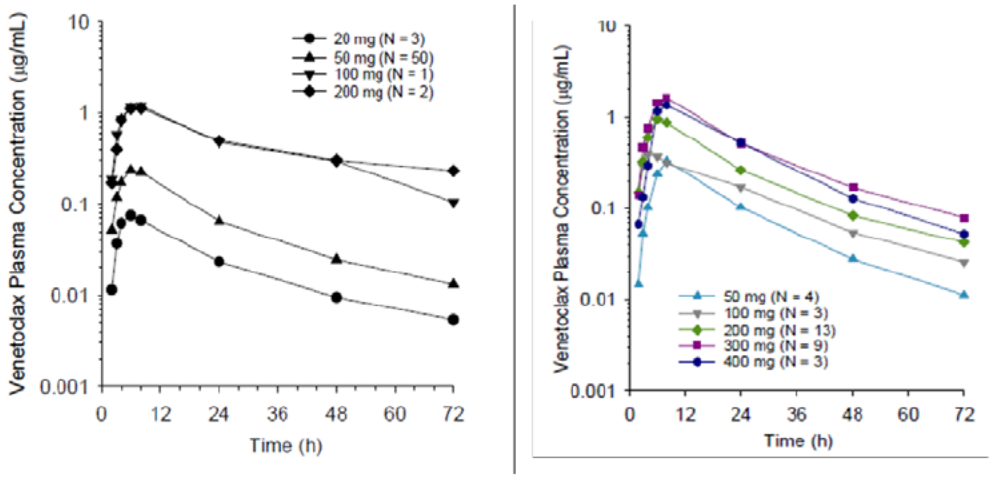
2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

PK characterization of venetoclax was performed in patients with R/R CLL/SLL or NHL after single and multiple doses. Accumulation ratio was < 2-fold with multiple doses. The absolute bioavailability of venetoclax was not determined. Venetoclax PK profile is adequately described by a two-compartmental PK model with first-order absorption and first-order elimination *via* popPK analyses.

Single Dose Pharmacokinetics
The mean venetoclax plasma concentration-time profiles following single dose in the dose escalation cohorts of Phase 1 study M12-175 are presented in **Figure 7**. Venetoclax plasma concentrations peaked at approximately 6 to 8 hours after single dose followed by exponential decline thereafter.

Figure 7: Mean venetoclax plasma concentration-time profiles following a single dose in CLL/SLL (left) and NHL (right) patients



Source: Applicant's M12-175 Clinical Study Report – Interim (R&D/14/1066)

The PK parameters after single dose in patients with CLL/SLL or NHL are summarized in **Table 8**. In CLL/SLL patients, venetoclax mean half-lives ranged from 16.9 to 40.9 hours, with longer

half-lives observed at the two higher doses (100 and 200 mg) which had very limited subjects (N = 1 and N = 2, respectively). Comparison of PK parameters after single oral doses between CLL/SLL and NHL patients suggests that PK of venetoclax is similar in these two cancer populations. Within the tested dose range, venetoclax PK appears to be linear after single dose administration.

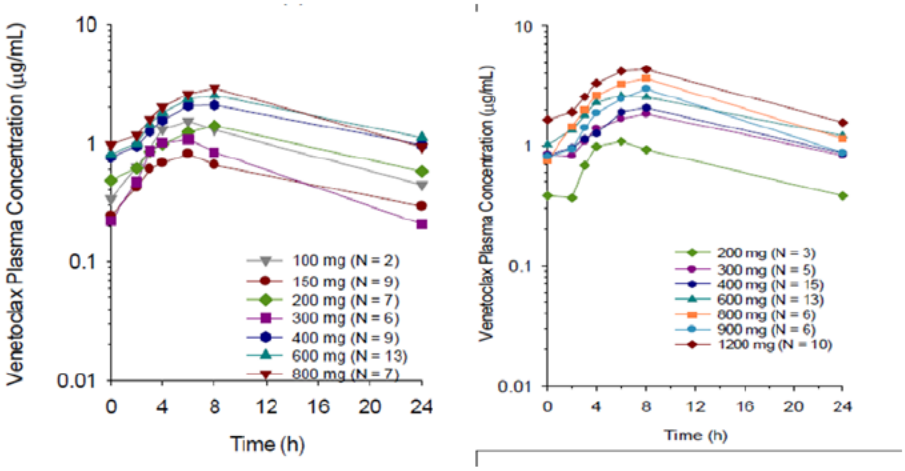
Table 8: Venetoclax PK parameters following single dose oral administration in patients in Study M12-175

Dose (mg)	N	C_{max} (µg/mL)	AUC_{∞} (µg*h/mL)	T_{max}* (h)	$T_{1/2}$ (h)	CL/F (L/h)
Arm A (R/R CLL/SLL), Week 1/ Day -7, with low-fat meal						
20	3	0.07 (21%)	1.99 (10%)	6.0 (6.0 - 6.0)	16.9 (18%)	9.7 (11%)
50	50	0.26 (45%)	5.23 (58%)	6.0 (2.0 - 18.2)	18.9 (34%)	13.6 (67%)
100	1	1.19	35.8	8.0	22.5	2.8
200	2	1.15	49.5	7.0 (6.0 – 8.0)	40.9	5.65
Arm B (NHL), Week 1/ Day -7, with high-fat meal						
50	5	0.34 (34%)	6.79 (48%)	8.0 (6.0 - 8.0)	15.3 (8%)	8.5 (37%)
100	3	0.50 (61%)	9.72 (63%)	4.0 (4.0 – 22.9)	18.2 (9%)	12.9 (63%)
200	13	1.05 (39%)	20.40 (29%)	6.0 (3.0 – 24.0)	16.0 (20%)	10.7 (35%)
300	9	1.81 (51%)	37.97 (51%)	8.0 (4.0 – 23.0)	16.7 (48%)	10.3 (51%)
400	3	1.43 (51%)	30.2 (36%)	6.9 (6.0 – 7.2)	14.1 (18%)	14.3 (30%)

**T_{max} presented as median (range) Source: Applicant's Study M12-175 Interim Report (R&D/14/1066)*

Multiple Doses Pharmacokinetics

Figure 8: Mean venetoclax plasma concentration-time profile at steady state in patients with CLL/SLL (left) and NHL (right)



The mean venetoclax plasma concentration-time profiles following multiple doses or at steady state in Phase 1 study M12-175 are presented in **Figure 8**.

Table 9: Summary of venetoclax PK parameters after multiple doses in Study M12-175

Dose (mg)	N	C_{max} (µg/mL)	AUC_{0-24} (µg*h/mL)	T_{max} (h)	CL/F (L/h)
Arm A (R/R CLL/SLL), Dose-escalation Cohorts, Steady State with low-fat meal					
100	2	1.58 (20%)	22.05 (12%)	5.0 (4.0 - 6.0)	4.6 (12%)
150	9	0.91 (28%)	12.74 (12%)	6.0 (3.0 – 23.5)	13.5 (42%)
200	7	1.44 (39%)	24.28 (44%)	8.0 (4.0 – 8.0)	9.7 (42%)
300	6	1.16 (53%)	16.13 (50%)	5.0 (3.0 – 8.0)	22.0 (41%)
400	8	2.18 (50%)	35.53 (57%)	7.0 (4.0 – 11.2)	15.7 (65%)
600	12	2.73 (54%)	45.96 (52%)	8.0 (4.0 – 24.0)	16.2 (46%)
800	7	2.99 (37%)	45.73 (31%)	8.0 (6.0 – 8.0)	19.4 (39%)
Arm A (R/R CLL/SLL), Safety Expansion Cohort, Steady State with low-fat meal					
400	52	2.05 (52%)	31.35 (48%)	6.0 (2.0 – 24.7)	16.5 (58%)
Arm B (NHL), Dose-escalation cohorts, Steady State with low-fat meal					
200	3	1.11 (27%)	16.26 (28%)	6.0 (4.0 – 6.0)	13.1 (33%)
300	5	1.94 (39%)	31.45 (35%)	6.0 (4.0 – 8.0)	10.9 (46%)
400	15	2.24 (59%)	36.92 (61%)	6.0 (4.0 – 8.0)	16.9 (90%)
600	12	2.70 (66%)	45.31 (81%)	6.0 (2.2 – 8.0)	17.3 (39%)
800	6	3.96 (59%)	53.02 (57%)	6.0 (4.0 – 8.0)	18.5 (44%)
900	6	2.93 (23%)	45.16 (14%)	7.7 (6.0 – 8.0)	20.3 (14%)
1200	10	4.60 (41%)	72.06 (39%)	8.0 (4.0 – 8.0)	19.5 (45%)
Arm B (NHL), Safety Expansion Cohort, Steady State with low-fat meal					
1200	22	3.53 (49%)	58.10 (47%)	8.0 (4.0 – 24.0)	25.0 (43%)

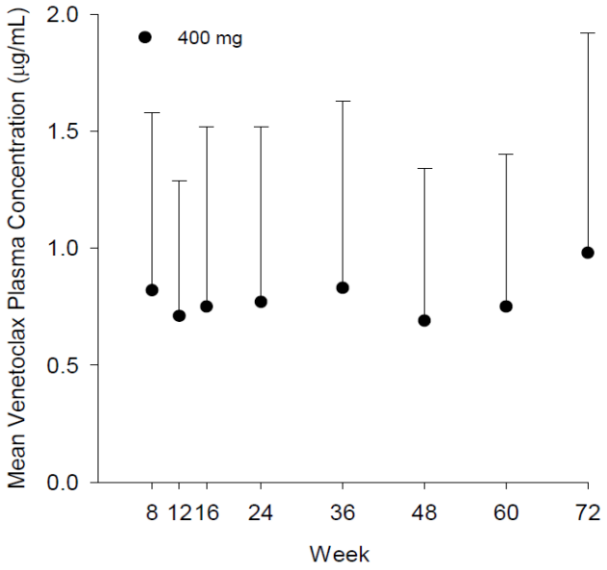
Source: Applicant's Study M12-175 Interim Report (R&D/14/1066)

As shown in **Figure 8** and **Table 9** above, in patients with CLL/SLL, the median T_{max} following multiple doses administration of venetoclax ranged from 5 to 8 hours and the steady state mean

C_{max} and AUC_{0-24} at the 400 mg dose in the safety expansion cohort were 2.1 µg/mL (2.4 µM) and 31.4 µg•hr/mL, respectively. The study was not powered to test the dose-exposure proportionality, but the data in both CLL/SLL and NHL patients suggested that venetoclax has linear PK at steady state over the dose range tested.

In the pivotal Phase 2 study, the mean predose plasma venetoclax concentration-time profile at 400 mg following dose ramp-up schedule is shown in **Figure 9**. The mean predose concentration at the 400 mg dose ranged from 0.69 to 0.98 µg/mL across visits between Week 8 and Week 72. The steady state is considered reached by Week 8 as there was no statistically significant difference in mean predose concentrations at any of the times tested from Week 8 to Week 24.

Figure 9: Venetoclax mean (+SD) predose plasma concentrations following 400 mg QD in Study M13-982



Source: Applicant's Study M13-982 Clinical Study Report-Interim (R&D/14/1067)

Metabolite M27 Single and Multiple-doses Pharmacokinetics

The mean metabolite M27 plasma concentration-time profiles following single and multiple doses of venetoclax in Phase 1 study M12-175 are presented in **Figure 10**. PK profiles of M27 after single dose were not well characterized. Steady state PK profiles of M27 indicated a dose-dependent increase in M27 exposure and a very flat concentration-time profile over the dosing intervals. Based on PK parameters summarized in **Table 10**, at the steady state 400 mg dose level in 7 patients with CLL/SLL and NHL, the mean C_{max} and AUC_{0-24} of M27 were 0.73 µg/mL and 14.5 µg*hr/mL, respectively. The metabolite-to-parent ratios for steady state C_{max} and AUC_{0-24} were 0.4 and 0.48, respectively.

Figure 10: Mean metabolite M27 plasma concentration-time profiles following single and multiple doses of venetoclax in patients with CLL/SLL and NHL (Study M12-175)

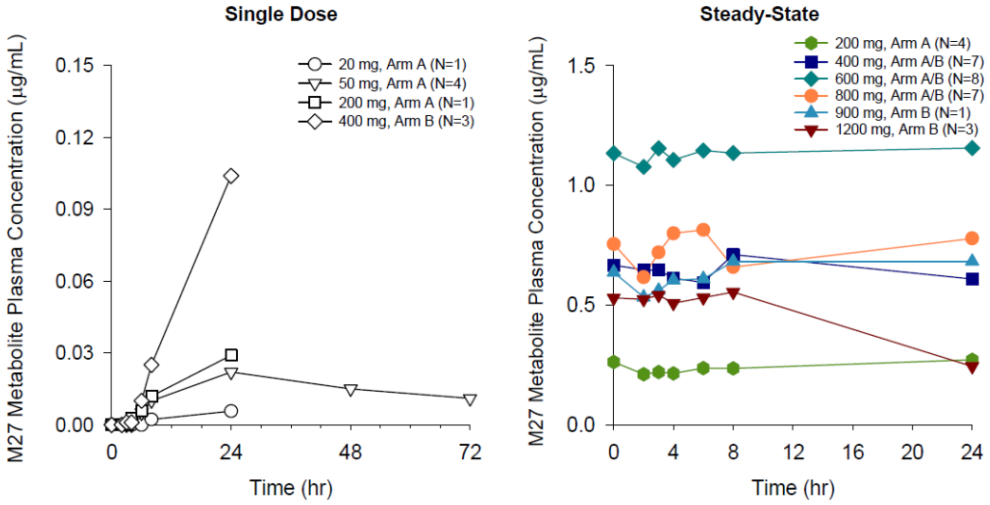


Table 10: Summary of metabolite M27 PK parameters after single and multiple doses of venetoclax in CLL/SLL and NHL patients (Study M12-175)

	Venetoclax Doses									
	Single Dose[a]				Steady State Dose[b]					
Pharmacokinetic Parameter (unit)	20 mg (N = 1)	50 mg (N = 4)	200 mg (N = 1)	400 mg (N = 3)	200 mg (N = 4)	400 mg (N = 7)	600 mg (N = 8)	800 mg (N = 7)	900 mg (N = 1)	1200 mg (N = 3)
C_{max} (µg/mL)	0.01	0.02 ± 0.01	0.03	0.10 ± 0.04	0.29 ± 0.20	0.73 ± 0.45	1.23 ± 1.10	0.88 ± 0.40	0.68	0.56 ± 0.47
AUC[c] (µg•h/mL)	0.07	1.04 ± 0.33	0.35	1.08 ± 0.46	6.82 ± 3.37[d]	14.5 ± 9.2[e]	27.4 ± 25.7	19.2 ± 9.38	15.7	10.4 ± 8.64
M:P Ratio C_{max}	0.10	0.09 ± 0.03	0.04	0.10 ± 0.06	0.19 ± 0.04	0.4 ± 0.4	0.3 ± 0.12	0.34 ± 0.16	0.16	0.11 ± 0.10
M:P Ratio AUC	0.08	0.24 ± 0.10	0.02	0.06 ± 0.03	0.27 ± 0.03[d]	0.48 ± 0.46[e]	0.41 ± 0.16	0.46 ± 0.19	0.28	0.12 ± 0.11

M:P = M27 Metabolite to Parent ratio

a. Data from Week 1 Day –3 (cohort 1) and Week 1 Day –7 (subsequent cohorts) in the dose-escalation cohorts.

b. Data from Week 6/7 Day 1 in the dose-escalation and safety-expansion cohorts.

c. AUC is AUC_{0-72} for 50 mg single dose data and AUC_{0-24} for data at Week 6/7.

d. N = 3.

e. N = 6.

Source: Applicant's Study M12-175 Interim Report (R&D/14/1066)

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Venetoclax PK exposure in healthy subjects is similar to that in cancer patients based on cross study comparison of PK and popPK analyses.

Cross Study Comparison

Venetoclax PK in healthy female subjects is only available after single dose oral administrations so comparison of PK parameters was made to those after single dose of venetoclax in patients in Phase 1 study M12-175. As shown in **Table 11**, the dose-normalized C_{max} and AUC_{∞} are similar or largely overlapping between healthy female subjects and patients with CLL/SLL and NHL.

Table 11: Summary of Geometric Mean (CV%) PK parameters of venetoclax in patients and healthy female subjects

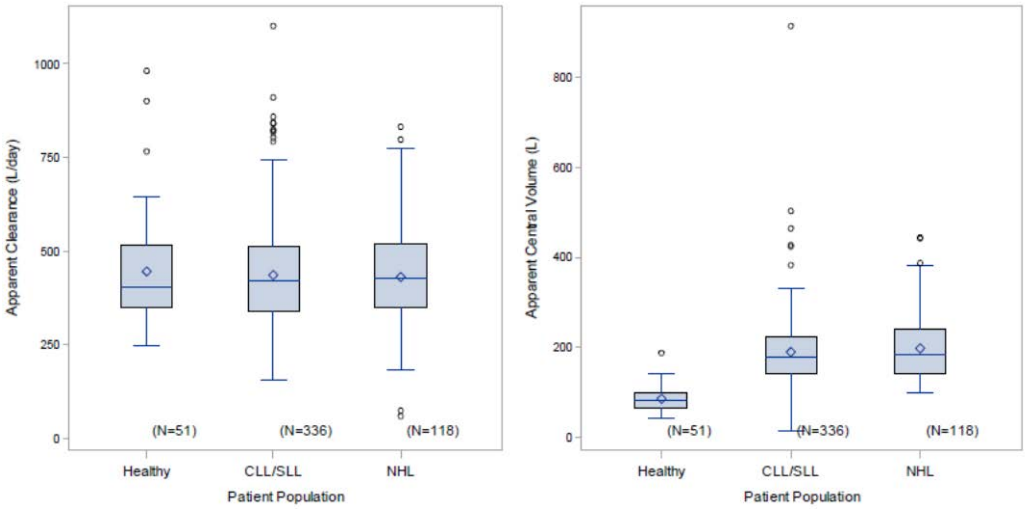
Population/Study	Venetoclax PK Parameters				Dose-normalized PK Parameters	
	Dose (mg)	C_{max} (μg/mL)	AUC_{∞} (μg*h/mL)	CL/F (L/h)	C_{max} (μg/mL/mg)	AUC_{∞} (μg*h/mL/mg)
CLL/SLL Patients						
M12-175 (N=50)	50	0.24 (45%)	4.43 (58%)	13.6 (67%)	0.0048	0.0886
M12-175 (N=60)*	400	1.79 (51%)	28.07 (49%)	16.5 (60%)	0.0045	0.0702
NHL Patients						
M12-175 (N=4)	50	0.33 (34%)	6.28 (48%)	8.5 (37%)	0.0066	0.1256
M12-175 (N=3)	100	0.45 (61%)	8.69 (63%)	12.9 (63%)	0.0045	0.0869
M12-175 (N=13)	200	0.97 (39%)	19.60 (29%)	10.7 (35%)	0.0049	0.0980
M12-175 (N=3)	400	1.28 (51%)	29.04 (36%)	14.3 (30%)	0.0032	0.0726
M13-364 (N=11)	50	0.20 (39%)	3.96 (53%)	14.4 (54%)	0.0040	0.0792
Healthy Female Subjects						
M14-253 (Trt B, N=15)	50	0.39 (28%)	4.22 (33%)	12.5 (35%)	0.0078	0.0844
M15-101 (Trt B, N=24)	100	0.50 (40%)	7.07 (41%)	16.0 (57%)	0.0050	0.0707
M14-497 (Trt A, N=12)	200	1.05 (41%)	13.53 (42%)	16.1 (44%)	0.0053	0.0677
M15-065 (N=3)	400	2.30 (24%)	38.69 (38%)	11.1 (48%)	0.0058	0.0967

**Steady-state PK with AUC_{0-24}*

Population PK Analyses

The population in the popPK analyses consists of 66.5% patients with CLL/SLL, 23.4% patients with NHL and 10.1% healthy subjects. Disease factor was tested as a covariate on CL/F, V_2/F and K_A in the modeling. The post-hoc analyses based on final model confirmed that there is no relationship between venetoclax CL/F and disease (**Figure 11**), indicating there is no difference in exposure (AUC) of venetoclax between healthy subjects and patients with CLL/SLL and NHL.

