ORIGINAL RESEARCH

Pharmacokinetics and Exposure-Response Analysis of Venetoclax + Obinutuzumab in Chronic Lymphocytic Leukemia: Phase 1b Study and Phase 3 CLL14 Trial

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ABSTRACT

Introduction: This study aims to investigate pharmacokinetics (PK) and exposure-response parameters of the 400 mg once-daily venetoclax dose regimen in combination with obinutuzumab, which was approved for the first-line (1L) treatment of chronic lymphocytic leukemia (CLL) based on data from the phase 3 CLL14 study and the phase 1b dose-finding GP28331 study.

Methods: Parameter estimates and uncertainty, which were estimated by a previously developed population PK (popPK) model, were used as informative priors for this analysis. They were re-estimated, and then used to evaluate additional covariate effects, describe venetoclax PK when administered with obinutuzumab, and provide empirical Bayes estimates of PK parameters and exposure. Exposure-progression-free survival (PFS) and exposure–safety relationships were assessed using data from CLL14, with steady-state nominal venetoclax exposure ($C_{meanSS,nominal}$) as the predictor variable. Exposure-safety analyses were conducted using logistic regression for selected treatment-emergent grade ≥ 3 adverse events (AEs) and serious AEs (SAEs). Dose intensities were summarized by tertiles of $C_{meanSS,nominal}$.

Results: PK data from 274 patients (CLL14, $n = 194$; GP28331, $n = 80$) were included. The final model provided good fit of the observed data. Obinutuzumab co-administration, history

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of prior treatments, and disease severity at baseline had no appreciable influence on venetoclax steady-state exposure. No significant correlations were observed between venetoclax exposure and PFS, or between venetoclax exposure and the probability of treatment-emergent grade ≥ 3 neutropenia, grade ≥ 3 thrombocytopenia, grade ≥ 3 infections, and SAEs. Median dose intensities for venetoclax and obinutuzumab remained similar across venetoclax exposure tertiles.

Conclusion: PopPK and exposure-efficacy, exposure-safety, and exposure-tolerability analyses support the 400 mg once-daily venetoclax dose plus obinutuzumab for 1L treatment in patients with CLL.

Clinical Trial Registration: ClinicalTrials.gov Identifiers NCT02242942 and NCT02339181.

Keywords: Drug safety; Effectiveness; Cancer; Pharmacokinetics

Key Summary Points

Why carry out this study?

Venetoclax 400 mg once-daily is approved as monotherapy and in combination with rituximab in patients with relapsed/refractory chronic lymphocytic leukemia (CLL), and in combination with obinutuzumab for first-line (1L) treatment in patients with CLL and co-existing medical conditions.

In preclinical studies, obinutuzumab has shown increased activity against B cell malignancies compared with rituximab. Further, in a randomized phase 3 study in patients with CLL and existing comorbidities, 1L treatment with obinutuzumab plus chlorambucil demonstrated significant improvements in survival and other outcome parameters compared with rituximab plus chlorambucil.

The current analysis aims to support the 400 mg once-daily dosage regimen for venetoclax plus obinutuzumab (venetoclax-obinutuzumab; used in the phase 3 CLL14 trial) as 1L treatment in patients with CLL, using population pharmacokinetics and exposure-response analyses from the CLL14 and GP28331 studies.

What was learned from this study?

Data from the pivotal phase 3 CLL14 study and the supportive phase 1b GP28331 study demonstrate that venetoclax-obinutuzumab as 1L treatment in adult patients with CLL provides a positive benefit-risk profile, with highly favorable efficacy and manageable safety.

Collectively, the pharmacokinetic, exposure-efficacy, exposure-safety, and exposure-tolerability analyses support the selected 400 mg once-daily venetoclax dose regimen in combination with obinutuzumab for 1L treatment in patients with CLL.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common leukemia in Western countries [1–3]. B cell lymphoma 2 (BCL2) is an anti-apoptotic protein that is overexpressed in CLL, and has led to the development of therapeutic approaches targeting BCL2. Venetoclax is an orally administered, highly selective BCL2 inhibitor, and is especially potent against cell lines expressing high levels of BCL2.

Venetoclax was first approved as monotherapy in relapsed/refractory (R/R) CLL at a dosage regimen of 400 mg once-daily (QD; on a ramp-

up dosing schedule starting at 20 mg), which was adequately supported using pharmacokinetic (PK) and exposure–response analyses [4–6]. Venetoclax 400 mg QD is also approved in combination with rituximab, a monoclonal antibody, in R/R CLL. In this setting, venetoclax is administered first, beginning with a ramp-up dosing schedule starting at 20 mg QD and rising to 400 mg QD; once the ramp-up period is completed, venetoclax treatment is continued for 2 years (24 × 28-day treatment cycles), with rituximab (500 mg/m^2) co-administered for the first six cycles [7]. This combination has shown significantly longer progression-free survival (PFS) than standard chemoimmunotherapy (bendamustine plus rituximab) in patients with R/R CLL, as demonstrated in the phase 3 MUR-ANO study [7]. The exposure-response analyses from MURANO showed no evidence that higher venetoclax exposure (i.e., greater than 400 mg QD) would improve PFS, or that lower exposure would reduce the probability of developing grade ≥ 3 neutropenia or infections [8].

Venetoclax 400 mg QD is approved in combination with obinutuzumab, a glycoengineered, humanized, anti-CD20 monoclonal antibody, for first-line (1L) treatment in patients with previously untreated CLL and co-existing medical conditions. In this setting, obinutuzumab (1000 mg) is administered intravenously for six 28-day cycles. Venetoclax treatment is initiated on day 22 of cycle 1, starting with a 5-week dose ramp-up as described previously [9], thereafter continuing at 400 mg QD until completion of cycle 12.

Obinutuzumab has shown increased activity against B cell malignancies compared with rituximab, through enhanced direct cell death, antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis, but reduced complement-dependent cytotoxicity, in preclinical studies [10, 11]. In a randomized phase 3 study in patients with CLL and existing comorbidities, 1L obinutuzumab plus chlorambucil demonstrated significant improvements in PFS, overall survival, and other outcome parameters when compared with rituximab plus chlorambucil or chlorambucil alone [12, 13]. The phase 3 CLL14 trial (BO25323; NCT02242942) in patients with previously untreated CLL and co-existing medical conditions, in which venetoclax treatment was administered following the same ramp-up schedule as used in MURANO, demonstrated that venetoclax 400 mg QD plus obinutuzumab resulted in a significantly higher PFS rate than chlorambucil plus obinutuzumab [14–16].

The current analysis aims to support the 400 mg QD dosage regimen for venetoclax plus obinutuzumab (venetoclax-obinutuzumab) as 1L treatment in patients with CLL, using population PKs (popPK) and exposure–response analyses from CLL14 and GP28331 (NCT02339181), a phase 1b dose-finding and safety study of venetoclax-obinutuzumab in patients with 1L or R/R CLL [17], to evaluate (1) whether co-administration of obinutuzumab alters venetoclax exposure; (2) the impact of demographic-, disease-, and/or treatment-specific factors as potential covariates on venetoclax PKs; and (3) potential associations between venetoclax exposure and the probability of treatment-emergent grade ≥ 3 adverse events (AEs) of concern and serious AEs (SAEs), and/or tolerability of the combination treatments.

METHODS

Patients and Sampling for PKs

The analyses described here were performed using data from the venetoclax-obinutuzumab arm of the phase 3 CLL14 study and data from the phase 1b GP28331 study, which have been described previously [14, 17]. All procedures performed in studies were in accordance with the ethical standards of the institutional review boards (Supplementary Material Tables S1 and S2) and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the studies.

In CLL14, eligible patients with previously untreated CD20+ CLL were randomized (1:1) to receive either venetoclax-obinutuzumab or obinutuzumab plus chlorambucil (obinutuzumab-chlorambucil), stratified according to Binet stage and geographic region.

Obinutuzumab 1000 mg was administered intravenously for six 28-day cycles (100 mg on cycle 1 day 1 and 900 mg on day 2 [or 1000 mg on day 1 with no administration on day 2], 1000 mg on cycle 1 day 8 and cycle 1 day 15, and 1000 mg on day 1 of cycles 2–6) while daily oral administration of venetoclax was initiated on cycle 1 day 22 with a 5-week dose ramp-up (1 week each of 20, 50, 100, 200, and 400 mg QD), thereafter continuing at 400 mg QD until completion of cycle 12. Plasma samples for PK analysis were collected pre-dose on cycle 4 day 1 and at 4 hours (h) post-dose for patients enrolled into the venetoclax-obinutuzumab arm only.

GP28331 enrolled patients with previously untreated or R/R CLL, and comprised dose finding and safety expansion phases for each patient population. Dose finding included venetoclax (ranging from 100 to 400 mg) in combination with obinutuzumab as described for the CLL14 trial, and explored two dosing schedules during cycle 1: (1) initiation and completion of the venetoclax ramp-up, immediately followed by initiation of obinutuzumab (arm A); and (2) initiation of obinutuzumab, followed by initiation of venetoclax on cycle 1 day 22 (arm B). Venetoclax-obinutuzumab was administered for six cycles, followed by venetoclax monotherapy until disease progression (PD), unacceptable toxicity, or death in patients with R/R CLL, or completion of a 1-year fixed treatment duration in patients with previously untreated CLL.

In arm A, venetoclax plasma samples were collected on ramp-up day 1 (pre-dose, and 2, 4, 6, 8, and 10 h post-dose), day 8, and day 15 (pre-dose and 8 h post-dose) for all cohorts, and also on day 22 and day 29 (pre-dose and 8 h post-dose) for selected cohorts. After that, for all patients in arm A, samples were collected on cycle 1 day 1 (pre-obinutuzumab infusion) and cycle 1 day 3 (pre-dose, and 2, 4, 6, 8, and 10 h post-dose), and on day 1 (pre-dose) for all remaining cycles. In arm B, venetoclax plasma samples were collected on cycle 1 day 22 (pre-dose, and 2, 4, 6, 8, and 10 h post-dose) and cycle 3 day 1 (pre-dose and 8 h post-dose) for all cohorts, and on cycle 2 day 1, day 8, day 15, and day 22 (pre-dose and 8 h post-dose) for selected

cohorts. Obinutuzumab serum samples for all cohorts were collected on cycle 1 day 1, day 2, day 3, day 8, and day 15, on day 1 for all remaining cycles, and at the end of the treatment. Actual dose and collection times of samples were used when available; otherwise dosing time was set to the pre-dose PK sample time plus 10 minutes on PK sampling days, or 8 am (08:00h) for other days. Samples with time after last dose more than 10 days were excluded.

Analytical Methods

Validated liquid chromatography methods with tandem mass spectrometric detection were used to determine plasma concentrations of venetoclax [18, 19]. The lower limit of quantification (LOQ) was 2.05–2.18 ng mL^{-1} (depending on the run and method utilized at the time of sample analysis).

PopPK Modelling

A previously developed popPK (legacy) model of venetoclax in R/R CLL, non-Hodgkin lymphoma and healthy subjects (based on 7483 quantifiable plasma samples from 505 subjects from eight different studies) was used as a starting point [20]. Point estimates and the variance-covariance matrix of parameter estimates of that model were used as priors for the current analysis. Covariate effects in the legacy model included: moderate and strong CYP3A inhibitors, rituximab co-administration, and co-administration of medications reported in the literature as OATP1B3 transporter inhibitors on apparent clearance (CL/F); sex and subject population (patients vs. healthy volunteers) on apparent central volume of distribution (V$_2$/F); as well as dose (using a power model with the reference value of 400 mg) and food (fasted, fed, low-, moderate-, and high-fat meal) on relative bioavailability (F$_1$). Covariates investigated in the previous analysis and not included in the final model were not re-tested. Then, the additional covariates of interest from CLL14 and GP28331, i.e., obinutuzumab administration and baseline disease characteristics (Binet stage, Cumulative Illness Rating Scale score, patient

population, Eastern Cooperative Oncology Group score, B symptoms, serum β2-microglobulin levels, mutational status [+*TP53*, immunoglobulin heavy chain variable gene (IGHV)] and cytogenetic factors [chromosome 17p deletion, chromosome 11q deletion, Trisomy 12, and chromosome 13q deletion]) were investigated in the popPK analysis using diagnostic plots. Additional covariates of interest that were not previously evaluated in the legacy model (obinutuzumab administration and Binet stage) were tested on CL/F and F_1 by incorporating each individually into the model. All model parameters were re-estimated, with priors (prior distributions) used for the model parameters of the previous model, and no priors set for the new covariate effects added to the model (equivalent to using non-informative flat priors for these parameters). For testing covariate–parameter relationships, a significance level of $\alpha = 0.01$ was used (corresponding to a 6.63-point change in the objective function value for models that differ by one parameter).