Figure 11: *Post Hoc* apparent clearance (CL/F, left) and volume of central compartment (V_2/F, right) by population (popPK)



2.2.5.3 What are the characteristics of drug absorption?

In patients with CLL/SLL, venetoclax plasma concentrations peaked at 5 to 8 hours after single and multiple doses administration with food. Administration with low- and high-fat meals increased venetoclax PK exposure by 3 to 5 folds (see Section 2.5.3).

Venetoclax is a substrate of P-gp and BCRP based on *in vitro* assessment.

2.2.5.4 What are the characteristics of drug distribution?

Venetoclax is highly bound to human plasma protein with $f_{ub} < 0.01$ independent of concentrations. Venetoclax does not partition preferentially into the blood cells as the mean blood-to-plasma ratio for venetoclax is 0.57.

The population estimated apparent volume of distribution (Vd_{ss}/F) of venetoclax ranged from 256 to 321 L in patients with CLL/SLL and NHL.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

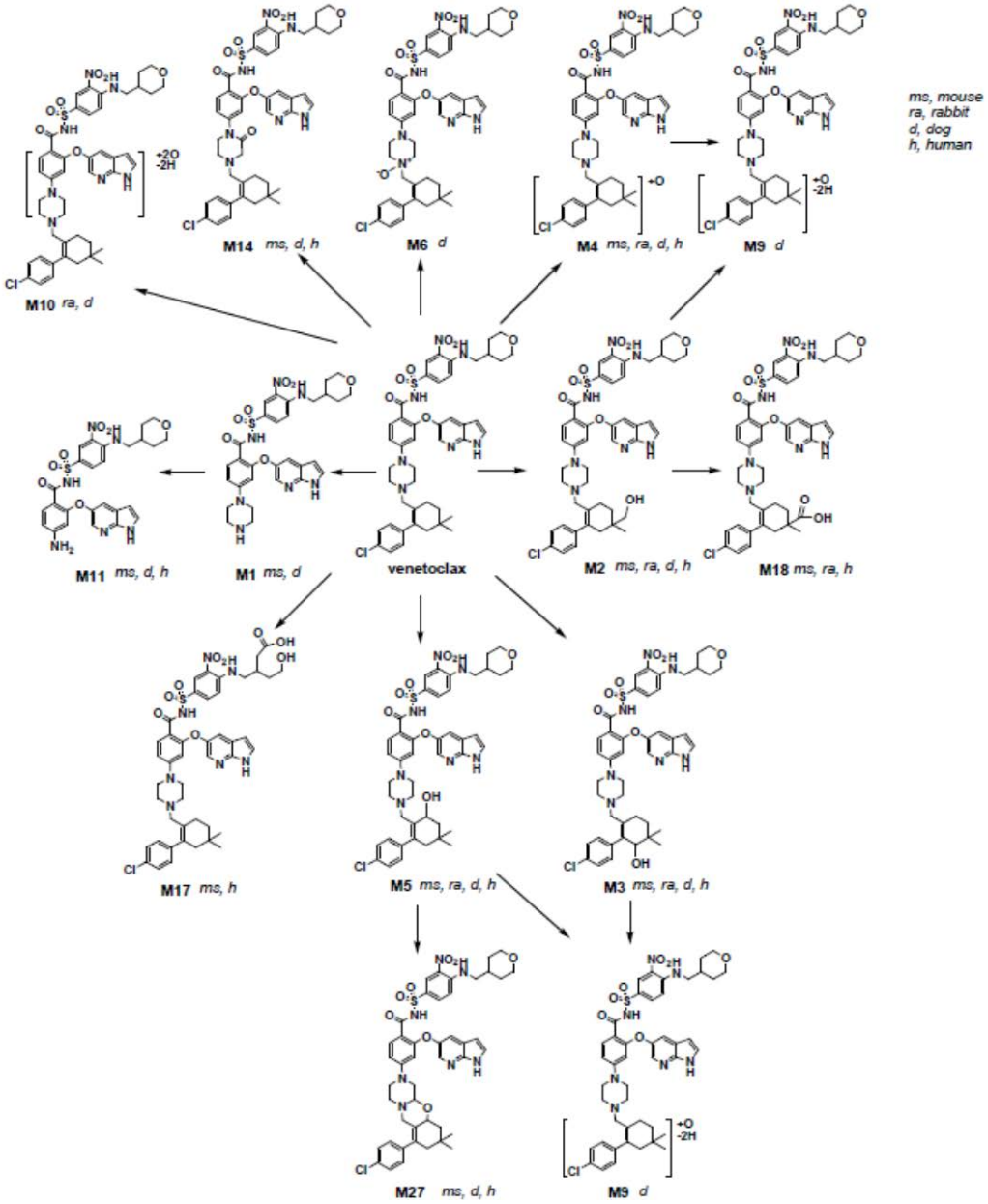
The human mass balance study M13-363 showed that more than 99.9% of the total radioactive dose was recovered in feces. Unchanged venetoclax accounted for 20.8% of the administered radioactive dose excreted in feces after a single 200 mg oral dose of [^{14}C]-venetoclax given with food.

2.2.5.6 What are the characteristics of drug metabolism?

Venetoclax is predominantly metabolized by CYP3A4/5 to a major metabolite M27 (**Figure 12**). In humans, a total of 9 oxidative metabolites were detected at steady state (M2, M3, M4, M5, M11, M14, M17, M18, M27), and M27 was also identified as a major metabolite in human plasma, representing 12% of plasma radioactivity after a single dose of 200 mg [^{14}C]-venetoclax in the human mass balance study M13-363.

The proposed venetoclax metabolic pathways are shown in **Figure 12** below.

Figure 12: Proposed biotransformation pathways for venetoclax based on metabolites observed in mouse, rabbit, dog and human plasma at steady state



Source: Applicant's CTD 2.6.4 Pharmacokinetic Written Summary (R&D/14/0659)

2.2.5.7 What are the characteristics of drug excretion?

After oral administration, venetoclax is mainly excreted into feces as metabolites or unchanged form (see Section 2.2.5.5).

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Analyses of combined dose-normalized steady state C_{max} and AUC_{0-24} of venetoclax in patients with CLL/SLL and NHL indicated that PK of venetoclax was linear over the dose range of 150 to 800 mg. In the popPK analyses, the relative bioavailability increased by 11.7% with doubled dose, consistent with the linear PK observation within the range of tested doses.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

Time-dependence of venetoclax PK parameters was not observed in clinical studies after multiple doses. There was no statistically significant difference of predose concentrations from Week 8 through 24 in pivotal Phase 2 study M13-982, and steady state was achieved by Week 8 following the 5-weeks dose ramp-up schedule.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The population PK parameter estimates and associated inter- and intra-individual PK variability in the final popPK model are summarized in **Table 12** below.

Table 12: Parameter estimates and variability for venetoclax pharmacokinetics: Final Model

	Population Value (θ)			Inter-Individual Variability (ω^2)			
Parameter	Estimate (SEE)	%RSE	95% Confidence Interval	Variance (%CV)	% RSE	95% Confidence Interval	Shrinkage
CL/F (L/day)	447 (15.7)	3.51	416 – 478	0.153 (40.7)	9.346	0.125 – 0.181	19.0%
$\theta_{CL/F,\ moderate\ CYP3A\ inhibitor}$	0.842 (0.036)	4.24	0.772 – 0.912				
$\theta_{CL/F,\ strong\ CYP3A\ inhibitor}$	0.184 (0.011)	6.03	0.162 – 0.206				
$\theta_{CL/F,\ rituximab}$	1.22 (0.036)	2.93	1.15 – 1.29				
$\theta_{CL/F,\ OATP1B3\ inhibitor}$	0.853 (0.022)	2.54	0.810 – 0.896				
V2/F (L)	118 (16.2)	13.7	86.2 – 150	0.205 (47.7)	6.341	0.180 – 0.230	27.7%
$\theta_{V2/F,\ female}$	0.680 (0.045)	6.68	0.591 – 0.769				
$\theta_{V2/F,\ CLL/SLL/NHL}$	1.71 (0.213)	12.5	1.29 – 2.13				
Q/F (L/day)	97.2 (5.38)	5.54	86.7 – 108				
V3/F (L)	119 (4.95)	4.16	109 – 129				
KA (1/day)	3.72 (0.152)	4.09	3.42 – 4.02				
F1	1.0 (fixed)			0.097 (32.0)	13.374	0.072 – 0.123	28.3%
$\theta_{F1,\ fasting}$	0.335 (0.003)	0.967	0.329 – 0.341				
$\theta_{F1,\ fed}$[a]	1.23 (0.053)	4.29	1.13 – 1.33				
$\theta_{F1,\ moderate\text{-}fat}$	1.31 (0.108)	8.24	1.10 – 1.52				
$\theta_{F1,\ high\text{-}fat}$	1.43 (0.019)	1.30	1.39 – 1.47				
Dose nonlinearity (400 mg as reference)	–0.180 (0.004)	2.38	–0.188 – –0.172				

Source: Applicant's Population PK report R&D/15/0256

As shown in **Table 12**, CYP3A inhibitors (moderate and strong) and concomitant medications of rituximab and OATP1B3 inhibitors appear to be sources of inter-individual variability on CL/F. Sex and subject populations appear to be sources of inter-individual variability on V_2/F.
The unexplained inter-individual variability for apparent clearance (CL/F) and apparent central volume of distribution (V_2/F) after accounting for the effect of covariates were 40.7% and 47.7%, respectively, indicating moderate PK variability of venetoclax.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The influence of these intrinsic factors on venetoclax PK was evaluated using the popPK analyses. Applicant's popPK analyses indicated that age, sex, race, weight, mild and moderate hepatic impairment, mild and moderate renal impairment does not have clinically significant effect on venetoclax exposure.

In a separate pharmacogenetic analysis performed by sponsor, transporter OATP1B1 genotype status has no statistically significant effect on exposure of venetoclax.

A list of PK covariates included in the popPK analyses and their summary statistics is shown in **Table 13**.

Table 13: Summary of covariates and values included in the popPK analyses

Covariates	Median (range), or categories (%)
Study population	Healthy/CLL/NHL: 10.1/66.5/23.4
Age (years)	65 (25, 88)
Weight (kg)	78.6 (36.9, 143.0)
Race	White/Black/Hispanic/Asian/Other: 91.88/4.55/0.2/1.19/2.18
Sex	Male/Female: 60.59/39.41
Albumin (g/dL)	4.0 (2.0, 7.2)
ALT (U/L)	18.0 (5.0, 141.0)
AST (U/L)	23.0 (9.0, 192.0)
Bilirubin (mg/dL)	0.5 (0.2, 2.5)
Creatinine clearance (mL/min)	83.1 (32.8, 218.9)
Renal function	Normal/Mild-impairment/Moderate-impairment: 42:42:16
Hepatic function	Normal/Mild-impairment/Moderate-impairment: 84.9:13.7:1.4
OATP1B1 transporter phenotype	Poor /Intermediate/Extensive/Not-tested: 1.2:17.4:46.7:34.7

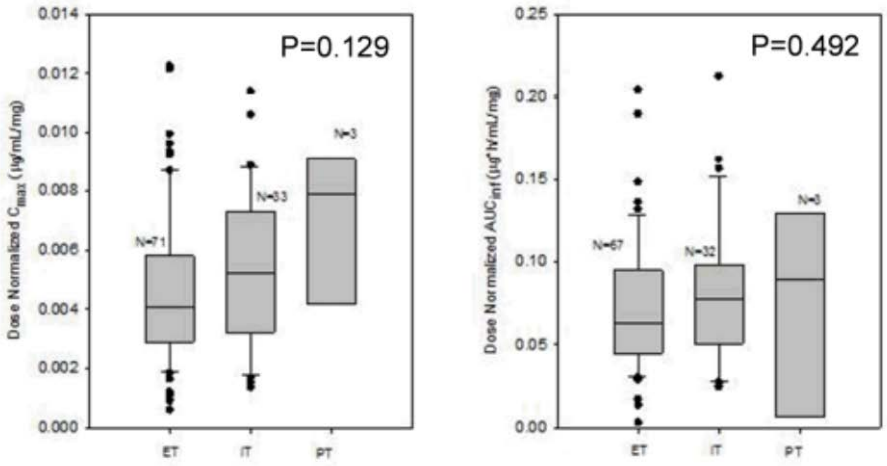
Source: Applicant's Population PK report R&D/15/0256

2.3.1.1 Genetics

In nonclinical studies, knockout of the Oatp1a/b cluster in mice resulted in a plasma clearance of venetoclax that was ~60% lower than that in wild-type mice, however HEK cells overexpressing OATP1B1 showed no active uptake of venetoclax or M27 *in vitro*. To evaluate whether

OATP1B1 transporter functional status affected patient's exposure to venetoclax, 8 sequence variants in the OATP1B1 gene (SLCOB1*1B, *2, *3, *5, *6, *8, *9, *10) were assessed in healthy subjects and CLL/SLL and NHL patients who provided a blood sample for exploratory pharmacogenetic analysis from studies M12-175, M13-364, M13-365, M13-982, M14-032, M14-253, M14-497, and M15-101. An in-house, pyrosequencing based assay was used to genotype SCLCOB1 and classify subjects into OATP1B1 transporter status categories (Extensive transporter [ET], Intermediate transporter [IT], or Poor transporter [PT]) inferred based on the genotyping results. Of the total subjects with both intensive PK data and genotype results available (N = 368), the distribution of ETs, ITs, and PTs were 257 (69.8%), 104 (28.3%), and 7 (1.9%), respectively. Based on the applicant's analyses in subsets of these patients, a statistically significant difference (p = 0.0094) was observed between ETs and ITs in healthy subjects for dose-normalized C_{max} after a single dose of venetoclax. However, this association was not observed when data from healthy subjects and CLL/SLL and NHL patients were combined. At steady state there appeared to be a trend toward increased C_{max} in CLL/SLL and NHL patients with reduced transporter status (**Figure 13**), but this was not statistically significant. There was also no significant difference observed for venetoclax AUC after single dose or at steady state. Overall, there is no clear relationship between OATP1B1 functional status and venetoclax PK and these results suggest that venetoclax is not a substrate for OATP1B1.

Figure 13: OATP1B1 transporter status and venetoclax dose-normalized C_{max} and AUC at steady state in subjects with CLL/SLL and NHL



Source: Applicant's Pharmacogenetic & Pharmacogenomics report (R&D/15/0588). ET: Extensive transporter; IT: Intermediate transporter; PT: Poor transporter.

In addition, 3 genetic variants in CYP2C9 were genotyped in patients from study M15-065. However, their effect on warfarin metabolism in the presence of venetoclax was not assessed due to the limited data (N = 8).

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups?

See sections below.

2.3.2.1 Elderly

No dose adjustment is needed in elderly. The popPK analysis didn't identify age (median age: 65 years, range: 25-88 years) as a significant covariate influencing venetoclax PK.

2.3.2.2 What is the status of pediatric studies and/or any pediatric plan for study?

The applicant has not conducted pediatric clinical studies for venetoclax. Venetoclax was granted orphan drug designation for CLL in September 2012. As orphan drugs are not required to comply with PREA requirement, the applicant will likely receive a waiver for pediatric studies.

2.3.2.3 Gender

No dose adjustment is needed based on patient gender. The popPK analysis did not identify sex (n=306, 61% male) as a significant covariate influencing venetoclax PK.

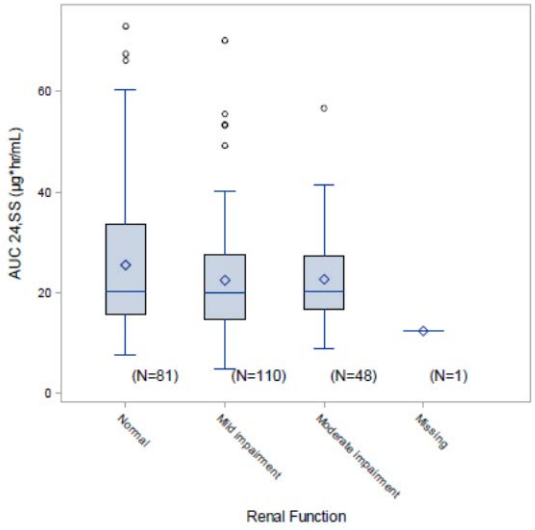
2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians

No dose adjustment is needed based on patient's race. The popPK analysis didn't identify race (n=464 White (92%), 27 Black (4.6%), 1 Hispanic (0.2%), 6 Asian (1.2%) and 11 Other (2.2%)) as a significant covariate influencing venetoclax PK.

2.3.2.5 Renal impairment

The applicant did not conduct a dedicated study to assess the effect of renal impairment on venetoclax PK exposure. The popPK analysis, which included patients with mild renal impairment (n=211), moderate renal impairment (n=83), and normal renal function (n=210), did not show relationship between venetoclax PK exposure and renal function (**Figure 14**). This is consistent with finding that renal excretion played a negligible role in the elimination of venetoclax in the human mass balance study M13-363.

Figure 14: Boxplot of the *Post Hoc* apparent clearance (CL/F) by renal function



Source: Applicant's PopPK report R&D/15/0256

Although both venetoclax PK and efficacy was not affected by renal impairment, there was a significant increase in TEAEs in patients with mild and moderate renal impairment.

The applicant proposed the following dose recommendation for patients with renal impairment:

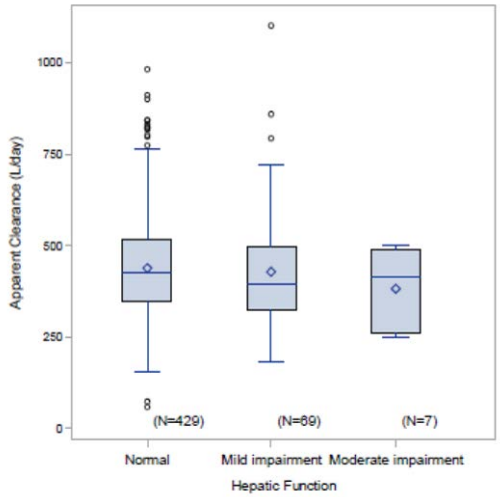
- No dose adjustment is needed for patients with mild and moderate renal impairment (CrCl ≥ 30 mL/min).
- Patients with reduced renal function (CrCl < 80 ml/min) may require more intensive prophylaxis and monitoring to reduce the risk of TLS when initiating treatment with venetoclax.
- A recommended dose has not been determined for patients with severe renal impairment (CrCl < 30 mL/min) or patients on dialysis.

The proposed dosing recommendation in patients with mild and moderate impairment appears acceptable since each patient will start at the low dose of 20 mg according to the dose ramp-up schedule. In addition, more intensive toxicity monitoring in these patients and the proposed dose modification for toxicity will decrease the safety risk.

2.3.2.6 Hepatic impairment

The applicant's popPK analysis indicated mild (N=69) and moderate (N=7) hepatic impairment has no effect on venetoclax PK (**Figure 15**). The hepatic impairment category was defined based on NCI-ODWG criteria. The applicant proposed no dose adjustment in patients with mild or moderate hepatic impairment. A recommended dose has not been determined for patients with severe hepatic impairment. The proposed dosing recommendation in patients with mild or moderate hepatic impairment appears acceptable.

Figure 15: Comparison of *Post Hoc* apparent clearance (CL/F) by hepatic function category



Source: Applicant's PopPK report R&D/15/0256

The proposed dose (400 mg QD) for mild and moderate hepatic impairment is further supported by the applicant's safety analysis by hepatic impairment subgroup (**Table 14**), where generally similar rates of TEAEs were observed in patients with normal hepatic function and those with mild or moderate hepatic. While there is a trend of slightly higher rates of adverse events in patients with moderate impairment, reliable conclusion can't be made regarding the safety of venetoclax in this group of patients due to the small number of patients with moderate hepatic impairment. The applicant plans to conduct a dedicated hepatic impairment trial post-approval to evaluate the PK of venetoclax in subjects with varying degree of hepatic impairment.

Table 14: Overview of TEAEs by hepatic function: venetoclax monotherapy in R/R CLL (Monotherapy Analysis Sets)

	Number (%) of Subjects											
	Venetoclax 400 mg QD						Venetoclax All Doses					
	All[a]			17p Del[b]			All[a]			17p Del[b]		
Type of TEAE	Normal Hepatic Function N = 198	Mild Hepatic Impair[c] N = 37	Moderate Hepatic Impair[c] N = 5	Normal Hepatic Function N = 137	Mild Hepatic Impair[c] N = 21	Moderate Hepatic Impair[c] N = 2	Normal Hepatic Function N = 237	Mild Hepatic Impair[c] N = 47	Moderate Hepatic Impair[c] N = 5	Normal Hepatic Function N = 149	Mild Hepatic Impair[c] N = 26	Moderate Hepatic Impair[c] N = 2
Any TEAE	194 (98.0)	37 (100)	5 (100)	133 (97.1)	21 (100)	2 (100)	232 (97.9)	47 (100)	5 (100)	144 (96.6)	26 (100)	2 (100)
CTCAE grade ≥ 3	148 (74.7)	25 (67.6)	4 (80.0)	100 (73.0)	14 (66.7)	1 (50.0)	177 (74.7)	34 (72.3)	4 (80.0)	110 (73.8)	18 (69.2)	1 (50.0)
Serious TEAEs	87 (43.9)	16 (43.2)	3 (60.0)	65 (47.4)	11 (52.4)	1 (50.0)	107 (45.1)	22 (46.8)	3 (60.0)	71 (47.7)	13 (50.0)	1 (50.0)

17p del = deletion of the p13 locus on chromosome 17; AST = aspartate aminotransferase; CLL = chronic lymphocytic leukemia; CTCAE = Common terminology Criteria for Adverse Events (version 4.0); R/R = relapsed or refractory; TEAE = treatment-emergent adverse event

a. Subjects with R/R CLL in Studies M13-982, M12-175 Arm A, and M14-032.

b. Subjects with R/R CLL harboring 17p del; Studies M13-982, M12-175 Arm A, and M14-032.

c. Normal hepatic function: total bilirubin ≤ 1 mg/dL and AST ≤ 40 U/
Mild impairment: total bilirubin ≤ 1 mg/dL and AST > 40 U/L, or
total bilirubin > 1.0 to ≤ 1.5 mg/dL and any AST;
Moderate impairment: total bilirubin > 1.5 to ≤ 3 mg/dL and any AST.

Source: Applicant's Clinical Summary of Safety, Table 56

2.3.2.7 What pregnancy and lactation use information is there in the application?

There are no available human data informing venetoclax-associated risk on the fetus; therefore, advise women of the potential risk of fetal toxicity. In mice, venetoclax was fetotoxic at exposures 1.2 times the human clinical exposure based on the AUC. Advise women of the potential risk of fetal toxicity was stated in the proposed labeling.

There are no data regarding effect of venetoclax on lactation. The proposed labeling advises nursing women to discontinue breastfeeding during treatment with venetoclax.

2.3.2.8 Other human factors that are important to understanding the drug's efficacy and safety?

There are no other known important human factors that are important to the understanding of venetoclax safety and efficacy.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

See sections below.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes, see Section 2.4.2.2 to Section 2.4.2.5 below.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Yes, *in vitro* studies indicated that venetoclax is predominantly metabolized by CYP3A4/5 to form the major circulating metabolite M27. M27 is also mainly metabolized by CYP3A4/5. Pharmacogenetic differences of CYP enzymes are unlikely to have effect on venetoclax metabolism.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Inhibitor

As shown in **Table 15**, venetoclax and metabolite M27 are inhibitors of several CYP enzymes including CYP2C8 and CYP2C9, M27 is also a weak inhibitor of CYP3A4 with IC_{50} of 6.07 μM. Both venetoclax and M27 are not inhibitors of CYP1A2, CYP2B6, CYP2C19, CYP2D6 as the tested IC_{50}s were greater than 30 μM.

Table 15: *In vitro* CYP enzyme inhibition potency of venetoclax and M27 in human liver microsomes and in human hepatocytes in the presence of serum albumin

CYP Enzymes	Venetoclax				M27			
	HLM			Human Hepatocytes with 4% BSA	HLM			Human Hepatocytes with 4% BSA
	IC_{50} (μM)	K_i (μM)*	R_1=1+[I]/K_i**	Total IC_{50} (μM)	IC_{50} (μM)	K_i (μM)*	R_1=1+[I]/K_i**	Total IC_{50} (μM)
CYP2C8	0.82	2.44		100	0.75	-		170
CYP2C9	0.14	0.32		53.3	0.31	-		293, >300
CYP3A4	>30	-	-	>300	6.07	-		>300

*Venetoclax K_i for CYP2C8 and CYP2C9 were determined experimentally. For enzymes without measure K_i values, assume K_i=IC_{50}/2

** [I] is estimated by the maximal total (free and bound) concentration of 2.4 μM in plasma at 400 mg steady state dose of venetoclax and the cut-off for R_1 is 1.1

Source: Applicant's Drug Metabolism Report R&D/14/0307

Inducer

In vitro studies indicated that venetoclax doesn't induce CYP1A2, CYP2B6 and CYP3A4 up to 5 μM. Metabolite M27 was considered as a potential inducer of CYP2C8 and CYP3A4 in cryopreserved human hepatocytes at predicted human efficacious concentration. However, due to high protein binding (f_{ub}<0.01) of both venetoclax and M27, induction of these CYP enzymes is unlikely even at the clinically relevant maximum concentrations for venetoclax (2.4 μM) and M27 (0.86 μM) after multiple doses of 400 mg, based on decreased induction potential in human hepatocytes when 4% of BSA was added.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Yes. Both venetoclax and M27 are substrates of P-gp, with net efflux ratio of 13 and 62, respectively.

Venetoclax and M27 are also inhibitors of P-gp, the IC_{50} values determined in *in vitro* studies were 0.79 μM and 0.83 μM, respectively. Therefore, inhibition of intestinal efflux is possible base on theoretical concentrations (400 mg/250 mL) of venetoclax in the GI tract with [I]/IC_{50} values >10. Inhibition of P-gp by venetoclax and M27 in other tissues maybe possible ($[I]_1$/IC_{50} values >0.1), however, due to very high protein binding of both venetoclax and M27 in systemic circulation, the DDI risk is low in systemic circulation.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Yes, *in vitro* studies also indicated that venetoclax and M27 are substrates of BCRP, with net efflux ratio of 6 and 8, respectively.

Venetoclax and M27 also inhibit BCRP with *in vitro* IC_{50} of 0.13 μM and 1.48 μM, respectively. Inhibition of BCRP by venetoclax and M27 in tissues is possible.

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

No. Venetoclax will be used as a monotherapy in the proposed indication based on labeling.

2.4.2.7 What other co-medications are likely to be administered to the target population?

Concomitant medications taken by ≥ 20% of patients in the 400 mg regimen were allopurinol (95.4%), sodium chloride (88.3%), rasburicase (52.5%), aciclovir (41.7%), furosemide (37.9%), paracetamol (41.3%), Bactrim® (sulfamethoxazole and trimethoprim) (37.9%), filgrastim (25.8%), pantoprazole (26.3%), potassium (24.2%), valaciclovir (21.3%), and levofloxacin (20.0%). Overall, the concomitant medications largely represent medications typically taken by a study population with the medical histories, such as antihypertensives and other cardiovascular agents, medications for gastric protection, and analgesics.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Yes, see below.

DDI with CYP3A Modulators

DDI with strong CYP3A inhibitor - Ketoconazole

Co-administration of 400 mg ketoconazole QD with venetoclax 50 mg under fed condition in 11 patients with relapsed or refractory NHL resulted in 2.3-fold increase in venetoclax C_{max} and 6.4-fold increase in AUC_{∞}, while the C_{max} and AUC_t of metabolite M27 decreased by approximately 50% and 30%, respectively (**Table 16**).

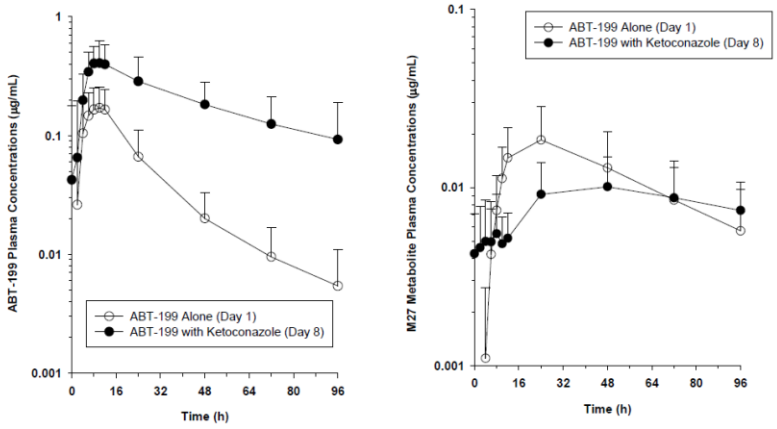
Table 16: Effect of concomitant administration of ketoconazole on venetoclax and metabolite M27 PK

Parameter	Venetoclax alone (Reference)	Venetoclax + Ketoconazole (Test)	Geometric Mean Ratio (90%CI) (Test/Reference)
Venetoclax			
C_{max} (μg/mL)	0.198	0.461	2.323 (1.996, 2.702)
AUC_t (μg*h/mL)	3.803	17.887	4.703 (3.549, 6.233)
AUC_{∞} (μg*h/mL)	3.961	25.366	6.403 (4.472, 9.168)
M27			
C_{max} (μg/mL)	0.018	0.009	0.499 (0.419, 0.595)
AUC_t (μg*h/mL)	0.968	0.694	0.717 (0.634, 0.818)
AUC_{∞} (μg*h/mL)	1.308	2.356	1.801* (0.961, 3.376)

*N=4

In addition, the elimination phase half-life was also increased by approximately 2-fold for venetoclax and 4-fold for M27 (**Figure 16**). The results are consistent with the *in vitro* finding that CYP3A4/5 are the predominant CYP enzymes involved in venetoclax metabolism and formation of M27. In addition, because ketoconazole is also an inhibitor of P-gp and venetoclax is a substrate of P-gp, inhibition of P-gp may have also contributed to the increase of venetoclax PK.

Figure 16: Mean + SD venetoclax and M27 plasma concentrations-time profiles (semi-log scale)



Source: Applicant's M13-364 Clinical Study Report

DDI with weak and moderate CYP3A inhibitor – Study M12-175

Thirty-five subjects enrolled in Phase 1 study 12-175 were reported to have been taking weak (n=26) and moderate (n=6) CYP3A inhibitors during the steady-state intensive PK samples collection visit (Week 6/7 Day 1), of which 31 have available PK data.

Table 17: Effect of weak and moderate CYP3A inhibitors on venetoclax PK at steady state in patients with CLL/SLL

Pharmacokinetic Parameter (units)	Venetoclax Alone (N = 150)	Venetoclax with Weak CYP3A Inhibitors (N = 25)	Venetoclax with Moderate CYP3A Inhibitors (N = 6)
T_{max} (hours)	6.0 (2 – 24.7)	6.0 (2.2 – 8.0)	8.0 (4.0 – 8.0)
Dose Normalized C_{max} (ng/mL/mg)	3.96 (0.90 – 18.0)	3.93 (1.64 – 13.4)	5.73 (3.48 – 8.22)
Dose Normalized AUC_{0-24} (ng•hr/mL/mg)	65.0 (15.7– 238)[a]	62.9 (25.2 – 263)[b]	103 (55.3 – 145)[c]
CL/F (L/hr)	15.4 (4.19 – 63.6)[a]	15.9 (3.8 – 39.7)[b]	9.73 (6.88 – 18.1)[c]

a. N = 139.
b. N = 24.
c. N = 5.

Source: Applicant's M12-175 Clinical Study Report

The median and range of PK parameters for venetoclax alone or with concomitant CYP3A inhibitors are shown in **Table 17**.

The dose-normalized C_{max} and AUC_{0-24} for venetoclax was not affected by weak CYP3A inhibitors, however, there was an approximately 40 to 60% increase in both C_{max} and AUC_{0-24} when venetoclax was co-administered with moderate CYP3A inhibitors (ciprofloxacin, dilitazem and fluconazole).

DDI with strong CYP3A inducer – Rifampin

Venetoclax C_{max} and AUC_{∞} increased by 106% and 78%, respectively, after single 600 mg dose administration of rifampin (**Table 18**). C_{max} of M27 increased by 56% and there was no change of AUC after single dose of rifampin. Because venetoclax is a substrate of P-gp but not a substrate of hepatic uptake transporters OATP1B1/1B3, the applicant suggested that the increase of venetoclax and M27 exposure was due to the inhibition of P-gp in the GI tract by rifampin.

After multiple doses of rifampin, C_{max} and AUC_{∞} of venetoclax decreased by approximately 42% and 71%, respectively (**Table 18**), while there was a 60% increase of C_{max} and 56% decrease of AUC_{∞} for M27. The decrease in both exposure and half-life of venetoclax and M27 are consistent with the predominant role of CYP3A4/5 in their metabolism and the predominant effect of CYP3A4/5 induction by multiple doses of rifampin. In addition, rifampin's induction of P-gp may have also contributed to the observed decrease in exposure.

Table 18: Effect of single and multiple doses of rifampin on PK of venetoclax and M27

Parameter		Rifampin Single Dose (SD)		Rifampin Multiple Doses (MD)	
	Venetoclax alone (Reference)	Venetoclax + Rifampin SD (Test)	Geometric Mean Ratio (90%CI) (Test/Reference)	Venetoclax + Rifampin MD (Test)	Geometric Mean Ratio (90%CI) (Test/Reference)
Venetoclax					
C_{max} (µg/mL)	1.01	2.15	2.06 (1.729, 2.445)	0.61	0.58 (0.484, 0.693)
AUC_t (µg*h/mL)	13.3	23.9	1.80 (1.518, 2.126)	3.8	0.29 (0.242, 0.343)
AUC_{∞} (µg*h/mL)	13.5	24.0	1.78 (1.501, 2.105)	3.9	0.29 (0.241, 0.342)
M27					
C_{max} (µg/mL)	0.12	0.19	1.56 (1.386, 1.751)	0.19	1.60 (1.413, 1.800)
AUC_t (µg*h/mL)	5.19	5.81	1.12 (1.013, 1.235)	2.60	0.50 (0.451, 0.554)
AUC_{∞} (µg*h/mL)	6.03	6.03	1.00 (0.908, 1.103)	2.65	0.44 (0.397, 0.486)

Source: Applicant's M14-497 Clinical Study Report

DDI with CYP2C9 substrate – warfarin

Co-administration with single dose venetoclax 400 mg under fed condition increased C_{max} and AUC_{∞} of *R*- and *S*- warfarin by approximately 18 to 28% (**Table 19**). It should be mentioned that warfarin is substrate of CYP2C9 and K_i of inhibition CYP2C9 by venetoclax was 0.32 μM. As the expected C_{max} of venetoclax after single dose of 400 mg is around 2 μM, the observed magnitude of DDI between venetoclax and warfarin is lower than expected based on *in vitro* prediction. This discrepancy could be due to the very high protein binding (f_{ub}<0.01) of venetoclax in the systemic circulation. In addition, the DDI potential might be underestimated in the DDI study because venetoclax was not dosed to steady state. It should also be noted that, due to safety concern, only three subjects completed both periods of the study. Taken together, the applicant stated that the international normalized ratio (INR) should be monitored in subjects who received warfarin and venetoclax in combination, which is acceptable.