The final model was evaluated using diagnostic plots, visual predictive checks (VPCs), and normalized prediction distribution errors (NPDE) plots. Correlations of CL/F with previously tested covariates and the additional covariates were investigated by diagnostic plots.

Prediction of Individual PK Parameters

Individual post-hoc PK parameters (CL/F, F_1, V_2/F, and CL/F to F_1 ratio) were estimated by the final model. These parameters were then used to compute individual steady-state exposures at 400 mg QD dosing (steady-state nominal venetoclax exposure [$C_{meanSS,nominal}$]). Baseline covariate values were used for prediction.

Determination of Venetoclax Exposure

The empirical Bayes post hoc estimates of CL/F and F_1 estimated using the final popPK model and the relevant PK covariates for each patient were used to estimate the individual exposure measure, $C_{meanSS,nominal}$, as follows:

$$C_{meanSS,nominal} = D_{nom} \times rmF_1/(CL/F)/\tau,$$

where D_{nom} was the nominal dose assigned to a patient at randomization (400 mg), and τ was the inter-dose interval (1 day). The PK model predicted dependence of F on dose; therefore, the nominal dose (D_{nom}) was used to compute F_1 for the exposure measures.

For patients without evaluable PK data that were not included in the popPK analysis, primary PK parameters were imputed using population estimates and the individual patient's covariate values.

Exposure-Response Analyses

Three sets of relationship analyses were carried out: (1) exposure-efficacy, (2) exposure-safety, and (3) exposure-dose intensity, using data collected from patients randomized to the venetoclax-obinutuzumab arm of CLL14.

Exposure-Efficacy Relationships

Both investigator-assessed and independent review committee (IRC)-assessed PFS were explored. Venetoclax $C_{meanSS,nominal}$ was used as a measure of exposure. The semi-parametric Cox proportional hazard (CPH) models were used to evaluate the effect of exposure on PFS. A significance level of $\alpha = 0.05$ was used for evaluation of the exposure coefficient of the model. The covariate analyses were then implemented using the forward addition procedure using a significance level of $\alpha = 0.01$.

The hazard function in the CPH model is expressed as

$$\lambda(t) = \lambda_0(t)\exp(\boldsymbol{\beta}^T \boldsymbol{X}_i),$$

where $\lambda_0(t)$ is the baseline hazard function and $\boldsymbol{X}_i$ is a vector of predictor variables. The vector of predictor variables included continuous exposure ($C_{meanSS,nominal}$) or exposure categories (tertiles of $C_{meanSS,nominal}$). The parameter vector $\boldsymbol{\beta}$ is estimated by maximum partial-likelihood.

Exposure-Safety Relationships

The following treatment-emergent AE parameters were explored: grade ≥ 3 neutropenia, grade ≥ 3 thrombocytopenia, grade ≥ 3 infections, and SAEs. For each AE type, logistic regression models were implemented to assess correlation of the probability of AE occurrence with venetoclax $C_{meanSS,nominal}$. A significance level of $\alpha = 0.05$ was used for evaluation of the exposure coefficient of the model. Covariate analysis was conducted for the logistic regression models, and a significance level of $\alpha = 0.01$ was used for the forward addition procedure.

Exposure-Dose Intensity Relationships

Individual estimates of venetoclax and obinutuzumab dose intensity were used to create summaries stratified by tertiles of venetoclax $C_{meanSS,nominal}$. Dose intensity was calculated as the total dose received by patients divided by the planned total dose. The planned cumulative dose was the sum of the planned doses administered until the last day of the study treatment received in each patient. For venetoclax, the actual and planned dose was considered from the day the patient attained the target dose of 400 mg.

Covariates

Covariates tested in the exposure-response analysis included demographics (body weight, sex, age, race), geographic region, baseline laboratory values (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, albumin, serum creatinine, serum $\beta 2$-macroglobulin), estimated creatinine clearance (CrCL), hepatic and renal impairment, and baseline disease characteristics (as described earlier). Where covariate data were missing, the median value was inputted for continuous covariates, while missing categorical covariates were presented as a separate "missing" category. There were no covariates with a missing data fraction exceeding 15% of the study data.

Software

The non-linear mixed-effects modelling software NONMEM Version 7.4.3 (ICON Development Solutions [21]), utilizing PRIOR subroutine and the first-order conditional estimation method with interaction, was used for the popPK analysis. Graphical and all other statistical analyses, including evaluation of NONMEM outputs, were performed using R, Version 3.4.4 for Windows (R project, http://www.r-project.org/).

RESULTS

Dataset for popPK Analysis

A total of 274 patients (194 from CLL14 and 80 from GP28331) had at least one quantifiable PK sample and were included in the analysis (1563 quantifiable samples; CLL14 $n = 371$, GP28331 $n = 1192$). Forty-five (2.9%) post-dose data points were excluded from model development, including 12 (0.8%) observations collected more than 10 days after the last dose, 31 (2.0%) that were below the LOQ less than 10 days post-dose, and two (0.1%) deemed unreliable because of missing prior dose information (both from CLL14). Additionally, four (0.3%) observations with pre-dose concentrations above the LOQ (all from GP28331) were excluded. Patient baseline characteristics and covariates are summarized in Table 1.