Table 19: Effect of single 400 mg dose venetoclax on warfarin PK

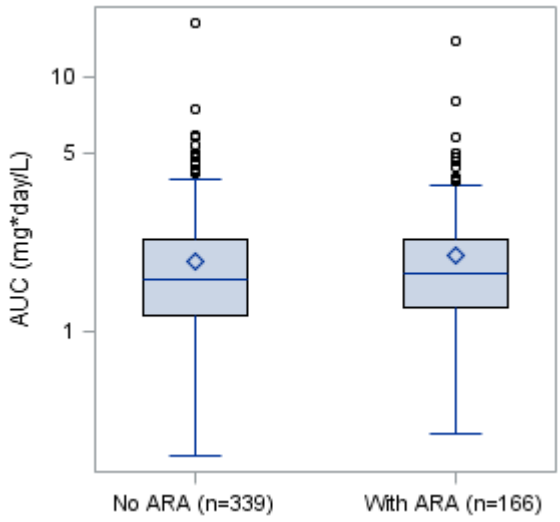
Parameter	Warfarin alone (Reference) (N=8)	Warfarin + Venetoclax (Test) (N=3)	Geometric Mean Ratio (90%CI) (Test/Reference) (N=3)
R-Warfarin			
C_{max} (ng/mL)	250	301	1.204 (1.131, 1.282)
AUC_t (ng*h/mL)	17547	21034	1.199 (1.129, 1.273)
AUC_{∞} (ng*h/mL)	20901	25631	1.226 (1.059, 1.420)
S-Warfarin			
C_{max} (ng/mL)	237	280	1.181(1.008, 1.382)
AUC_t (ng*h/mL)	9575	12210	1.275 (1.199, 1.356)
AUC_{∞} (ng*h/mL)	10970	13996	1.276 (1.238, 1.315)

Source: Applicant's M15-065 Clinical Study Report

DDI with gastric acid reducing agents

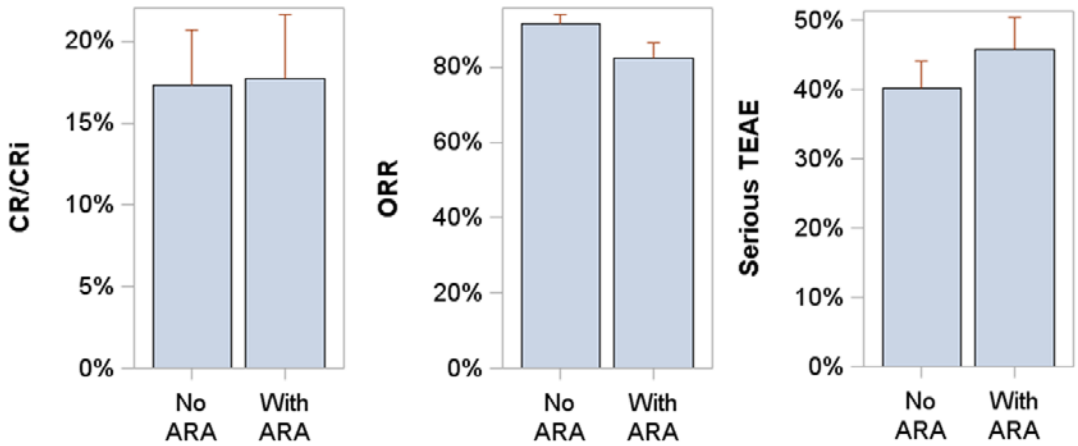
Venetoclax is a weak base that demonstrated low and pH-dependent aqueous solubility (Section 2.1.1). The applicant didn't conduct a dedicated study to evaluate the effect of co-administration of gastric acid reducing agents (ARAs) on venetoclax PK. In the popPK analyses, ARAs were found to have no effect on PK of venetoclax (**Figure 17**). The applicant stated that venetoclax is considered practically insoluble or insoluble (≥ 10,000 parts of solvent to dissolve 1 part of solute) in aqueous solutions at physiological pH range, therefore, ARAs (e.g., proton pump inhibitors, H_2-receptor antagonists, antacids, etc.) are not expected to impact the PK of venetoclax.

Figure 17: AUC comparison between patients with and without concomitant administration of ARAs



In addition, the efficacy (ORR, CR) and safety profile (Serious TEAEs) does not seem to be different with or without ARA co-administration (**Figure 18**), and thus no dose-adjustment is recommended for patients taking ARAs.

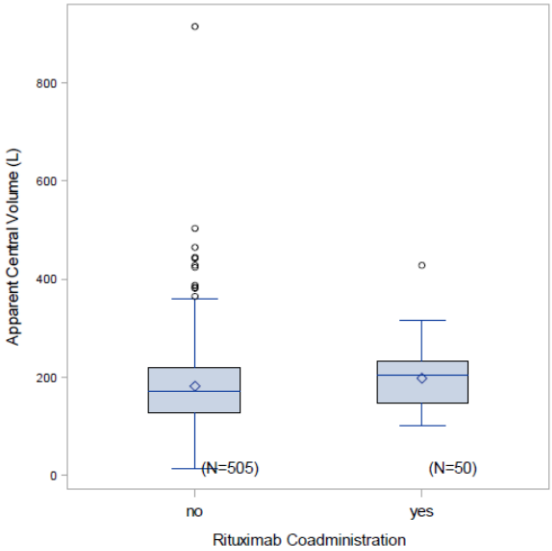
Figure 18: Effect of acid-reducing agent co-administration on CR, ORR and Serious TEAEs



DDI with rituximab

The applicant's popPK analyses indicated that co-administration of rituximab increased apparent clearance (CL/F) of venetoclax by 1.22-fold (90% CI: [1.15, 1.29]) as shown in **Figure 19**. Although this effect is statistically significant, the increase of venetoclax exposure is not clinically meaningful in combination therapy with rituximab.

Figure 19: *Post Hoc* analyses of rituximab co-administration on apparent clearance (CL/F) of venetoclax



Source: Applicant's population PK report (R&D/15/026)

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There is no known mechanistic basis for PD drug-drug interactions.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Yes. The drug interaction potential of venetoclax on P-gp substrates has not been evaluated. The impact of severe organ impairment (hepatic and renal) on venetoclax PK and corresponding dose recommendation has not been addressed.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

No.

2.5 General Biopharmaceutics

Venetoclax is formulated as film-coated tablets for oral administration.

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

The solubility of venetoclax drug substance in aqueous buffer is a function of pH and very low at physiological pH. The permeability of venetoclax is not well understood because of its low recovery in the Caco-2 permeability experiments. Therefore, venetoclax is considered either BCS Class 2 or 4 based on the poor solubility.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the clinical trial formulation?

In the clinical studies supporting the NDA application, two formulations of venetoclax were used: uncoated tablet and film-coated tablet. The tablet core compositions were unchanged throughout the clinical development of venetoclax. The uncoated tablets were used in the early clinical studies (M12-175, M13-365, GP28331, GO28440), the film-coated tablets were used in subsequent clinical studies (M12-175, M13-364, M13-365, M13-982, M14-497, M15-065, M14-032, GP28331 and GO28440). The applicant will market the film-coated tablets.

To bridge the data from their clinical studies, the applicant evaluated the relative bioavailability of the uncoated and film-coated tablet formulations.

Study M14-253 (uncoated vs. coated)
The oral bioavailability of venetoclax 50 mg uncoated tablet was compared with that of venetoclax 50 mg film-coated tablet. The results showed that after single 50 mg taken orally approximately 30 minutes after a standard breakfast, the 90% CI of the geometric mean ratios of primary PK parameters (C_{max}, AUC_t and AUC_∞) from the two formulations were contained in the range of [0.80, 1.25], and the geometric mean ratios were around 1 (**Table 20**). Therefore, under fed condition, the film-coated 50 mg venetolcax tablet formulation is bioequivalent to the uncoated 50 mg venetoclax tablet formulation.

Table 20: Relative bioavailability of uncoated vs. film-coated 50 mg tablets of venetoclax

Parameters	Geometric Means		Relative Bioavailability
	Film-coated (Test)	Uncoated (Reference)	Point Estimate and 90% CI
C_{max} (μg/mL)	0.387	0.373	1.037 (0.962, 1.117)
AUC_t (μg*h/mL)	4.058	4.093	0.991 (0.928, 1.059)
AUC_∞ (μg*h/mL)	4.186	4.216	0.993 (0.930, 1.060)

Source: Applicant's M14-253 Clinical Study Report

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effect of food on venetoclax PK was evaluated in two separate studies (studies M12-175 and M15-101) and in the popPK analyses.

Study M12-175 in patients with NHL (Cohorts 1 to 6 of Arm B)
In the first-in-human Phase 1 study M12-175, effect of food on venetoclax PK was evaluated in 32 patients with NHL from cohorts 1 to 6 of Arm B following a high-fat meal (Week 1 Day -7), and a low-fat meal (Week 6 Day 1) relative to the same patients dosed under fasting condition (Week 1 Day 1). The results showed that single dose of venetoclax with high-fat meals increased venetoclax C_{max} and AUC_∞ approximately 4-fold compared to single dose under fasting condition (**Table 21**). The dose-normalized AUC after multiple doses (steady state) of venetoclax with low-fat meal was approximately 4-fold of that from single dose under fasting

condition. However, this comparison might overestimate the food effect from low-fat meal because PK data for comparison were those after single dose under fasting condition, not at steady state.

Table 21: Assessment of food effect on venetoclax PK in NHL patients

Regimens Test vs. Reference	Pharmacokinetic Parameter	Relative Bioavailability	
		Point Estimate	(90% Confidence Interval)
High-Fat Week 1 Day –7 vs. Fasting Week 1 Day 1	C_{max} (µg/mL)	3.676	3.005 – 4.497
	AUC_{∞} (µg•h/mL)	4.418	3.370 – 5.790
Low-Fat Week 6 Day 1 vs. Fasting Week 1 Day 1	AUC[a] (µg•h/mL)	4.268	2.977 – 6.117

a. Dose-normalized AUC_{0-24} (low-fat)/Dose-normalized AUC_{∞} (fasting).

Source: Applicant's M12-175 Clinical Study Report – Interim

Table 22: Effect of low- and high-fat meals on venetoclax PK in healthy female subjects

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value[a]		Relative Bioavailability	
		Test	Reference	Point Estimate[b]	90% Confidence Interval[c]
B vs. A	C_{max} (µg/mL)	0.499	0.146	3.412	2.864 – 4.065
	AUC_t (µg•h/mL)	6.774	1.960	3.457	2.924 – 4.086
	AUC_{∞} (µg•h/mL)	7.066	2.081	3.396	2.878 – 4.007
C vs. A	C_{max} (µg/mL)	0.777	0.146	5.319	4.465 – 6.336
	AUC_t (µg•h/mL)	10.111	1.960	5.159	4.364 – 6.099
	AUC_{∞} (µg•h/mL)	10.542	2.081	5.067	4.294 – 5.979
C vs. B	C_{max} (µg/mL)	0.777	0.499	1.559	1.309 – 1.857
	AUC_t (µg•h/mL)	10.111	6.774	1.492	1.262 – 1.764
	AUC_{∞} (µg•h/mL)	10.542	7.066	1.492	1.264 – 1.760

Regimen A: One 100 mg venetoclax tablet (manufactured in Sligo, Ireland) administered under fasting conditions.

Regimen B: One 100 mg venetoclax tablet (manufactured in Sligo, Ireland) administered after a low-fat breakfast.

Regimen C: One 100 mg venetoclax tablet (manufactured in Sligo, Ireland) administered after a high-fat breakfast.

a. Antilogarithm of the least squares means for logarithms.

b. Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

c. Antilogarithm of the endpoints of confidence intervals for the difference of logarithms means.

Source: Applicant's M15-101 Clinical Study Report

Study M15-101 in healthy subjects (Regimen A, B and C)

Food effect on venetoclax PK was also evaluated with the to-be-marketed film-coated tablet formulation manufactured in Sligo, Ireland in Phase 1 study M15-101. Twenty-four healthy female subjects received single dose of venetoclax 100 mg under fasting condition (regimen A), after low-fat breakfasts (regimen B) and high-fat breakfasts (regimen C) according to a complete crossover design. As shown in **Table 22**, administration of venetoclax following low-fat and high-fat meals increased venetoclax PK exposure (both C_{max} and AUC_{∞}) by approximately 3.4-

fold and 5-fold, respectively, compared to fasting conditions. There was an approximately 1.5-fold increase in venetoclax PK following high-fat meals compared to low-fat meals.

Population PK analyses
The effect of food on relative bioavailability of venetoclax was evaluated under fasting, fed-state (without specification of meal fat-content), low-, moderate- and high-fat meal conditions in the popPK analyses. The results suggested that the relative bioavailability of venetoclax with a low-fat meal was 2.99-fold of that in the fasting condition. Similarly, the relative bioavailability increased by 3.67-, 3.91- and 4.27-fold following administration in the fed state (without specification of meal fat-content), with moderate-fat meals, and with high-fat meals, respectively, compare to the fast condition. Overall, the popPK analysis results are consistent with the findings in those relative BA studies.

Venetoclax was administered with food in all clinical studies, and without specific recommendation for fat or caloric content in studies M13-982, M14-302 and M13-365 to evaluate the safety and efficacy of venetoclax in the target population.

The applicant proposed that venetoclax should be taken with a meal to ensure adequate oral bioavailability. The applicant also stated that the specification of the fat content of the meals taken with venetoclax is not necessary because there was only a 1.5-fold increase of venetoclax exposure from low-fat to high-fat meal and the exposure-response relationship at steady state dose of 400 mg is relatively flat, which is acceptable.

2.5.4 When would a fed BE study be appropriate and was one conducted?

Yes, a fed BE study is appropriate and it has been conducted, see Section 2.5.3.

2.5.5 How do dissolution conditions and specifications ensure in vivo performance and quality of the product?

Refer to Biopharmaceutics review.

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of various strengths of the to-be-marketed product?

Not applicable.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the 'to-be-marketed' product? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable.

2.5.9 What other significant, unresolved issues in relation to in vitro dissolution of in vivo BA and BE need to be addressed?

None.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Following oral administration of venetoclax, the active pharmacological moiety is venetoclax. The major metabolite M27 is at least 58-fold less active than parent venetoclax on Bcl-2 inhibition so it is not considered a pharmacologically active moiety. High performance liquid chromatograph coupled with tandem mass spectrometry (LC-MS/MS) methods were developed and validated for the identification and quantification of venetoclax and M27 in human plasma and urine from patients and healthy volunteers.

2.6.2 Which metabolites have been selected for analysis and why?

Not applicable. Venetoclax metabolites including M27 were not considered or known to have pharmacological activity and were not measured in clinical studies.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Because venetoclax is highly bound (>99%) to human plasma proteins, total plasma concentrations were measured.

2.6.4 What bioanalytical methods are used to assess concentrations?

Venetoclax concentrations in human plasma and urine were measured using validated LC-MS/MS methods. Two analytical methods (R&D/11/278 and R&D/14/0548) were developed and later updated to analyze PK samples of venetoclax. In addition, a LC-MS/MS method was developed for the measurement of M27 metabolite but this method was not validated.

A validated enzyme-linked immunosorbent assay (ELISA) method was validated to measure the concentration of rituximab plasma concentrations in combination therapy.

A LC-MS/MS method was also developed and validated for the quantitative determination of (*R*)-warfarin and (*S*)-warfarin in human plasma in the DDI study M15-065.

The assay accuracy and precision of the above bioanalytical methods are summarized in **Table 23** below.

Table 23: Summary of bioanalytical methods and their applications in clinical studies

Validation Report No.	Analyte	Method	Individual Study Report	LLOQ (ng/mL)	Linear Range (ng/mL)	Accuracy, % Bias	Precision, % CV	Incurred Sample Analysis
R&D/11/278 with method update in R&D/14/0465	Venetoclax (Plasma)	LC-MS/MS	m12175 m13364 m13365 m13982 m14253 gp28331	2.05	2.05 - 2050	-1.5 to 3.7	1.6 to 3.2	Yes
R&D14/0548 with method update in R&D/15/0131	Venetoclax (Plasma)	LC-MS/MS	m12175 m13363 m13364 m13365 m13982 m14032 m14497 m15065 m15101 go28440 gp28331	2.11	2.11 - 2030	-1.4 to 0.0	1.6 to 5.5	Yes
R&D/14/1078	Venetoclax (Urine)	LC-MS/MS	M12175	2.00	2.00 to 200	3.0 to 3.8	2.6 to 2.8	Yes
c-da-6281575-val-elisa-ser-rituximan; c-da-c2b8004-val-elisa-ser-rituximab	Rituximab (Serum)	ELISA	m13365	500	500 - 12800	-12.6 to -2.13	5.56 to 9.46	Yes
c-da-p1044-val-update-lcms-pla-warfarin	(R)-Warfarin; (S)-Warfarin (Plasma)	LC-MS/MS	m15065	5.00	5.00 - 1500	-6.74 to 0.473 (R); -6.78 to 1.38 (S)	4.17 to 5.42 (R); 3.83 to 5.90 (S)	Yes

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

The range of the standard curves are shown in **Table 23** above in Section 2.6.4. The concentrations of the analytes were either within the bounds of the standard curve ranges or require further dilution.

2.6.6 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See **Table 23** in Section 2.6.4 above.

2.6.7 What are the accuracy, precision, and selectivity at these limits?

See **Table 23** in Section 2.6.4 above.

3 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY
PHARMACOMETRIC REVIEW

NDA	208573
Brand Name: **Generic Name:**	VENCLEXTA® Venetoclax
Applicant:	AbbVie Inc.
Formulation; Strength(s):	Oral Tablets: 10 mg, 50 mg, 100 mg
Proposed Indication:	For the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, including those with 17p deletion (17p del)
OND Division:	Division of Hematology Products (DHP)
OCP Division:	Division of Pharmacometrics (DPM)
Pharmacometrics Reviewers:	Lian Ma, Ph.D. (DPM) Justin Earp, Ph.D. (DPM)
Pharmacometrics Team Leader:	Nitin Mehrotra, Ph.D. (DPM)

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1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Do the dose/exposure-response relationship for efficacy & safety support the proposed dosing regimen of venetoclax (starting at 20 mg once daily for 7 days, followed by a weekly ramp-up dosing schedule (through 50, 100, and 200 mg) to the recommended daily dose of 400 mg)?

Yes. The proposed dosing regimen of venetoclax is generally supported by the following rationales:

- Under initially studied regimen with higher starting doses and no ramp-up schedule (Pre-May 2013 Amendment), 11.7% (9/77) of subjects experienced AEs of tumor lysis syndrome (TLS) with 6.5% (5/77) experiencing clinical tumor lysis syndrome (CTLS), including 2 fatal events. The ramp-up dosing schedule, which includes a lead-in period and a step-wise increase in dose, likely led to gradual debulking of the tumor and thereby mitigating the risk of TLS. It has shown a marked reduction in the frequency and severity with AEs of TLS reported in 4.3% (10/234) of subjects, and no events of CTLS (0/234).

- Exposure-response relationship for objective response rates (ORR) was generally flat, indicating that increase in venetoclax exposure will not result in additional benefit in ORR. For clinical remission (CR/CRi), there was a trend showing increasing probability of CR with higher exposure, suggesting potential benefit in remission might be gained by dose higher than 400 mg. However, given the limited IRC data available for CR, and the risk consideration for TLS, the recommended steady state dose was selected at 400 mg QD based on ORR.

- No apparent exposure-response relationship was identified for adverse events, including grade 3/4 infection and grade 3/4 neutropenia.

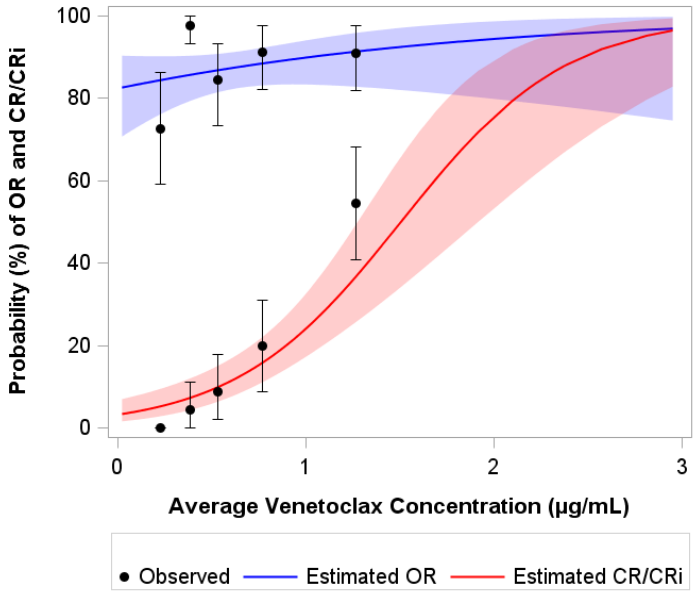
The selection of starting dose and ramp-up dosing schedule was determined based on the efficacy, PK, and safety findings from the first-in-human Phase 1 study M12-175. Refer to Section 2.2.4.4 for details on dose selection.