PopPK Analysis

The prediction-corrected VPC plot (Fig. 1) showed that the legacy model generally fitted the new data. This model was re-fitted using the prior point estimates and the associated variance-covariance matrix as Bayesian priors. Forward addition testing of additional covariates indicated that obinutuzumab co-administration had no effect on CL/F and F_1, and none of the Binet stage effects on CL/F or F_1 were significant; thus the refitted model (two-compartment with first-order absorption and elimination) was selected as the final model, and was nearly

Table 1 Patient baseline characteristics/covariates for PK and exposure-response analyses

	PKs patient population			Exposure-response patient population CLL14 $N = 203$
	CLL14 $n = 194^a$	GP28331 $n = 80$	Total $N = 274$	
Demographics				
Age (years), median (range)	72 (43–89)	63 (42–80)	70 (42–89)	72 (43–89)
Patient population, n (%)				
Previously untreated CLL	–	10 (12.5)	10 (3.6)	
Previously untreated unfit CLL	194 (100.0)	–	194 (70.8)	
Previously untreated fit CLL	–	22 (27.5)	22 (8.0)	
R/R CLL	–	48 (60.0)	48 (17.5)	
Sex, n (%)				
Male	131 (67.5)	52 (65.0)	183 (66.8)	139 (68.5)
Female	63 (32.5)	28 (35.0)	91 (33.2)	64 (31.5)
Ethnicity, n (%)				
White	156 (80.4)	75 (93.8)	231 (84.3)	160 (78.8)
Black	–	3 (3.8)	3 (1.1)	–
Hispanic	18 (9.3)	–	18 (6.6)	21 (10.3)
Asian	–	1 (1.2)	1 (0.4)	–
Other	20 (10.3)	1 (1.2)	21 (7.7)	22 (10.8)
Region, n (%)				
USA/Canada	21 (10.8)	61 (76.2)	82 (29.9)	
Australia/New Zealand	31 (16.0)	–	31 (11.3)	
Western Europe	79 (40.7)	19 (23.8)	98 (35.8)	
Central/Eastern Europe	50 (25.8)	–	50 (18.2)	
Latin America	13 (6.7)	–	13 (4.7)	
Weight (kg), median (range)	75.0 (40–138)	79.8 (48–133)	76.0 (40–138)	74 (40–138)
Baseline laboratory values (median [range] unless stated otherwise)				
Aspartate aminotransferase (U.L^{-1})	22.0 (9–95)	26.5 (12–62)	23.0 (9–95)	22 (9–102)
Alkaline phosphatase (U.L^{-1})	16.1 (5–164)	21.0 (7–129)	17.0 (5–164)	16.2 (5–164)
Bilirubin (mg.dL^{-1})	0.5 (0.2–2.3)	0.6 (0.2–1.6)	0.5 (0.2–2.3)	0.5 (0.2–3.4)
Serum albumin (g.dL^{-1})	4.2 (2.4–5.4)	4.1 (2.8–4.8)	4.2 (2.4–5.4)	4.2 (2–5.4)
Serum creatinine (µmol.L^{-1})	90 (15–201)	84 (38–132)	88.7 (15–201)	–

Table 1 continued

	PKs patient population			Exposure-response patient population CLL14 N = 203
	CLL14 n = 194[a]	GP28331 n = 80	Total N = 274	
Calculated creatinine clearance (mL min−1)	65.2 (22.4–275)	87.1 (37.4–171)	70.3 (22.4–275)	65.8 (22.4–275)
Renal impairment, n (%)				
Normal	38 (19.6)	39 (48.8)	77 (28.1)	40 (19.7)
Mild	74 (38.1)	30 (37.5)	104 (38.0)	79 (38.9)
Moderate	78 (40.2)	11 (13.8)	89 (32.5)	81 (39.9)
Severe	4 (2.1)	–	4 (1.5)	3 (1.5)
Hepatic impairment, n (%)				
Normal	164 (84.5)	61 (76.2)	225 (82.1)	171 (84.2)
Mild	22 (11.3)	18 (22.5)	40 (14.6)	22 (10.8)
Moderate	8 (4.1)	1 (1.2)	9 (3.3)	9 (4.4)
Severe	–	–	–	1 (0.5)
Baseline disease characteristics				
Binet stage, n (%)				
Stage A	45 (23.2)	–	45 (16.4)	46 (22.7)
Stage B	70 (36.1)	–	70 (25.5)	74 (36.5)
Stage C	79 (40.7)	–	79 (28.8)	83 (40.9)
Missing	–	80 (100)	80 (29.2)	–
Cumulative illness rating scale score, median (range)	8.5 (0–23)	–	8.5 (0–23)	9 (0–23)
11q deletion, n (%)				
Yes	33 (17.0)	–	33 (12.0)	34 (16.7)
Missing	16 (8.2)	80 (100.0)	96 (35.0)	12 (5.9)
13q deletion, n (%)				
Yes	53 (27.3)	–	53 (19.3)	59 (29.1)
Missing	16 (8.2)	80 (100.0)	96 (35.0)	12 (5.9)
12 trisomy, n (%)				
Yes	32 (16.5)	–	32 (11.7)	34 (16.7)
Missing	16 (8.2)	80 (100.0)	96 (35.0)	12 (5.9)

Table 1 continued

	PKs patient population			Exposure-response patient population CLL14 N = 203
	CLL14 n = 194[a]	GP28331 n = 80	Total N = 274	
17p deletion, n (%)				
Yes	15 (7.7)	–	15 (5.5)	16 (7.9)
Missing	16 (8.2)	80 (100)	96 (35.0)	12 (5.9)
IGHV mutation, n (%)				
Yes	67 (34.5)	–	67 (24.5)	72 (35.5)
Missing	21 (10.8)	80 (100)	101 (36.9)	16 (7.9)
TP53 mutation, n (%)				
Yes	15 (7.7)	–	15 (5.5)	17 (8.4)
Missing	46 (23.7)	80 (100)	126 (46.0)	38 (18.7)
Serum β2-microglobulin, n (%)				
Abnormal	113 (58.2)	–	113 (41.2)	117 (57.6)
Missing	6 (3.1)	80 (100)	86 (31.4)	9 (4.4)
CYP3A, n (%)				
Weak	63 (32.5)	18 (22.5)	81 (29.6)	
Moderate	17 (8.8)	13 (16.2)	30 (10.9)	
Strong	6 (3.1)	5 (6.2)	11 (4.0)	
Not administered	108 (55.7)	44 (55.0)	152 (55.5)	
P-gp, n (%)				
Administered	13 (6.7)	6 (7.5)	19 (6.9)	
Not administered	181 (93.3)	74 (92.5)	255 (93.1)	
OATP1B1, n (%)				
Administered	7 (3.6)	5 (6.2)	12 (4.4)	
Not administered	187 (96.4)	75 (93.8)	262 (95.6)	
OATP1B3, n (%)				
Administered	7 (3.6)	5 (6.2)	12 (4.4)	
Not administered	187 (96.4)	75 (93.8)	262 (95.6)	