Exposure-Response Analysis for Efficacy

The exposure-response relationship for ORR and CR was conducted using logistic regression analysis, based on pooled data from 2 studies (studies M13-982, M12-175). The exposure metric was average venetoclax concentration up to the first time of the response (e.g., ORR or CR), calculated as the cumulative AUC (derived from the final population PK model) across dosing intervals up to the first time of the respective response, divided by the time (i.e., from the first dose administration until the time of the response). The average concentration across the entire treatment period was utilized for subjects who did not achieve the response under consideration. See Section 2.1.2 for more details.

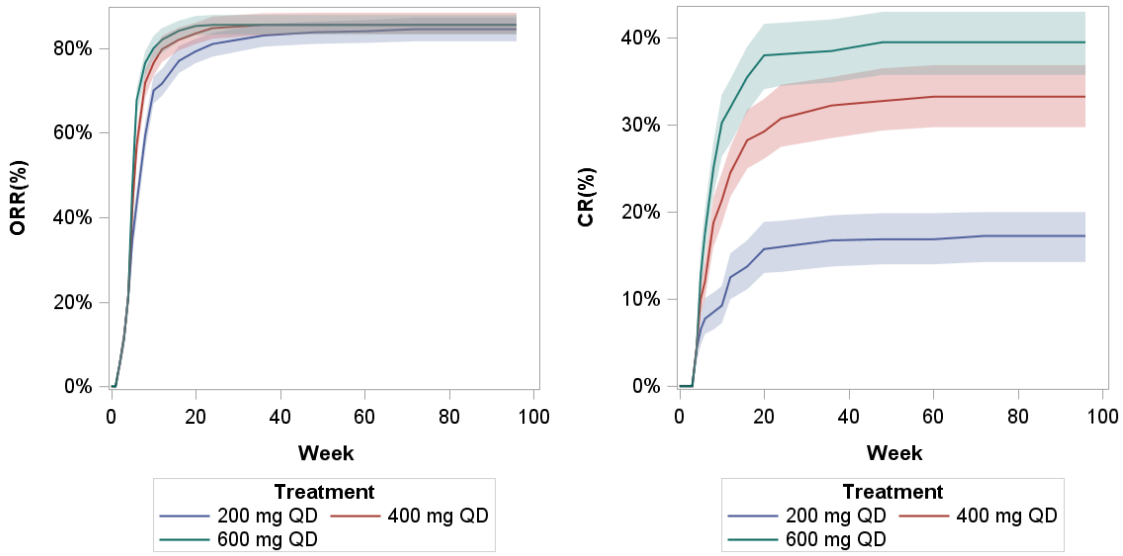
The analysis results were generally consistent with the observed dose-response in study M12-175. No evident exposure-response relationship was identified for probability of ORR (**Figure 1**). A dose of 400 mg QD, associated with an average concentration of 1.10 µg/mL, is in the plateau part of the exposure-response curve. There appears to be a clear trend for CR, showing increasing probability of CR with higher exposure of venetoclax, which suggests potential benefit in remission might be gained by administering doses higher than 400 mg. This trend is consistent with or without adjusting for baseline lymphocytes and tumor size, which were identified as significant covariates for CR based on multivariate analysis. In addition, 17p deletion mutation status was not identified as a significant covariate for ORR or CR, thus these relationships are not expected to be different between patients with 17p deletion and those without 17p deletion, given similar response rates in these two patient population.

Figure 1. Increase in probability of achieving ORR and CR with increasing venetoclax exposure (Study M12-175 and M13-982)



A population PK/PD model for lymphocytes and tumor size response was developed by the applicant to further refine the exposure-response relationship. The final population PK/PD models were subsequently used to simulate ORR and CR at various dosing regimens. Simulated ORR and CR time profiles by the designated dosage regimen (including ramp-up doses) of 200, 400, and 600 mg QD are shown in **Figure 2**. Simulation results indicated that by 6 months of venetoclax treatment, the ORR reached 80.9%, 84.8% and 85.5% at the 200, 400 and 600 mg dosage regimens, respectively. The model predicted a separation in ORR between the 400 and 600 mg doses at early time points; however, the difference diminished after 24 weeks of treatment. The CR at end of 6 months was 17.2%, 33.2%, 39.5% for the 200, 400 and 600 mg dosage regimens, with 6.3% difference between 400 and 600 mg dosing regimen.

Figure 2. Time courses of simulated ORR (left) and CR (right) on the 200, 400 and 600 mg QD target dosing regimens



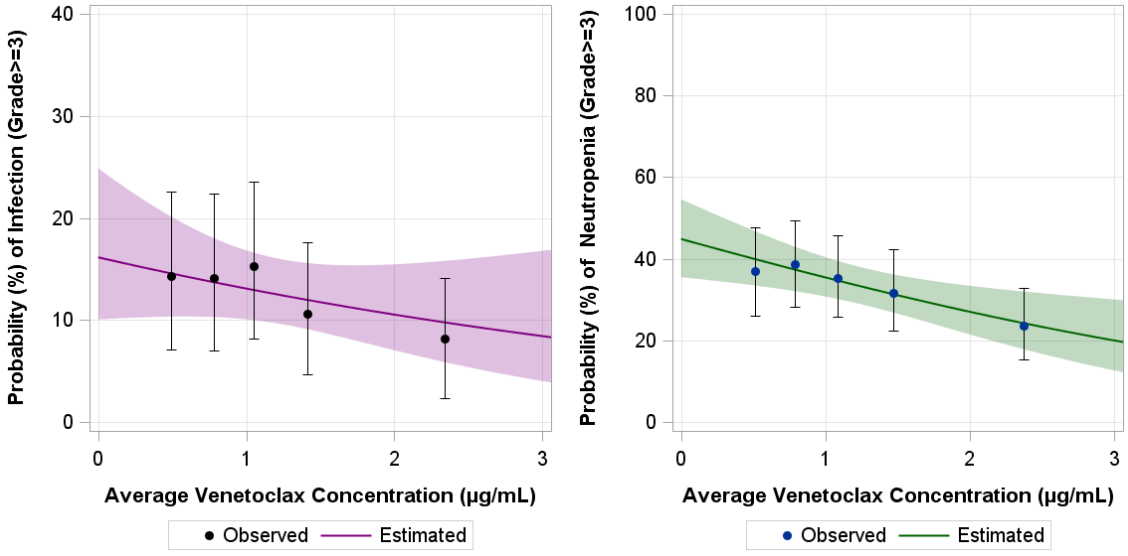
Note: ORR was defined as a decrease in lymphocytes of ≥ 50% from baseline and a decrease in tumor size of ≥ 50%; CR was defined as lymphocyte levels below 4000/µL and tumor size smaller than 1.5 cm.

Overall, both the logistic regression analyses and the PK/PD model simulations suggested minimal differences between the 400 or 600 mg QD dose in ORR, while a potential increase in CR with the higher dose. However, it was noted that IRC data for CR was only available for 400 mg, and the exposure-response analyses (dose ranges from 150 to 1200 mg) were based on investigator assessment data. Considering the observed discrepancy between the IRC assessed CR rate (7.5%) and the investigator assessed CR rate (16.0%) in the pivotal Phase 2 study M13-982, the potential increase in CR with higher doses is inconclusive. Further, based on discussion with the clinical review team, ORR is the most relevant efficacy endpoint for the indicated population (CLL patients with 17p deletion), thus 400 mg dose is acceptable given the flat exposure-response for ORR and lack of evidence of exposure-safety relationship.

Exposure-Response Analysis for Safety

Exposure-response relationship for venetoclax TEAEs (grade 3/4 neutropenia and infection) were evaluated based on pooled data from studies M12-175, M13-982, M13-365 and M14-032. Logistic regression analyses, similar to that used for the exposure-efficacy analyses, were employed. The sensitivity analysis after removing the confounding dose ramp-up phase data showed that increase of venetoclax exposure was not associated the occurrence of these AEs (**Figure 3**). Please see Reviewer's Analysis in Section 3.1 for more details.

Figure 3. Sensitive analyses of logistic regression model of the probability of Grade 3/4 infection (left) and Grade 3/4 neutropenia (right) vs. average venetoclax concentration - excluded the 30 days lead-in period



This is consistent with the summary of observed serious TEAEs in CLL subjects from studies M13-982, M12-175 Arm A, and M14-032, by dose cohorts (**Table 1).** The safety profile of venetoclax is generally comparable across the dose groups. Although the sample size across the dose groups is limited (sample size of 5 -15 subjects), except for the 400 mg dose group.

Table 1. Serious TEAEs reported in ≥ 1% of all subjects or the 400 mg dose group (all treated subjects in CLL venetoclax monotherapy studies by assigned dosage – 90-Day Safety Update)

	Number (%) of Subjects[a]							
System Organ Class Preferred Term (MedDRA v17.1)	150 mg N = 6	200 mg N = 9	300 mg N = 7	400 mg N = 279	600 mg N = 15	800 mg N = 7	1200 mg N = 5	Total N = 328
Any SAE	4 (66.7)	7 (77.8)	3 (42.9)	123 (44.1)	9 (60.0)	2 (28.6)	3 (60.0)	151 (46.0)
Blood and lymphatic system disorders	1 (16.7)	4 (44.4)	1 (14.3)	33 (11.8)	0	1 (14.3)	0	40 (12.2)
Anaemia	0	0	0	5 (1.8)	0	0	0	5 (1.5)
Autoimmune haemolytic anaemia	0	0	0	8 (2.9)	0	0	0	8 (2.4)
Febrile neutropenia	1 (16.7)	2 (22.2)	1 (14.3)	13 (4.7)	0	1 (14.3)	0	18 (5.5)
Immune thrombocytopenic purpura	1 (16.7)	1 (11.1)	0	2 (0.7)	0	0	0	4 (1.2)
Neutropenia	0	0	0	5 (1.8)	0	0	0	5 (1.5)
Thrombocytopenia	0	0	0	5 (1.8)	0	0	0	5 (1.5)
Cardiac disorders	0	0	1 (14.3)	9 (3.2)	1 (6.7)	0	0	11 (3.4)
Atrial fibrillation	0	0	0	4 (1.4)	0	0	0	4 (1.2)
Gastrointestinal disorders	1 (16.7)	1 (11.1)	0	16 (5.7)	3 (20.0)	1 (14.3)	0	22 (6.7)
Small intestinal obstruction	0	0	0	3 (1.1)	0	0	0	3 (0.9)
General disorders and administration site conditions	1 (16.7)	2 (22.2)	0	21 (7.5)	1 (6.7)	0	1 (20.0)	26 (7.9)
Multi-organ failure	0	1 (11.1)	0	3 (1.1)	0	0	0	4 (1.2)
Pyrexia	1 (16.7)	0	0	9 (3.2)	0	0	0	10 (3.0)

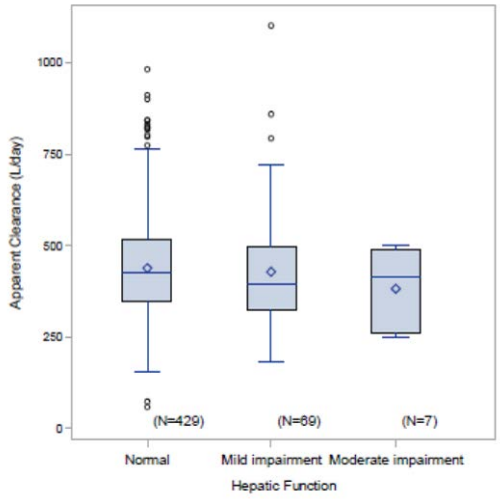
(Source: applicant's response to FDA information request, January 27, 2016)

1.1.2 What is the appropriate dosing recommendation for patients with hepatic impairment?

There is no need for dose adjustment for mild or moderate hepatic impairment. Although no dose-adjustment is recommended for patients with moderate hepatic impairment, monitoring and dose-modification based on tolerability during the dose ramp-up period may be required. A recommended dose has not been determined for patients with severe hepatic impairment and a post-marketing requirement will be issued to inform the dosing in this patient population.

The applicant proposed no dose adjustment in patients with mild or moderate hepatic impairment. The applicant's popPK analysis indicated mild (N=69) and moderate (N=7) hepatic impairment had no effect on venetoclax PK (**Figure 4**). The hepatic impairment category was defined based on NCI-ODWG criteria.

Figure 4: Comparison of post hoc apparent clearance by hepatic function category



Source: applicant's popPK report R&D/15/0256

The claim of no dosage adjustment for mild hepatic impairment is further supported by the applicant's safety analysis by hepatic impairment subgroup (**Table 2**), where similar safety profiles were observed for patients with mild hepatic impairment compared to those with normal hepatic function. See Section 3.2 for further details.

In addition to lack of effect of moderate hepatic impairment on venetoclax PK, we looked at the exposures in patients with moderate hepatic impairment relative to exposures observed in patients with normal hepatic function. It was observed that the exposures in seven moderate hepatic impairment patients were generally within the range of exposures observed in patients with normal hepatic function in the pivotal Phase 2 trial (**Figure 5**) except for one patient shown with solid red dots in the figure below who had exposures higher than the observed exposures in the Phase 1 trial (M12-175). Steady state doses for patients with moderate hepatic impairment were further evaluated and was seen that a dose of 1200 mg was administered to this particular patient which can explain higher exposures compared to others. Of the seven patients with moderate hepatic impairment, four were dosed to 400 mg, one to 600 mg, and another to 1200

mg. The last patient was dosed to 200 mg and left the trial before the titration permitted adjustment to 400 mg. Although no dose-adjustment is recommended for patients with moderate hepatic impairment, due to slightly higher incidence of TEAEs in these patients based on limited data (N=7), monitoring and dose-modification based on tolerability during the dose ramp-up period may be required.

Figure 5: Exposures in seven moderate hepatic impairment patients (Trials: M12-175 n=4 subjects, and M13-982 n=3 subjects) overlaid with exposures observed in patients with normal hepatic function in the pivotal Phase 2 trial M13-982

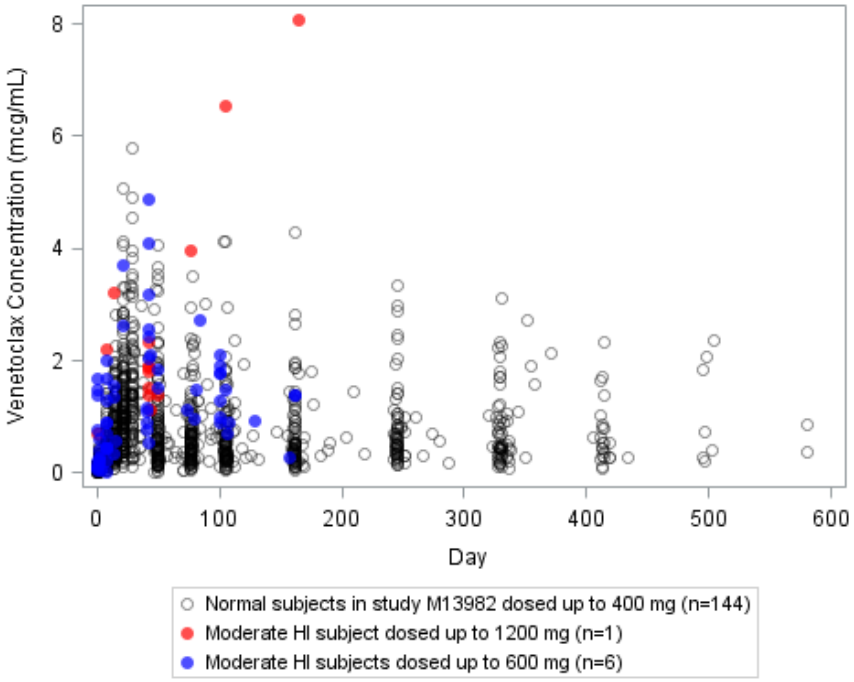


Table 2: Overview of TEAEs by hepatic function: venetoclax monotherapy in R/R CLL (Monotherapy Analysis Sets)

	Number (%) of Subjects											
	Venetoclax 400 mg QD						Venetoclax All Doses					
	All[a]			17p Del[b]			All[a]			17p Del[b]		
Type of TEAE	Normal Hepatic Function N = 198	Mild Hepatic Impair[c] N = 37	Moderate Hepatic Impair[c] N = 5	Normal Hepatic Function N = 137	Mild Hepatic Impair[c] N = 21	Moderate Hepatic Impair[c] N = 2	Normal Hepatic Function N = 237	Mild Hepatic Impair[c] N = 47	Moderate Hepatic Impair[c] N = 5	Normal Hepatic Function N = 149	Mild Hepatic Impair[c] N = 26	Moderate Hepatic Impair[c] N = 2
Any TEAE	194 (98.0)	37 (100)	5 (100)	133 (97.1)	21 (100)	2 (100)	232 (97.9)	47 (100)	5 (100)	144 (96.6)	26 (100)	2 (100)
CTCAE grade ≥ 3	148 (74.7)	25 (67.6)	4 (80.0)	100 (73.0)	14 (66.7)	1 (50.0)	177 (74.7)	34 (72.3)	4 (80.0)	110 (73.8)	18 (69.2)	1 (50.0)
Serious TEAEs	87 (43.9)	16 (43.2)	3 (60.0)	65 (47.4)	11 (52.4)	1 (50.0)	107 (45.1)	22 (46.8)	3 (60.0)	71 (47.7)	13 (50.0)	1 (50.0)

17p del = deletion of the p13 locus on chromosome 17; AST = aspartate aminotransferase; CLL = chronic lymphocytic leukemia; CTCAE = Common terminology Criteria for Adverse Events (version 4.0); R/R = relapsed or refractory; TEAE = treatment-emergent adverse event

a. Subjects with R/R CLL in Studies M13-982, M12-175 Arm A, and M14-032.

b. Subjects with R/R CLL harboring 17p del; Studies M13-982, M12-175 Arm A, and M14-032.

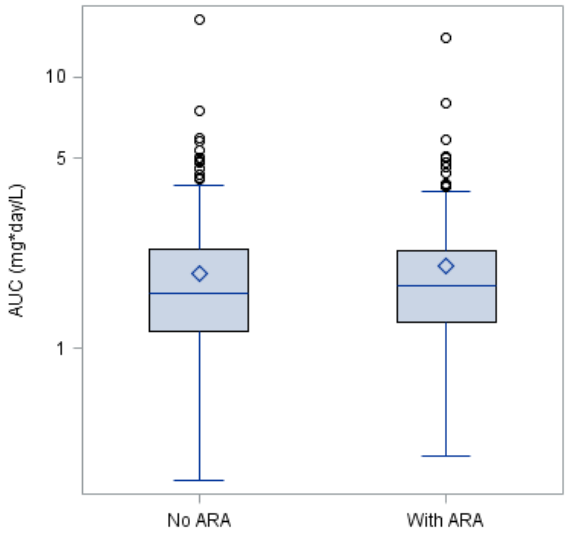
c. Normal hepatic function: total bilirubin ≤ 1 mg/dL and AST ≤ 40 U/
Mild impairment: total bilirubin ≤ 1 mg/dL and AST > 40 U/L, or
total bilirubin > 1.0 to ≤ 1.5 mg/dL and any AST;
Moderate impairment: total bilirubin > 1.5 to ≤ 3 mg/dL and any AST.

Source: Applicant's Clinical Summary of Safety, Table 56

1.1.3 What is the appropriate dosing recommendation for patients taking gastric acid reducing agents (ARA)?

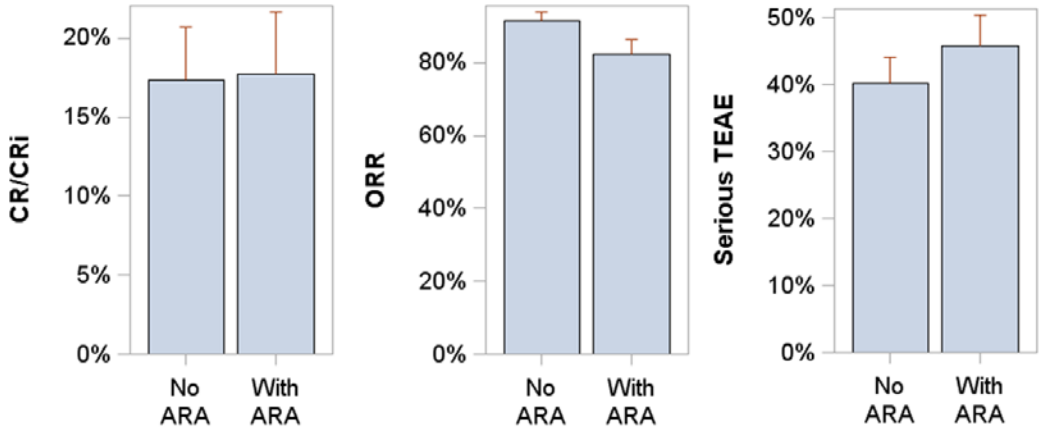
No dose adjustment is needed for venetoclax in patients taking ARAs, given similar PK, efficacy and safety profiles. Venetoclax is a weak base that demonstrated low and pH-dependent aqueous solubility. The applicant didn't conduct a dedicated study to evaluate the effect of co-administration of gastric acid reducing agents (ARAs) on venetoclax PK. In the popPK analyses, ARAs were found to have no effect on PK of venetoclax (**Figure 6**). The applicant stated that venetoclax is considered practically insoluble or insoluble (≥ 10,000 parts of solvent to dissolve 1 part of solute) in aqueous solutions at physiological pH range, therefore, ARAs (e.g., proton pump inhibitors, H_2-receptor antagonists, antacids, etc.) are not expected to impact the PK of venetoclax. There were PK data from 264 patients that did not receive ARAs and PK data from 241 subjects who did. Inclusive to this dataset, there were data from 68 subjects with concomitant acid reducing agents from study M12-175 where the PK sampling was more robust >4 samples per subject compared with the rest of the clinical trial data. Additionally, the majority of subjects taking these concomitant medications were on them for weeks at a time, and the population PK analysis was sensitive to whether or not they were on the medication, therefore any effect acid-reducing agents may have had on the PK of venetoclax should have been detected.

Figure 6. AUC is not different between patients receiving and not receiving acid-reducing agents (ARA)



In addition, the efficacy (ORR, CR) and safety profile (Serious TEAEs) does not seem to be different with or without ARA co-administration (**Figure 7**), and thus no dose adjustment is recommended for patients taking ARAs.

Figure 7. Effect of acid-reducing agent co-administration on CR, ORR and serious TEAEs



1.2 Recommendations

Division of Pharmacometrics/Office of Clinical Pharmacology has reviewed the information provided in the submission and considers that the data are acceptable for supporting the approval and labeling of venetoclax for the indicated patient population.

1.3 Label Statements

Please refer to Clinical Pharmacology QBR for detailed labeling recommendations.

2 RESULTS OF APPLICANT'S ANALYSIS

2.1.1 Population PK analysis

2.1.1.1 Data

The population pharmacokinetic analysis included five studies in cancer patient subjects (Studies M13-982, M12-175, M14-032, M13-365 and M13-364) and three studies in healthy subjects (Studies M14-253, M14-497 and M15-101). An overview of the studies is provided in **Table 3**.

Data from 505 subjects who received venetoclax that had at least one measurable venetoclax plasma concentration were included in the population pharmacokinetic analyses. In total, 7483 plasma venetoclax observations were collected from venetoclax doses ranging from 10 mg to 1200 mg QD. The majority of subjects (68.3%) included in the pharmacokinetic analysis received a 400 mg dose. Specific information regarding the disposition of subjects is presented in the respective CSRs/interim clinical study reports.

Table 3. Summary of studies included in population PK analysis

Study/Type/Status (N)	Phase	Study Design and Population	Dose Range and Pharmacokinetic Sampling
M12-175/FIH Safety and PK study/Ongoing (N = 222)	1	Open-label, multicenter, monotherapy study evaluating the safety profile and PK of venetoclax administered once daily to subjects with R/R CLL/SLL (Arm A) and NHL (Arm B)	Dose range evaluated: 150 to 1200 mg once daily. Intensive PK sampling: Arm A: 0, 2, 3, 4, 6, 8, 24, 48, 72 hours post-dose on Week 1 Day −7 (dose escalation cohorts only) and 0, 2, 3, 4, 6, 8, and 24 hours post-dose on Week 6 Day 1 (dose escalation cohorts) or Week 7 Day 1 (safety expansion cohort) Arm B: 0, 2, 3, 4, 6, 8, 24, 48, 72 hours post-dose on Week 1 Day −7 (dose escalation cohorts 1 – 6 only) and 0, 2, 3, 4, 6, 8, and 24 hours post-dose on Week 1 Day 1 (all dose escalation cohorts) and 0, 2, 3, 4, 6, 8, and 24 hours post-dose on Week 6 or 7 Day 1 (all cohorts) Sparse PK sampling: Arm A: Dose escalation cohorts – 0 hours (pre-dose) on Day 1 of Weeks 8, 12, 16, and 24 Arm A safety expansion and all Arm B cohorts: 8 hours post-dose on Day 1 of Weeks 1, 2, 3, 4, 5 and 0 hours (pre-dose) on Day 1 of Weeks 8, 12, 16, and 24
M13-364/DDI study/Complete (N = 12)	1	Open-label study in subjects with R/R NHL to assess the effects of ketoconazole on the pharmacokinetics of venetoclax	Dose evaluated: 50 mg on Day 1 and Day 8 PK sampling: 0, 2, 4, 6, 8, 10, 12, 24, 48, 72, 96 hours on Day 1 and Day 8
M13-365/Safety and PK study/Ongoing (N = 49)	1b	Open-label, multicenter study designed to determine the safety and tolerability of venetoclax when administered once daily in combination with rituximab in subjects with relapsed CLL and SLL	Dose range evaluated: 200 to 600 mg once daily Intensive PK sampling: Cohorts 1 and 2: 0, 2, 4, 6, 8 hours post-dose on Week 2 Day 4 (venetoclax alone) and Week 6 Day 1 (venetoclax + rituximab); Cohorts 3 to 5: 0, 2, 4, 6, 8 hours post-dose on Month 2 Day 1 (venetoclax + rituximab) Sparse PK sampling: Cohorts 1 to 6: 8 hours post-dose on dose escalation days and 0 hour (pre-dose) at scheduled visits
M13-982/Efficacy study/Ongoing (N = 145)	2	Open-label, single arm, multicenter study evaluating efficacy of venetoclax administered once daily to subjects with R/R CLL harboring 17p deletion	Dose evaluated: 400 mg once daily PK sampling: 8 hours post-dose on Day 1 of Weeks 1, 2, 3, 4, 5 and 0 hours (pre-dose) on Day 1 of Weeks 8, 12, 16, 24 and every 12 weeks thereafter (e.g., Weeks 36, 48, 60, etc.)
M14-032/Efficacy and Safety study/Ongoing (N = 28)	2	Open-label, multicenter study evaluating efficacy and safety of venetoclax administered once daily to CLL subjects who are R/R to treatment with BCR signaling pathway inhibitors (ibrutinib-Arm A and idelalisib-Arm B)	Dose evaluated: 400 mg once daily PK sampling: 8 hours post-dose on Day 1 of Weeks 1, 2, 3, 4, 5 and 0 hours (pre-dose) on Day 1 of Weeks 8, 12, 16, and 24
M14-253/ Bioavailability/ Complete (N = 15)	1	Open-label study to evaluate the relative oral bioavailability of coated vs. uncoated venetoclax tablets under fed conditions in healthy female subjects of non-child bearing potential	Dose evaluated: 50 mg once in each period PK sampling: 0, 2, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48, and 72 hours after each dose
M14-497[a]/DDI study/Complete (N = 12)	1	Open-label, single center study to assess the effect of rifampin in healthy female subjects of non-child bearing potential	Dose evaluated: 200 mg orally on Period 1 Day 1, Period 2 Day 1, and Period 2 Day 14 PK sampling: 0, 2, 4, 6, 8, 10, 12, 16, 24, 48, 72, 96 hours after each dose
M15-101/Food effect and bioavailability study/Complete (N = 24)	1	Open-label, randomized, crossover study to evaluate bioavailability and food effect in healthy female subjects of non-child bearing potential	Dose evaluated: 100 mg in each of 4 periods PK sampling: 0, 2, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48, 72 hours after each dose

FIH = first in human; PK = Pharmacokinetics; DDI = Drug-drug interaction

a. Only the venetoclax monotherapy portion included in the analysis.

(Source: Applicant's Population PK Report, Table 1)

2.1.1.2 Methods

Population pharmacokinetic models were built using nonlinear mixed effects modeling based on NONMEM 7.3 compiled with the GNU Fortran compiler (Version 4.5.1). The first-order conditional estimation method with η-ε interaction (FOCE-INT) was employed for all model runs within NONMEM.

First, a base model was developed that defined the structural model, as well as the models for the inter-individual- and residual variabilities. The development of the structural model involved a

comparison of potential model representations based on available data and parameter identifiability. Based on prior experience, structural model development began with a 2-compartment model parameterized in terms of apparent clearance with an absorption compartment. Furthermore, as prior studies indicated a food effect and that venetoclax exposure was less than dose proportional, both the effect of food intake and dose were incorporated on venetoclax relative bioavailability in the base model building. Covariate effects were included into the model in a multiplicative fashion. Continuous covariates were normalized to a reference value and included in the model with a power function. Categorical covariates were tested with a multiplicative model in order to obtain the fractional difference of pharmacokinetic parameters between the tested categorical groups. Additionally, inter-individual variability (IIV) in pharmacokinetic parameters was modeled using a log-normal distribution, resulting in:

$$\theta_{i,k} = \theta_k \cdot \left(\prod_{p=1}^{n_p} \left(\frac{cov_{i,p}}{ref_p} \right)^{\theta_{k,p}} \cdot \prod_{q=1}^{n_q} (\theta_{k,q})^{cov_{i,q}} \right) \cdot exp(\eta_{i,k})$$

where $\theta_{i,k}$ is the value of the k^{th} parameter in the i^{th} subject, θ_k is the typical value of the k^{th} parameter, n_p is the number of continuous covariates, $cov_{i,p}$ is the p^{th} continuous covariate value in the i^{th} subject, ref_p is the reference values for the p^{th} continuous covariate, $\theta_{k,p}$ is the p^{th} continuous covariate parameter estimate for the k^{th} parameter, n_q is the number of categorical covariates, $\theta_{k,q}$ is the q^{th} categorical covariate parameter estimate for the k^{th} parameter, $cov_{i,q}$ is the q^{th} categorical covariate indicator value (0 or 1) for the i^{th} subject, and $\eta_{i,k}$ is the individual-specific random effects for the k^{th} parameter in the i^{th} subject. The $\eta_{i,k}$ values are assumed to be multivariate normally distributed with mean vector $\mathbf{0}$ and variance-covariance matrix Ω: $\boldsymbol{\eta} \sim MVN(\mathbf{0}, \Omega)$, with the k^{th} diagonal variance elements denoted by ω_k^2.

Residual variability was modeled using the proportional (constant coefficient of variation) additive or a combination error model (additive and proportional).

Relevant covariate-parameter relationships were investigated using forward inclusion/backward elimination procedures. Confidence intervals of secondary model parameters were calculated from the primary model parameters using a parametric bootstrap of 10,000 parameter replicates and the parameter covariance matrix.

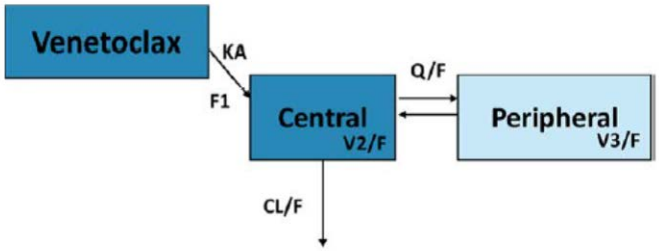
During the process of model development, graphical methods were employed to assess model goodness-of-fit. When selecting the variability models, both the selection criteria, as well as the appropriateness of the model in relation to the nature of the observations, were considered. Correlations between parameters were investigated.

Hepatic function was defined based on National Cancer Institute Organ Dysfunction Working Group Classification of Hepatic Dysfunction with upper limits of the normal range defined as 1.0 mg/dL for bilirubin and 40 IU/L for AST.

2.1.1.3 Results

A schematic of the applicant's population PK structural model is shown in **Figure 8** and the final model parameters are shown in **Table 4**.

Figure 8. Structural PK model for venetoclax



Notes: KA is the absorption rate constant.
F1 is the relative bioavailability.
Q/F is the apparent intercompartmental clearance.
V2/F and V3/F are the apparent volumes of distribution of the central and peripheral compartments, respectively.
CL/F is the apparent clearance from the central compartment.

(Source: Applicant's Population PK Report)

Table 4. Parameter estimates and variability for venetoclax: Final Model

	Population Value (θ)			Inter-Individual Variability (ω^2)			
Parameter	Estimate (SEE)	%RSE	95% Confidence Interval	Variance (%CV)	% RSE	95% Confidence Interval	Shrinkage
CL/F (L/day)	447 (15.7)	3.51	416 – 478	0.153 (40.7)	9.346	0.125 – 0.181	19.0%
$\theta_{CL/F,\ moderate\ CYP3A\ inhibitor}$	0.842 (0.036)	4.24	0.772 – 0.912				
$\theta_{CL/F,\ strong\ CYP3A\ inhibitor}$	0.184 (0.011)	6.03	0.162 – 0.206				
$\theta_{CL/F,\ rituximab}$	1.22 (0.036)	2.93	1.15 – 1.29				
$\theta_{CL/F,\ OATP1B3\ inhibitor}$	0.853 (0.022)	2.54	0.810 – 0.896				
V2/F (L)	118 (16.2)	13.7	86.2 – 150	0.205 (47.7)	6.341	0.180 – 0.230	27.7%
$\theta_{V2/F,\ female}$	0.680 (0.045)	6.68	0.591 – 0.769				
$\theta_{V2/F,\ CLL/SLL/NHL}$	1.71 (0.213)	12.5	1.29 – 2.13				
Q/F (L/day)	97.2 (5.38)	5.54	86.7 – 108				
V3/F (L)	119 (4.95)	4.16	109 – 129				
KA (1/day)	3.72 (0.152)	4.09	3.42 – 4.02				
F1	1.0 (fixed)			0.097 (32.0)	13.374	0.072 – 0.123	28.3%
$\theta_{F1,\ fasting}$	0.335 (0.003)	0.967	0.329 – 0.341				
$\theta_{F1,\ fed}$[a]	1.23 (0.053)	4.29	1.13 – 1.33				
$\theta_{F1,\ moderate\text{-}fat}$	1.31 (0.108)	8.24	1.10 – 1.52				
$\theta_{F1,\ high\text{-}fat}$	1.43 (0.019)	1.30	1.39 – 1.47				
Dose nonlinearity (400 mg as reference)	–0.180 (0.004)	2.38	–0.188 – –0.172				

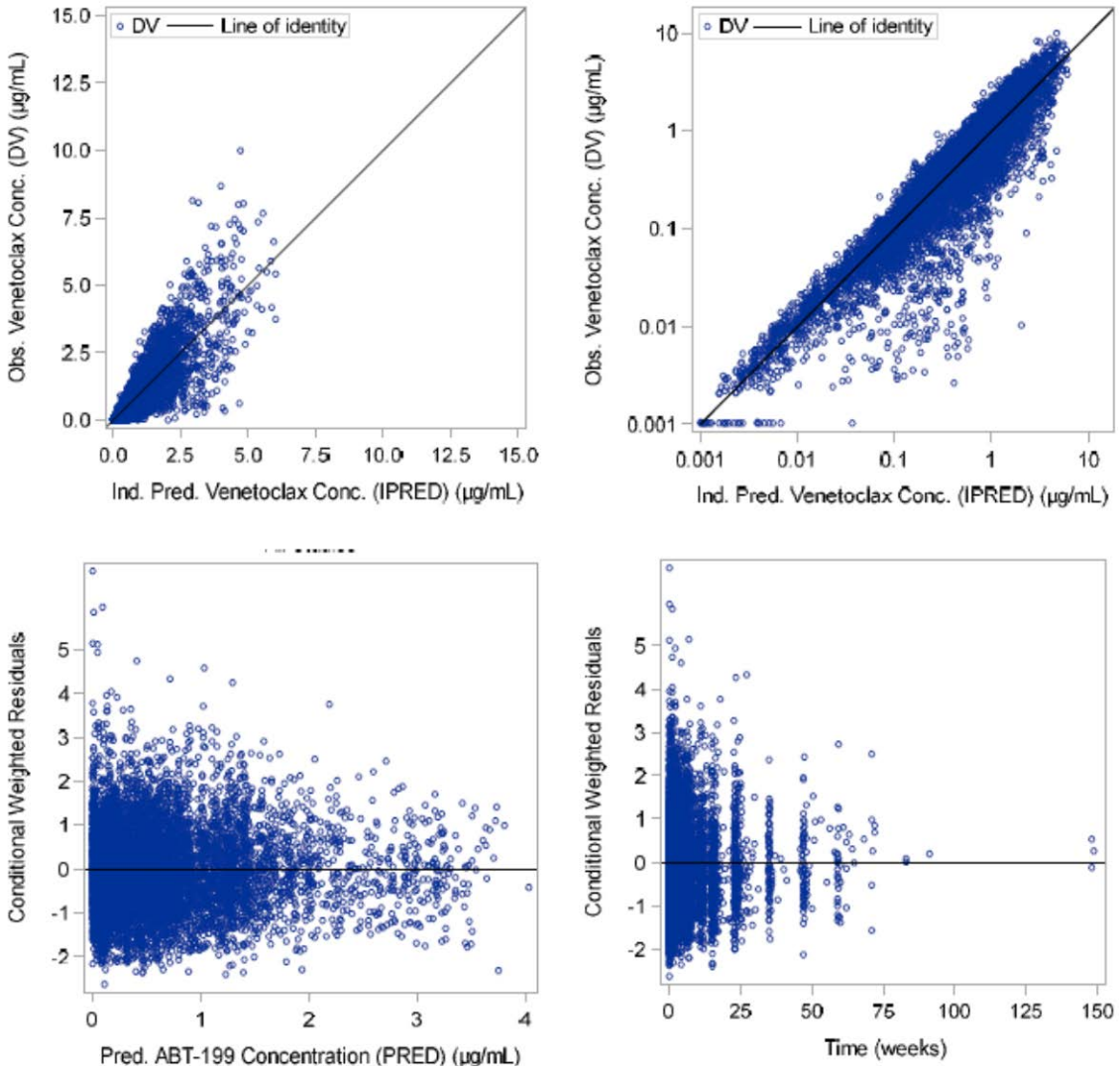
	Residual Variability (σ^2)		
Parameter	Estimate (SEE)	%RSE	95% Confidence Interval
σ_1^2 (Proportional)	0.223 (0.004)	1.67	0.216 – 0.230
σ_2^2 (Additive)	3.07×10^{-07} (1.22×10^{-07})	39.7	6.79×10^{-08} – 5.46×10^{-07}

a. Without specification of fat-content.
SEE = Standard Error of Estimate.
% Relative Standard Error (RSE) was estimated as the SEE divided by the population estimate multiplied by 100.
CV = Coefficient of Variation.
95% confidence interval (CI) was approximated as the point estimate ± 1.96 × SEE.
Cross reference: Table 14.1 3.5

(Source: Applicant's Population PK Report)

The goodness-of-fit diagnostic plots for the final popPK model are shown in **Figure 9**.