Table 1 continued

| | PKs patient population | | | Exposure-response patient population |
	CLL14 $n = 194^{a}$	GP28331 $n = 80$	Total $N = 274$	CLL14 $N = 203$
CYP3A inducer, n (%)				
Administered	12 (6.2)	11 (13.8)	23 (8.4)	
Not administered	182 (93.8)	69 (86.2)	251 (91.6)	
Maximum venetoclax dose administered, n (%)				
400 mg	190 (97.9)	68 (85.0)	258 (94.2)	
300 mg	–	1 (1.2)	1 (0.4)	
200 mg	3 (1.5)	6 (7.5)	9 (3.3)	
100 mg	1 (0.5)	1 (1.2)	2 (0.7)	
50 mg	–	3 (3.8)	3 (1.1)	
20 mg	–	1 (1.2)	1 (0.4)	

CLL chronic lymphocytic leukemia, *IGHV* immunoglobulin heavy chain variable gene, *P-gp* P-glycoprotein, *PK* pharmacokinetic, *popPK* population pharmacokinetics, *R/R* relapsed/refractory

[a] 9 patients without evaluable PKs data were excluded from the popPK analysis
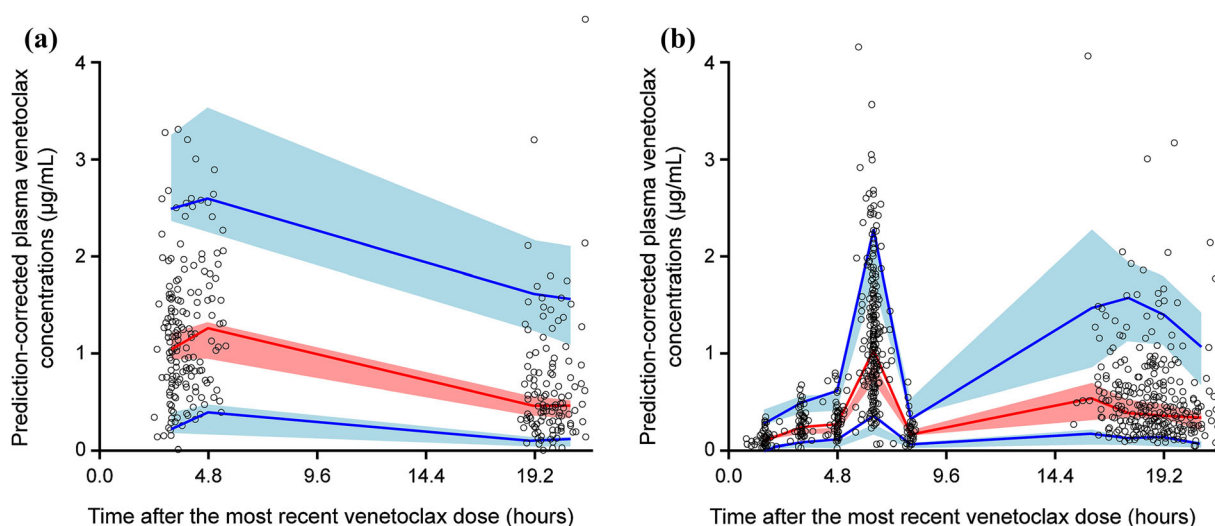
Fig. 1 Prediction-corrected VPC using the final popPK model to predict the observed data for CLL14 (**a**) and GP28331 (**b**). *CI* confidence interval, *h* hours, *popPK* population pharmacokinetics, *VPC* visual predictive check. Points are prediction-corrected venetoclax concentrations plotted vs. time after most recent venetoclax dose. The lines show median (red), and the 5th and 95th percentiles (blue) of the prediction-corrected venetoclax concentrations. The shaded regions show the 90% CIs on these quantities obtained by simulations. The simulated values were computed from 500 trials with dosing, sampling, and the covariate values of the analysis dataset

Table 2 Final model parameter estimates

Parameter	Estimate	RSE (%)	95% CI
CL/F (L/day)	446	2.48	425–468
V_2/F (L)	116	13.2	86.2–146
Q/F (L/day)	98.8	4.95	89.1–108
V_3/F (L)	121	3.74	112–130
k_a (day^{-1})	3.76	3.76	3.48–4.04
$F_{1,fasting}$	0.34	0.95	0.33–0.34
$F_{1,moderate\ fat}$	1.4	8.00	1.18–1.62
$F_{1,high\ fat}$	1.4	1.28	1.41–1.48
$F_{1,fed}$	1.3	3.85	1.19–1.39
$F_{1,DOSE}$	-0.15	2.16	− 0.16 to − 0.14
CL_{RTX}[a]	1.2	2.90	1.17–1.32
$CL_{C3AHIB\ =\ 2}$[a]	0.86	4.08	0.79–0.93
$CL_{C3AHIB\ =\ 3}$[a]	0.18	5.95	0.16–0.20
$V_{2,PTOP>0}$	1.73	12.0	1.33–2.14
$V_{2,SEX\ =\ 1}$	0.70	5.65	0.63–0.78
$CL_{OATP1B3}$	0.86	2.41	0.82–0.91