Figure 9. Applicant's goodness-of-fit plots for the final population PK model



(Source: Applicant's Population PK Report, Figure 2)

Reviewer's Comments:
The applicant's population PK model appears acceptable. The validity of the covariates in the population PK model are based on a reviewer's assessment of the data and is discussed further in detail in both Section 1 and Section 3.2.

The applicant's assessment ruling CRCL out as covariate was also evaluated by the reviewer and is acceptable (Refer to the Clinical Pharmacology Review for further details).

2.1.2 Exposure-response relationship for Efficacy

Relationship between venetoclax exposure and efficacy were assessed by two approaches: population PK/PD modeling and logistic regression analyses.

Population PK/PD Modeling of Lymphocytes and Tumor Size

The final structural model for both lymphocytes and tumor size was an indirect response model with a linear effect of venetoclax on the stimulation of output:

$$\frac{dR}{dt} = k_{in} - \left(1 + E_{slope} \cdot C\right) \cdot k_{out} \cdot R, \qquad R(t_0) = R_0 = k_{in}/k_{out}$$

where E_{slope} is the slope of the venetoclax effect parameter. In both cases, steady-state initial conditions were assumed. The lymphocyte model was extended to account for a lymphocyte sub-population unaffected by venetoclax concentrations (lymphocyte counts not dropping to zero) as follows:

$$R_{Total} = R + MinLym$$

where R_{Total} is the total lymphocyte response (affected and unaffected) and *MinLym* is the constant minimum lymphocyte response of cells unaffected by venetoclax.

The final models were evaluated based on goodness-of-fit plots, prediction corrected visual predictive checks, and non-parametric bootstrap. Simulations of the OR rate (ORR) by dosage regimen were conducted based on the final lymphocyte and tumor size pharmacodynamic models. The inter-individual variability in the pharmacodynamic model parameter estimates was incorporated into these simulations using the empirical Bayes *post-hoc* estimates from the bootstrap replicates, with typical subject population PK parameter estimates used to generate the plasma venetoclax concentrations.

Logistic regression analysis was conducted to simultaneously characterize the exposure-efficacy relationship between venetoclax concentrations and OR (PR or better) and CR/CRi. Additionally, time-to-event analysis was conducted to further characterize the exposure-efficacy relationship between venetoclax concentrations and CR/CRi. Model fits were evaluated graphically using probability plots with the 95% confidence intervals (CIs) to determine whether the observed data fell into the predicted probability range.

Individual subject exposures were determined based on a prior population PK analysis using the post-hoc empirical Bayes parameter estimates. Covariates that accounted for the variability in efficacy and safety were determined and quantified using a stepwise forward inclusion (α= 0.01), backward elimination (α= 0.001) covariate model building procedure. Specific covariates evaluated in the exposure-efficacy analyses included demographics (bodyweight, sex, age and race), baseline disease characteristics (baseline lymphocyte count, baseline tumor size, number of prior treatment regimens, Eastern Cooperative Oncology Group (ECOG) score, prior idelalisib or ibrutinib therapy, and somatic mutations [17p del, 11q del, 12q trisomy, and 13q del]), and the co-administration of rituximab. The additional demographic covariate of subject population (CLL/SLL or NHL) and co-medication covariate of granulocyte colony stimulation factor (GCSF) were also evaluated in the exposure-safety analyses.

Based on the stepwise forward inclusion, backward elimination procedure, no covariates were included for the lymphocyte model, while body weight was included as a covariate on R_0 for the tumor size model. The estimated PD parameter values for the final exposure-lymphocyte and exposure-tumor size models are listed in **Table 5**.

Table 5. Parameter estimates for the exposure-lymphocyte relationship: Final Model

	Population Value (θ)			Inter-individual Variability (ω^2)			
	Model Result	Bootstrap Result		Model Result		Bootstrap Result	
Parameter	Estimate	Median	95% Confidence Interval	Estimate (%CV)	Shrinkage	Median (%CV)	95% Confidence Interval
E_{slope} (mL/μg)	138	138	66.1 – 851	10.9 (23532)	18.4%	10.9 (23841)	4.48 – 15.7
k_{out} (1/day)	0.0034	0.003	0.00051 – 0.00741	11.1 (26164)	18.5%	10.8 (22318)	4.67 – 16.8
R_0 (10^9/L)	8.91	8.511	5.85 – 11.5	3.91 (700)	4.46%	3.95 (714)	3.32 – 4.87
$MinLym$ (10^9/L)	0.774	0.777	0.662 – 0.956	0.551 (85.8)	12.7%	0.530 (83.6)	0.354 – 1.09

	Residual Variability (σ^2)		
	Model Result	Bootstrap Result)	
Parameter	Estimate (%CV)	Median (%CV)	95% Confidence Interval
σ_2^2 (Exponential)	0.135 (38.0)	0.136 (38.2)	0.117 – 0.162

Population value calculated as 10^{THETA} from the NONMEM output.
Variance calculated as $[\ln(10)]^2 \times$ OMEGA from the NONMEM output.
Variance %CV calculated as sqrt(exp[(ln[10])^2 × OMEGA] – 1) × 100 from the NONMEM output.
Residual variability %CV calculated as sqrt(exp[SIGMA] – 1) × 100 from the NONMEM output.

(Source: Applicant's Exposure-Response and Safety-Response Report, Table 7)

Table 6. Parameter estimates for the exposure-tumor size relationship: Final Model

	Population Value (θ)			Inter-individual Variability (ω^2)			
	Model Result	Bootstrap Result		Model Result		Bootstrap Result	
Parameter	Estimate	Median	95% Confidence Interval	Estimate (%CV)	Shrinkage	Median (%CV)	95% Confidence Interval
E_{slope} (mL/μg)	6.84	6.55	5.24 – 7.75	0.991 (130)	19.7%	0.885 (169)	0.626 – 1.24
k_{out} (1/day)	0.0066	0.006	0.004 – 0.013	0.657 (96.4)	25.2%	1.07 (235)	0.00018 – 2.14
R_0 (cm^2)	25.7	24.5	21.4 – 28.2	0.827 (113)	7.30%	0.806 (125)	0.642 – 1.07
$\theta_{R0,\ Bodyweight}$ [a]	1.42	1.18	0.599 – 1.89				

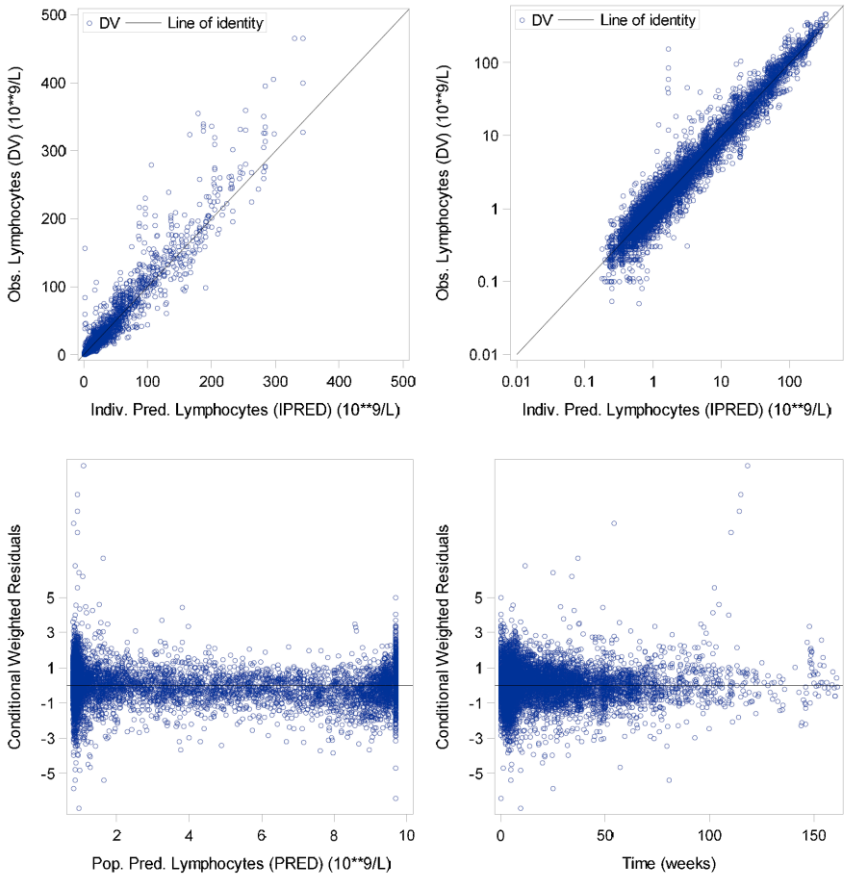
	Residual Variability (σ^2)		
	Model Result	Bootstrap Result	
Parameter	Estimate (%CV)	Median (%CV)	95% Confidence Interval
σ_1^2 (Proportional)	0.4250 (65.2)	0.409 (63.4)	0.342 – 0.503

a. Bodyweight centered at a reference value of 75 kg.
Population value calculated as 10^{THETA} from the NONMEM output.
Variance calculated as $[\ln(10)]^2 \times$ OMEGA from the NONMEM output.
Variance %CV calculated as sqrt(exp[(ln[10])^2 × OMEGA] – 1) × 100 from the NONMEM output.
Residual variability %CV calculated as sqrt(SIGMA) × 100 from the NONMEM output.

(Source: Applicant's Exposure-Response and Safety-Response Report, Table 9)

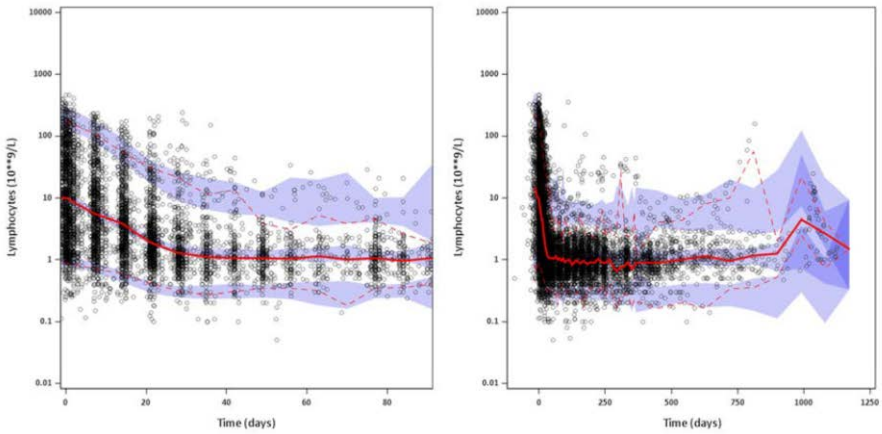
The goodness-of-fit for the final models was evaluated graphically for lymphocyte (**Figure 10**, **Figure 11**), and tumor size (**Figure 12**, **Figure 13**).

Figure 10. Goodness-of-fit plots of final exposure-lymphocyte model



(Source: Applicant's Exposure-Response and Safety-Response Report, Figure 1)

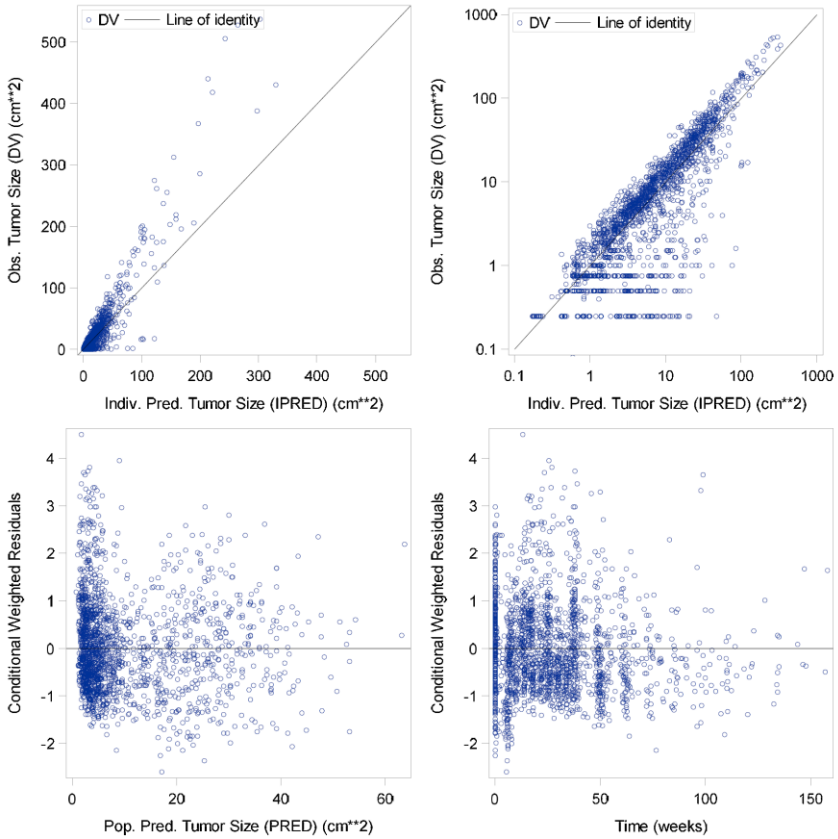
Figure 11. Exposure-Lymphocyte prediction corrected visual predictive checks



pcVPCs display lymphocyte versus time from 0 to 90 days (left) and over the entire observed time range (right). The shaded blue areas represent the 90% prediction interval of the 5th, 50th and 95th percentiles of prediction corrected simulated lymphocyte counts, the solid red line represents median of prediction corrected observed lymphocyte count and dashed red lines represent the 5th and 95th percentile of the prediction corrected observed lymphocytes. Observed values are represented as open circles.

(Source: Applicant's Exposure-Response and Safety-Response Report, Figure 2)

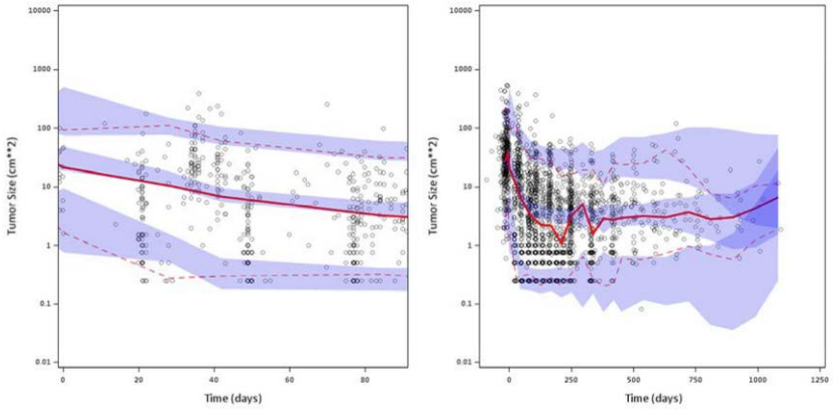
Figure 12. Goodness-of-fit plots of final exposure-tumor size model



Goodness of fit plots of observed versus individual subject predicted on linear (top left) and log (top right) scales. Conditional weighted residuals versus population predicted (bottom left) and time (bottom right).

(Source: Applicant's Exposure-Response and Safety-Response Report, Figure 3)

Figure 13. Exposure-tumor size prediction corrected visual predictive checks



pcVPCs display tumor size versus time from 0 to 90 days (left) and over the entire observed time range (right). The shaded blue areas represent the 90% prediction interval of the 5th, 50th and 95th percentiles of prediction corrected simulated tumor size, the solid red line represents median of prediction corrected observed tumor size and dashed red lines represent the 5th and 95th percentile of the prediction corrected observed tumor size. Observed values are represented as open circles.

(Source: Applicant's Exposure-Response and Safety-Response Report, Figure 4)

To further investigate the relationship of venetoclax concentration on efficacy, simulations were conducted to predict the impact of venetoclax dosing regimen and the resulting concentrations on the ORR over time. Simulations were conducted to predict the plasma concentrations of venetoclax with different dosage regimens using the final population pharmacokinetic model typical value (θ) point estimates in CLL/SLL subjects in the fed state (without specification of the fat-content of the meal). Designated doses of 200, 400, and 600 mg were simulated with ramp-up dosing regimens of 20 mg (Week 1) → 50 mg QD (Week 2) → 100 mg QD (Week 3) → 200 mg QD (Week 4) → Designated Dose QD (Week 5 Onward). In addition to simulations of concentrations by designated dosages, simulations were also conducted at an exactly 50% decrease and 100% increase (i.e., 0.5- to 2.0-fold range) of the plasma venetoclax concentrations achieved at the 400 mg dosage regimen.