Derived parameters

$t_{1/2}$ (day)			1.08

C3AHIB CYP3A inhibitor indicator variable (2 = moderate, 3 = strong), *CI* confidence interval, *CL* clearance, *CL/F* apparent clearance, *CLL* chronic lymphocytic leukemia, F_1 relative bioavailability (F_1 = 1 corresponds to 400 mg QD with low-fat food), k_a absorption rate constant, *OATP1B3* organic anion transporting polypeptide 1B3 indicator variable (0 = OATP1B3 transporter inhibitors never administered, 1 = OATP1B3 transporter inhibitors were administered at least once), *RTX* rituximab indicator variable, *PTOP* patient population (where 0 corresponds to a healthy subject; 1, R/R CLL; 4, previously untreated unfit CLL; 5, previously untreated fit CLL; 6, previously untreated CLL), *Q/F* apparent inter-compartmental clearance, *RSE* relative standard error, *SEX = 1* female, $t_{1/2}$ terminal half-life, V_2 central volume, V_2/F apparent central volume, V_3/F apparent peripheral volume
[a]Covariate coefficients on clearance
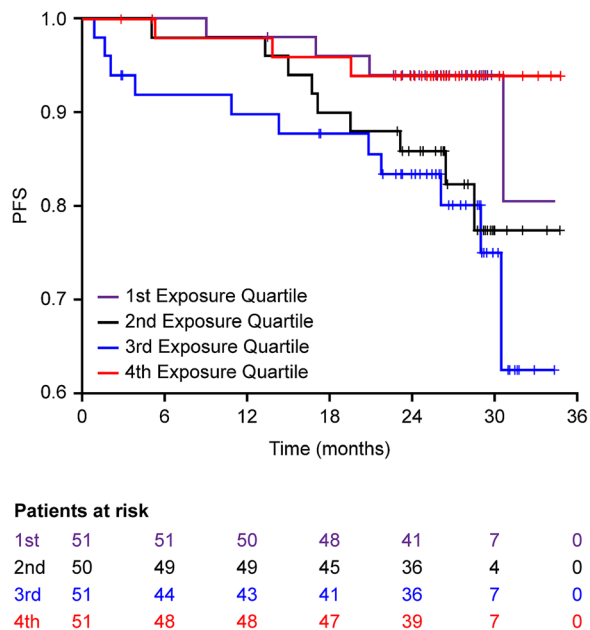
Fig. 2 Kaplan-Meier analysis of time to progression (investigator data). Exposure groups correspond to quartiles of $C_{meanSS,nominal}$. $C_{meanSS,nominal}$ nominal exposure at steady state, *PFS* progression-free survival

identical to the legacy model. Key parameter estimates are summarized in Table 2. Notable key covariate effects were:

- CL/F was decreased by 82.2% (95% confidence interval [CI] 80.1–84.3) and 13.9% (95% CI 7.0–20.7) with strong and moderate CYP3A inhibitors, respectively. OATP1B3 hepatic uptake transporter inhibitors decreased CL/F by 13.6% (95% CI 9.5–17.7).
- V_2/F was 73.3% higher (95% CI 32.6–114.1) in patients compared with healthy individuals and 29.7% lower (95% CI 21.9–37.5) in females than in males.
- F_1 for the 400 mg dose with a low-fat meal was fixed at 1. Administration in the fasting state decreased F_1 by 66.2% (95% CI 65.6–66.8) relative to the low-fat state, while moderate- and high-fat meals increased F_1 by 40.4% (95% CI 18.4–62.4) and 44.3% (95% CI 40.7–47.9), respectively. Additionally, administration with a meal-fed state (without specification of fat content) increased F_1 by 28.9% (95% CI 19.2–38.7). A dose decrease from 400 to 200 mg increased F_1 by 11.0% (95% CI 10.5–11.5),
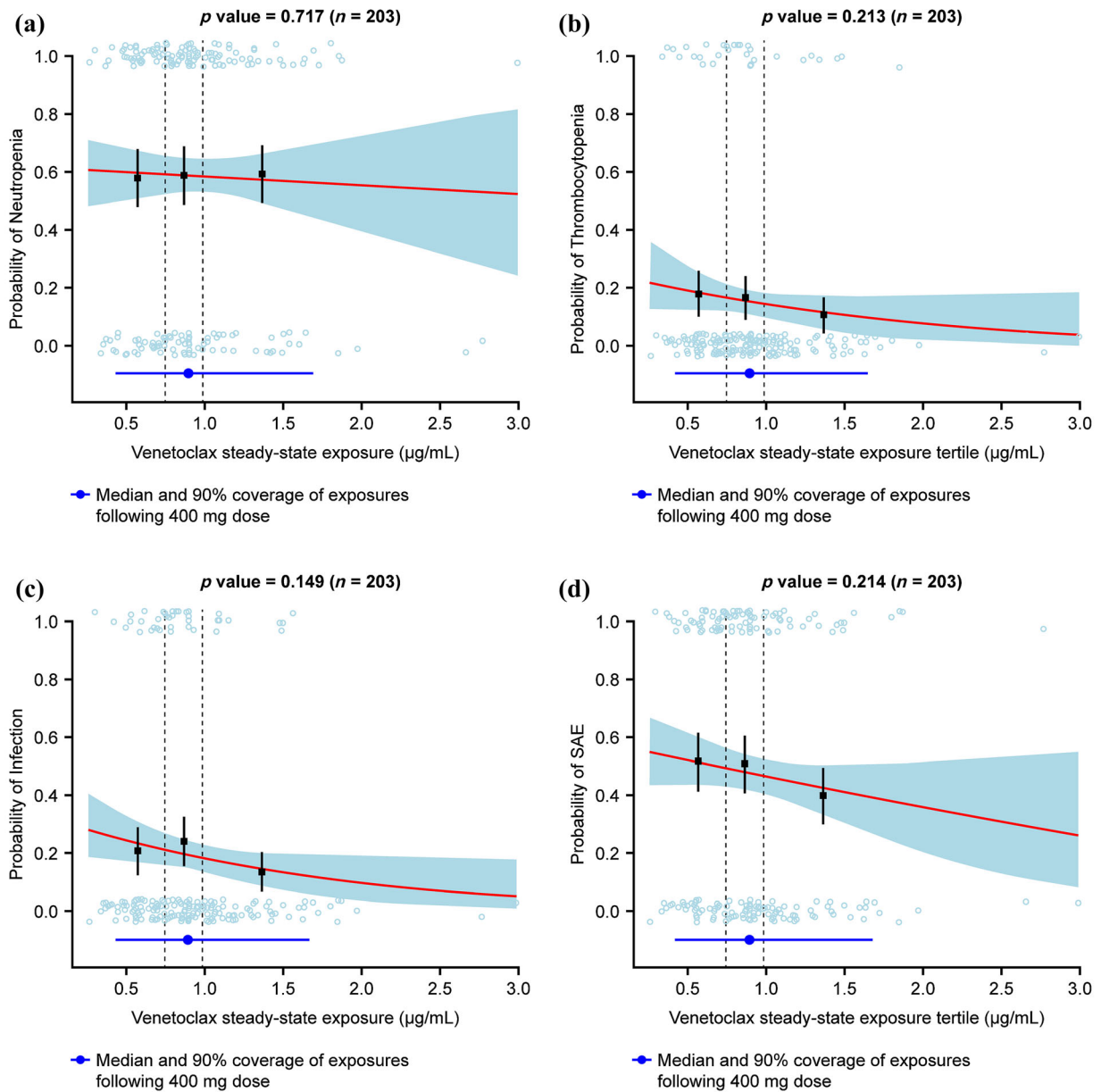
Fig. 3 Logistic regression analyses of exposure-safety relationships for treatment-emergent grade ≥ 3 neutropenia (**a**), grade ≥ 3 thrombocytopenia (**b**), grade ≥ 3 infections (**c**), and SAEs (**d**). *CI* confidence interval, *glm* generalized linear models, *QD* once-daily, *SAE* serious adverse event. The red solid line and blue shaded area represent the logistic regression model prediction and 90% CI of predictions, respectively. Points show exposure of individual patients with events ($p = 1$) and without events ($p = 0$). Black squares and vertical black lines show observed fraction of patients with events in each exposure group and 90% CI for these fractions. Dashed vertical lines show bounds of exposure groups. Blue line and point indicate point estimate and 95% coverage interval of steady-state exposure following 400 mg QD doses, respectively. *p* value is provided by *glm()* function

whereas a dose increase from 400 to 800 mg decreased F_1 by 9.9% (95% CI 9.5–10.3).

In the final model evaluation, goodness-of-fit of the data for both studies was confirmed (Supplementary Material Figs. S1 and S2), with
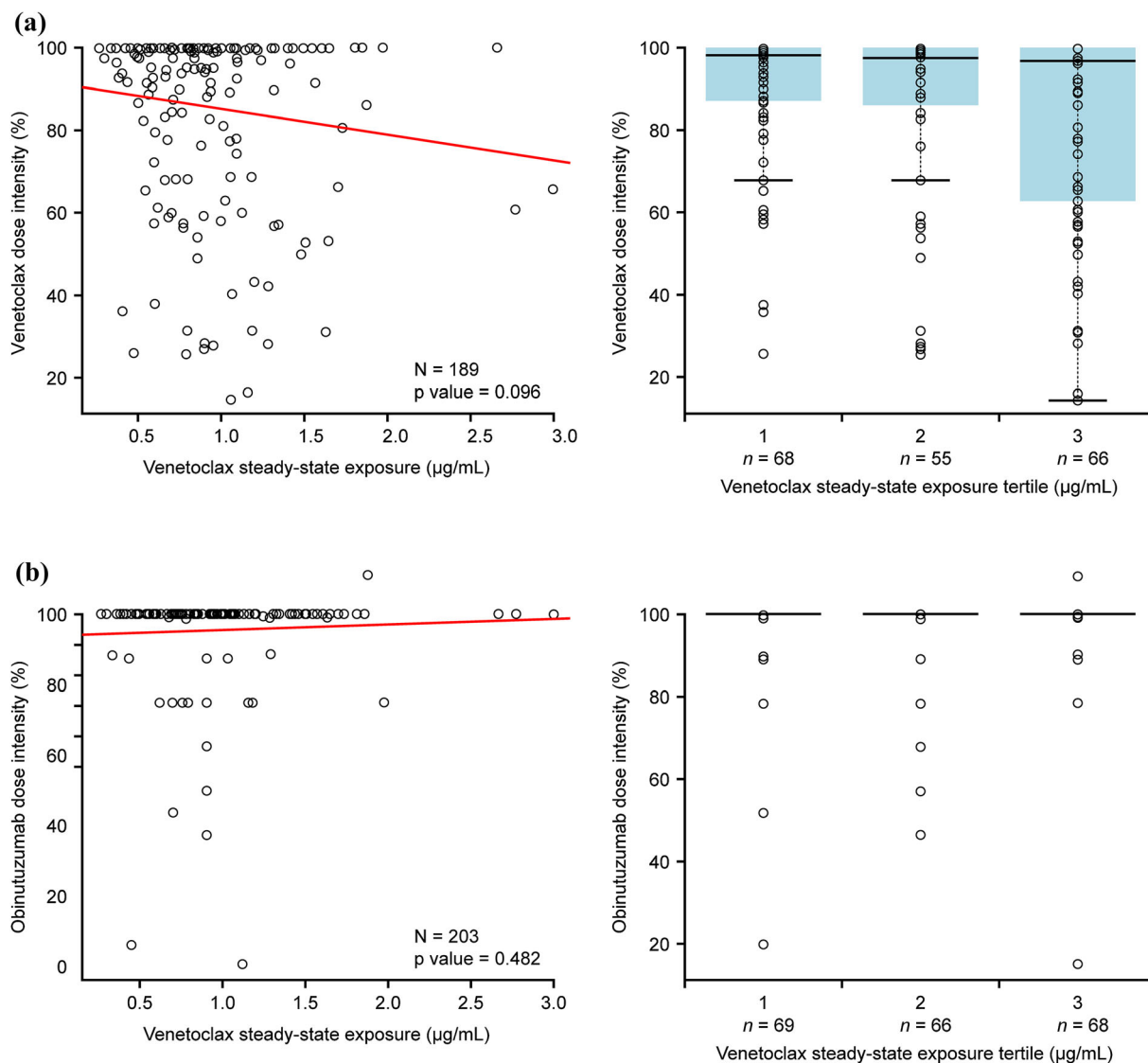
Fig. 4 Venetoclax (**a**) and obinutuzumab (**b**) dose intensity vs. venetoclax exposure. $C_{meanSS,nominal}$ nominal exposure at steady state. Circles correspond to individual dose intensity values. $C_{meanSS,nominal}$ was used as a measure of exposure. The bold red lines are the LOWESS (local weighted scatterplot smoothing) trend lines. Median values are designated by black lines in the center of the blue boxes. Boxes indicate the interquartile range (IQR). Whiskers represent $1.5 \times$ IQR

no apparent model deficiencies. The conditional weighted residuals (CWRES) showed no major trends when plotted against population predicted values, with most values within ± 2 standard normal deviations for both CLL14 (Supplementary Material Fig. S1, panel 3) and GP28331 (Supplementary Material Fig. S2, panel 3), indicating that the model was adequately unbiased and appropriately described variability. Examination of the final model

CWRES vs. time for CLL14 (Supplementary Material Fig. S1, panel 6) and GP28331 (Supplementary Material Fig. S2, panel 6) indicated no apparent trend over time for either study, confirming the lack of time-dependent PKs for venetoclax. The dependencies of the random effects on covariates did not show any further trends unaccounted for by the model. Random effects on CL/F and F_1 were independent of weight, age, CrCL, patient population (R/R CLL

vs. previously untreated unfit CLL vs. previously untreated CLL), gender, Binet stage, cytogenetic factors, mutational status, renal and hepatic impairment, geographic region, and concomitant medications (data not shown). The VPC and NPDE plots further supported good description of the observed CLL14 and GP28331 data by the Bayesian popPK model (Fig. 1; Supplementary Material Figs. S3 and S4).