Logistic Regression of ORR and CR

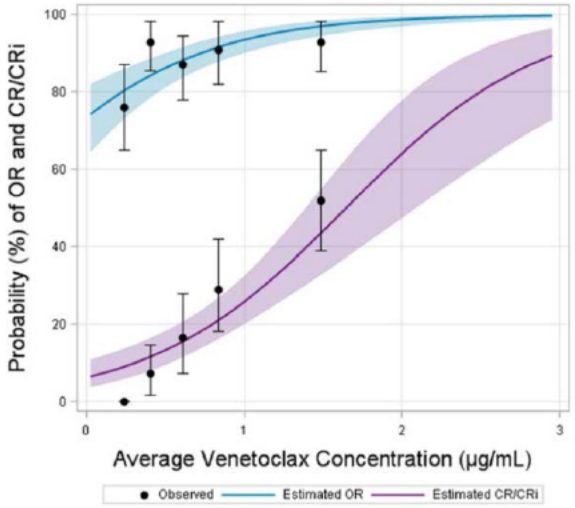
Ordinal logistic regression was conducted to evaluate the relationships between exposure (i.e., average concentration) and response (i.e., OR and CR/CRi) utilizing the ordered structure of the remission states as follows:

$$logit\left(P(Y_i \geq j)\right) \equiv log\left(\frac{P(Y_i \geq j)}{1 - P(Y_i \geq j)}\right) = \alpha_j + \beta_{\text{Cavg}} \cdot C_{avg,i} + \beta_1 \cdot x_{1,i} + \cdots + \beta_k \cdot x_{k,i}$$

where $P(Y_i \geq j)$ is the probability that observation Y from subject i is greater than or equal to response category j, with $j = 1$ for PR and $j = 2$ for CR/CRi, α_j is the intercept parameter associated with response category >= j, β_{Cavg} is the average concentration slope parameter, $C_{avg,i}$ is the average concentration in subject i, and $\beta_1 \ldots \beta_k$ and $x_{1i} \ldots x_{ki}$ are the slope parameters and subject i covariate values for up to k evaluated covariates, respectively.

The ordinal logistic regression model showed that increasing venetoclax concentrations across the observed range were associated with an increase in the probability of achieving CR/CRi (**Figure 14**).

Figure 14. Probability of achieving OR and CR/CRi versus average venetoclax concentration: Base Model



The cumulative logistic regression final model results with baseline lymphocyte value (natural logarithm transformed) as a covariate are displayed in **Table 7**.

Table 7. Parameter estimates of the logistic Regression: Final Model

Parameter	DV	DF	Estimate	Standard Error	95% Confidence Interval		Wald χ^2	$P > \chi^2$
α_2	CR/CRi	1	–3.8812	0.4203	–4.7051	–3.0574	85.2581	< 0.0001
α_1	PR	1	0.0685	0.3180	–0.5547	0.6918	0.0465	0.8293
β_{Cavg} (mL/μg)		1	1.8527	0.2821	1.2999	2.4056	43.1432	< 0.0001
$\beta_{base.\ lymph.}$ [a]		1	0.3515	0.0808	0.1932	0.5098	18.9475	< 0.0001

DV = dependent variable

a. Natural logarithm transformed.

(Source: Applicant's Exposure-Response and Safety-Response Report, Table 12)

Reviewer's Comments:

- *The final model captured the observed data reasonably well. Some bias in the predictions the tumor size model is evident for observed tumor sizes <100 cm^2 (over-prediction) and >100 cm^2 (under-prediction). The CWRES did not show any trends when plotted over population predicted values. However some minor trends in CWRES were observed when plotted across time, indicating bias. The VPCs for the tumor size versus time showed that the model was able to describe the overall central tendency and variability of the data.*
- *Applicant's ordinal logistic regression analysis is acceptable. Reviewer's independent analysis fitting logistic regression model for ORR and CR separately, yielded consistent results.*

2.1.3 Exposure-response relationship for Safety

Logistic regression analyses were conducted to separately characterize the exposure-safety relationship between venetoclax concentrations and the adverse events (Grade 3/4) of neutropenia and infection. Model fits were similarly evaluated graphically using probability plots with the 95% CIs to determine whether the observed data fell into the predicted probability range. The logistic regression analyses of the adverse events (Grade 3/4) of neutropenia and infection both indicated that higher average venetoclax concentrations were associated with a decrease in adverse events. Sensitivity analyses supported that increasing venetoclax concentration did not increase these adverse events and further indicated that the association may be driven by disease treatment and not by directly affecting neutrophils or granulocyte progenitor cells. Granulocyte colony stimulating factor was identified as a covariate associated with neutropenia adverse events. No other covariates were identified to be associated with neutropenia or infection adverse event (Grade 3/4) rates.

Reviewer's Comments:
The inverse relationship between grade 3/4 neutropenia/infection and venetoclax exposures is confounded by the initial dose ramp-up phase, the exposure-response relationship for safety was corrected by the sensitivity analysis by the applicant and independently verified by the reviewer which confirmed that the relationship between exposure and safety is flat.

3 REVIEWER'S ANALYSIS

3.1 Exposure-Response Analyses

3.1.1 Introduction

The purpose of the analysis is to evaluate the applicant's analysis on safety and the proposed dose recommendation.

3.1.2 Objectives

Analysis objective was to evaluate the applicant's exposure-response analysis for safety to justify the proposed dosing regimen.

3.1.3 Data Sets

Data sets used are summarized in **Table 8**.

Table 8. Analysis data sets

Study Number	Name	Link to EDR
Exposure-Safety analysis	pkpdsteae xpt	\\cdsesub1\evsprod\nda208573\0014\m5\datasets\rd150255\analysis\legacy\datasets\pkpdsteae xpt

3.1.4 Software

SAS (version 9.3) was used for statistical and graphical analyses.

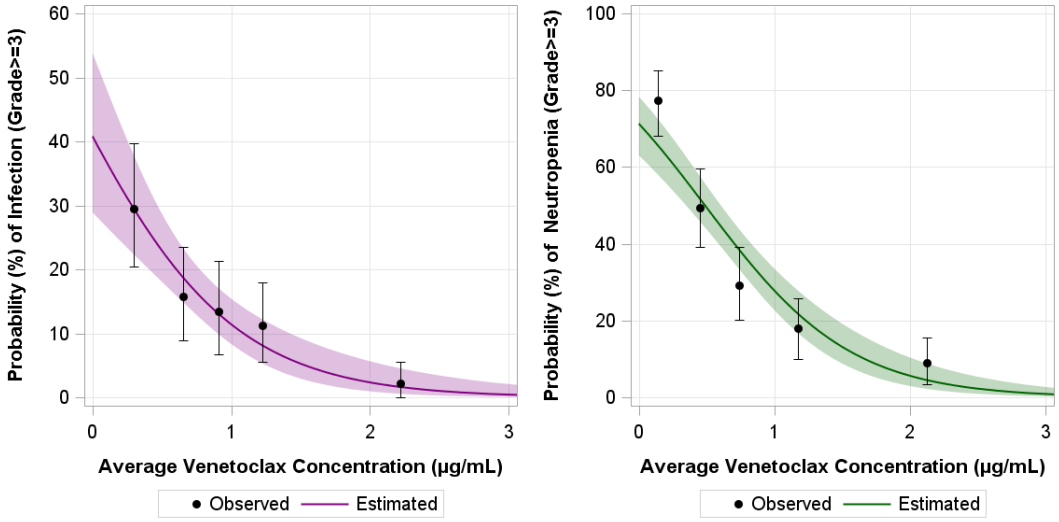
3.1.5 Models

Exposure (daily AUC) was estimated in each individual using *post-hoc* estimates of individual clearance using population PK analysis and actual dose given to the individual. Cumulative AUC for each individual up to the day an event occurred was averaged by the day.

3.1.6 Results

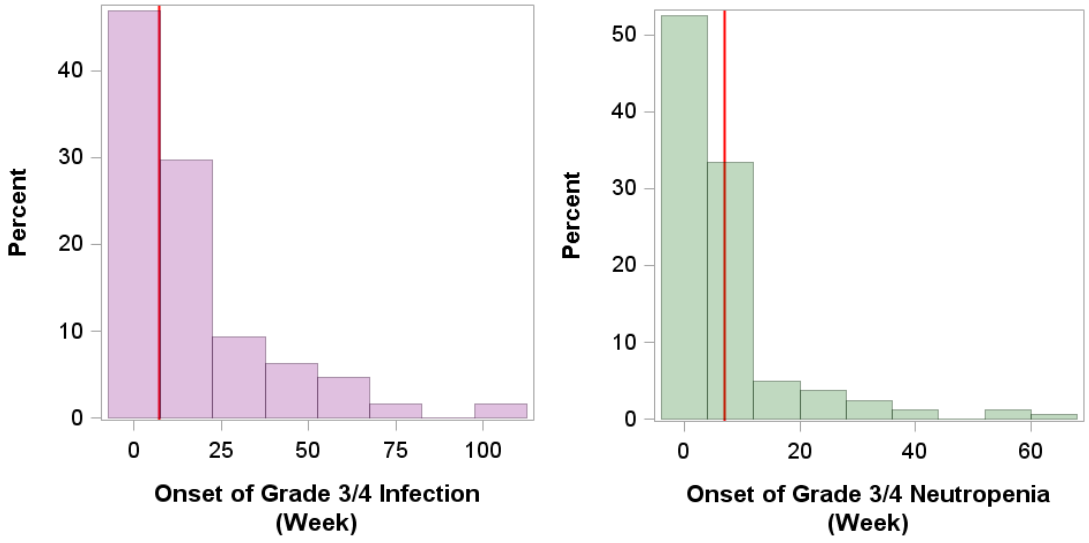
The results including data throughout the treatment showed higher average venetoclax concentrations were associated with a decreased probability of AEs (**Figure 15**).

Figure 15. Logistic regression model of the probability of Grade 3/4 infection (left) and Grade 3/4 neutropenia (right) vs. average venetoclax concentration



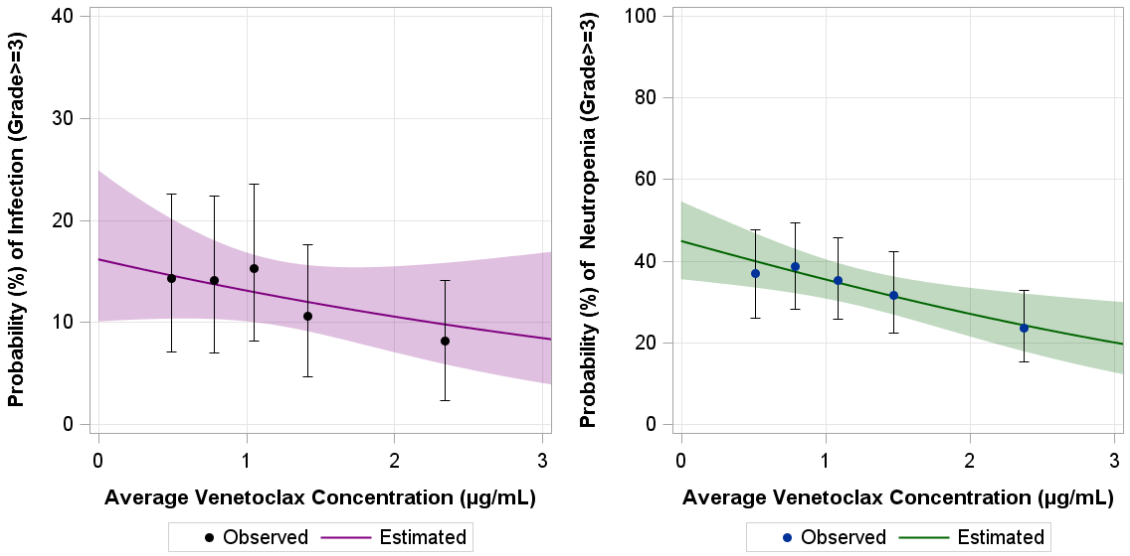
However, since most of the grade 3/4 infection and neutropenia (>50%) occurred at early phase of the treatment (**Figure 16**), where the patients were on the dose ramp-up phase and have not received the target maintenance dose, the concentrations associated with these events would be lower compared to that in the later phase. Therefore, the analyses for safety were confounded by the trial design (initial dose ramp-up) and cannot represent exposure-response relationship for venetoclax.

Figure 16. Onset of Grade 3/4 infection (left) and Grade 3/4 neutropenia (right)



Based on this, sensitivity analysis was conducted after removing data during the dose ramp-up period. The biased relationship was then corrected and the results showed that increase of venetoclax exposure was not associated the occurrence of these AEs (**Figure 17**).

Figure 17. Sensitive analyses of logistic regression model of the probability of Grade 3/4 infection (left) and Grade 3/4 neutropenia (right) vs. average venetoclax concentration - excluded the 30 days lead-in period



3.2 Population Pharmacokinetics analysis

3.2.1 Introduction

A review of the population PK dataset and model results were performed to better understand if the data supported the claims the applicant was making with regards to hepatic impairment, drug-drug interactions, and the lack of effect for co-administration with acid-reducing agents.

3.2.2 Objectives

Analysis objectives are:

1. Substantiate that the data is sufficient to detect an effect on the PK
2. The model captures the effect or lack of effect in an unbiased manner for each relevant subpopulation.

3.2.3 Data Sets

Data sets used are summarized in **Table 9**.

Table 9. Analysis data sets

Study Number	Name	Link to EDR
Population PK Analysis	Poppk.xpt	\\cdsesub1\evsprod\NDA208573\0001\m5\datasets\rd150256\analysis\legacy\datasets
ISS Adverse Events	Adae.xpt	\\cdsesub1\evsprod\NDA208573\0001\m5\datasets\summary-of-clinical-safety\analysis\legacy\datasets\
12175	cm.xpt, ex.xpt	\\CDSESUB1\evsprod\NDA208573\0001\m5\datasets\m12-175\tabulations\sdtm\

3.2.4 Software

The statistical software R (version 3.05) and SAS (version 9.3) was used for statistical and graphical analyses. The software NONMEM was utilized to run the applicant's population PK model.

3.2.5 Models

No original modeling analysis was performed by the reviewer.

3.2.6 Results

3.2.6.1 Hepatic Impairment

Three additional plots (**Figure 18, Figure 19**, and **Figure** 20) were generated to support an understanding of the data and whether the model captured the data well for patients with moderate hepatic impairment.

Figure 18. Venetoclax exposures (dose normalized) in seven patients with moderate hepatic impairment (Trials M12-175 and M13-982) appear to overlap with patients with normal hepatic function (left: in PopPK datasets; right: in Phase 1/2 studies)

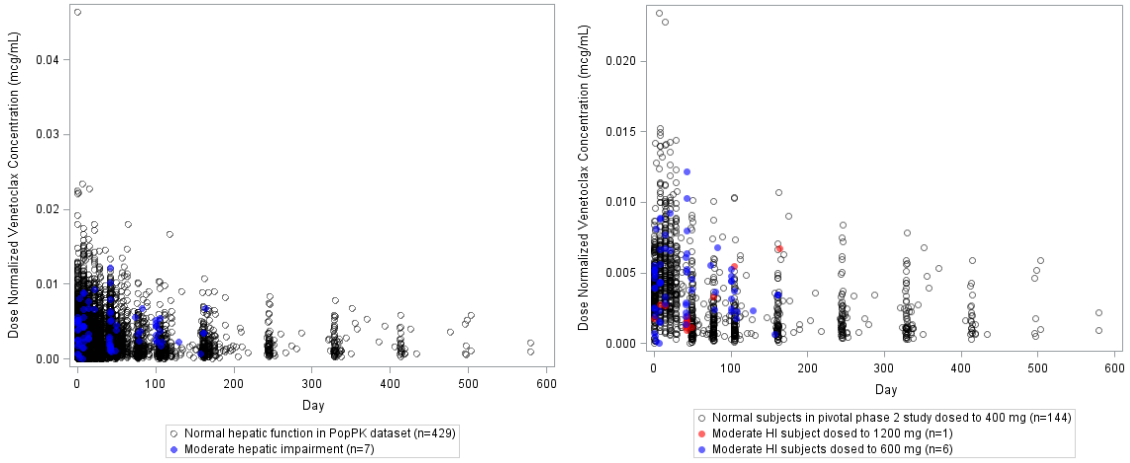
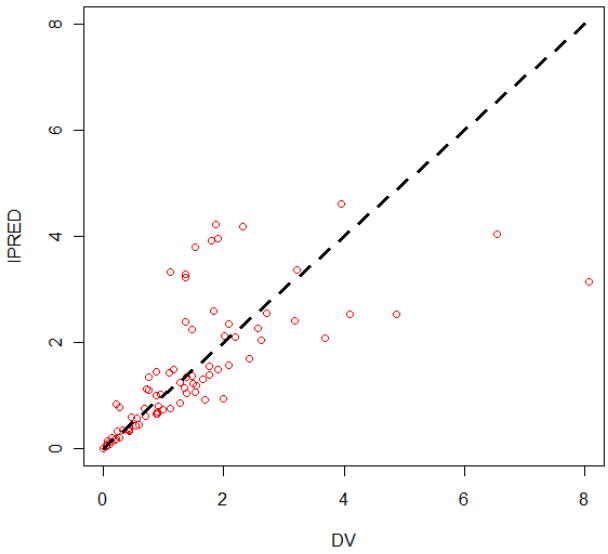


Figure 19. The final population PK model, in general, appears to capture the central tendency of the observed venetoclax PK data for patients with moderate hepatic impairment

Figure 20. Goodness-of-fit plot for the final population PK model for patients with moderate hepatic impairment



3.2.6.2 Drug-Drug Interactions with CYP3A Inhibitors

The reviewer's analysis focused on the robustness of the data available to assess the PK DDI for CYP3A inhibitors. The applicant utilized data from both dedicated DDI studies and Phase 2 clinical trials.

For patients with strong CYP3A inhibitors (primarily ketoconazole), data were available from a dedicated Phase 1 DDI study with ketoconazole in 11 patients and from two patients in the Phase 2 clinical trials. The fold-change in exposure in the dedicated DDI study was 6.4-fold increase in venetoclax AUC when administered with ketoconazole. The population PK estimate gave a 5.6-fold change in AUC. When the model was run on only the data from the Phase 2/3 subjects (n=2, 1 subject only had 1 PK observation post dose) the effect trended in the other direction. Therefore, the population PK estimates were driven by data from dedicated Phase 1 study due to lack of adequate data from Phase 2 studies.

With regards to the DDI for patients receiving concomitant moderate CYP3A inhibitors, there were 6 patients from a phase 1 study with rich PK sampling (study M12-175) and 67 patients from the Phase 2 clinical trials with sparse sampling. The sparse sampling was insufficient to maintain the degree of effect of the interaction in the model and added noise to the effect observed with the six patients from the Phase 1 study.

It is important to note that popPK can be used to assess DDI claims if adequate data is collected in the late phase trials. In this case, dedicated Phase 1 studies are available to assess effect of moderate or strong inhibitors on venetoclax PK. Additionally, the PK data collected in Phase 2 trials does not appear to be adequate to reliably assess DDI using popPK. Therefore, the conclusions regarding the DDI appear to be best taken from the studies designed to test the interactions (Study M13-364 to evaluate effect of strong CYP3A inhibitors and study M12-175 for assessment of the effect of moderate CYP3A inhibitors on venetoclax PK).

3.2.6.3 Drug-Drug Interactions with Gastric Acid Reducing Agents

See Section 1.1.3.

4 LISTING OF ANALYSIS CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\Reviews\PM Review Archive\2016\ Venetoclax_NME_NDA208573_LM\
Catab, patab, sdtab, cotab	Output files	..\PPK_Analyses\
Run1 mod	Final population PK model	..\PPK_Analyses\run1\

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BAHRU A HABTEMARIAM
03/14/2016

NAM ATIQUR RAHMAN
03/14/2016
I concur with the recommendation of the review team.