Individual PK Parameters

Individual PK parameters and exposures predicted from the model were similar for CLL14 and GP28331 (Supplementary Material Table S3). Furthermore, venetoclax steady-state exposure was not significantly influenced by obinutuzumab co-administration, patient population, or Binet stage (Supplementary Material Tables S4 and S5). Consistent with the previous legacy model, no relationship was observed between venetoclax CL/F and body weight, age, gender, mild or moderate hepatic or renal impairment, calculated CrCL, bilirubin, ALT, AST, albumin, and co-administration of P-glycoprotein or weak CYP3A inhibitors (data not shown). The final model was used to estimate individual exposure parameters for the subsequent exposure-response analyses.

Dataset for Exposure–Response Relationships

Exposure–safety and exposure-efficacy analyses were performed using data from 203 patients from the venetoclax–obinutuzumab arm of the CLL14 study, who received at least one dose of venetoclax and obinutuzumab. Patient background characteristics and covariates for the exposure–response population are summarized in Table 1.

Exposure-Efficacy Relationships

PD or death was reported in 27 patients (13.3%) by investigator assessment and in 26 patients (12.8%) by IRC assessment. The CPH analysis showed that exposure is not a significant predictor of investigator-/IRC-assessed PFS

($p > 0.05$; Fig. 2; Supplementary Material Table S6 and Fig. S5), indicating that venetoclax concentrations following 400 mg QD dosing could be on the plateau of the exposure–response relationship.

Exposure-Safety Relationships

Treatment-emergent grade ≥ 3 neutropenia, grade ≥ 3 thrombocytopenia, grade ≥ 3 infections, and SAEs occurred in 118 (58.1%), 30 (14.8%), 39 (19.2%), and 96 (47.3%) patients, respectively. Logistic regression analyses showed no statistically significant association between venetoclax $C_{meanSS,nominal}$ and the probability of grade ≥ 3 neutropenia ($p = 0.717$; Fig. 3a), grade ≥ 3 thrombocytopenia ($p = 0.213$; Fig. 3b), grade ≥ 3 infections ($p = 0.149$; Fig. 3c), or SAEs ($p = 0.214$; Fig. 3d).

Exposure-Dose Intensity Relationships

The median dose intensity in the venetoclax-obinutuzumab arm of CLL14 was 95.1% for venetoclax and 100% for obinutuzumab. Across the tertiles of venetoclax exposure ($C_{meanSS,nominal}$), venetoclax mean and median dose intensities ranged from 81.1% to 89.5% and 96.8% to 98.1%, respectively; obinutuzumab mean dose intensity ranged from 92.4% to 97.2% and median dose intensity was 100%. The summary of venetoclax and obinutuzumab dose intensity by tertiles of venetoclax exposure showed that venetoclax exposure had no apparent effect on mean or median venetoclax and obinutuzumab dose intensities (Fig. 4a and b, respectively). The values of the first quartile of venetoclax dose intensity within each exposure group (lower bounds of the boxes) declined with increasing venetoclax exposure. The obinutuzumab dose intensities were independent of venetoclax exposure, with medians of 100% for all exposure groups.

DISCUSSION

Data from the pivotal phase 3 CLL14 study and the supportive phase 1b GP28331 study

demonstrate that 1L treatment with venetoclax-obinutuzumab provides meaningful clinical benefit in adult patients with CLL. The popPK and exposure-response analyses continue to support the venetoclax dose and schedule in combination with obinutuzumab, as evaluated in CLL14 and recommended for the approved indication of 1L treatment in patients with CLL and pre-existing comorbidities.

The PK data from both CLL14 and GP28331 aligned with the legacy popPK model, and were adequately described by a two-compartment model with first-order absorption and elimination. The updated popPK model successfully characterized venetoclax plasma concentrations over time, and venetoclax PKs at the 400 mg QD dose level with obinutuzumab in CLL14 and GP28331 were comparable with PK data seen in previous studies of venetoclax monotherapy, in line with theoretical expectations [6, 22, 23]. Although co-administration of rituximab was a significant covariate on CL/F in the legacy model [20], and was therefore present as a covariate in the current analysis given the Bayesian modelling approach, it must be noted that no patient in CLL14 or GP28331 received rituximab. Furthermore, on the basis of the popPK evaluation of patients randomized to venetoclax plus rituximab in the MURANO study [24], the estimate for rituximab co-administration effect (7% decrease in CL/F) was lower than in the legacy popPK analysis (22% increase in CL/F) and lower than that observed in the current analysis (7% increase in CL/F). The legacy model included data from 505 patients, of whom only 50 had co-administration of rituximab. In contrast, in MURANO, most patients randomized to treatment received rituximab, thus yielding considerably more robust combination therapy data. Therefore, the 7% rituximab effect determined by the MURANO analysis provided the most reliable estimate of the potential impact of rituximab on venetoclax PKs, confirming that there was no clinically significant influence of rituximab on venetoclax exposure.

We estimated that venetoclax V_2/F was 29.7% lower in women than in men, but this had no effect on venetoclax steady-state exposures (maximum steady-state concentration, steady-state concentration at the end of a dosing interval, and area under the concentration-time curve at steady state), supporting the proposed fixed-dosing regimen of venetoclax, independent of sex.

Additional observations using the final popPK model indicated that administration of strong and moderate CYP3A inhibitors resulted in CL/F decreases of 82.2% and 13.9%, respectively. This finding was consistent with the previous pooled analysis for the legacy model [20] and the known PK characteristics of venetoclax [9, 25–28]. Of note, the dataset for the present analysis included data from only 11 patients with strong CYP3A inhibitor usage and 30 with moderate CYP3A inhibitor usage. Therefore, the estimated covariate effect for CYP3A inhibitors was driven almost entirely by the legacy model as an informative prior, with the new dataset providing little additional information, thereby providing support for existing dosage recommendations for venetoclax when administered with CYP3A inhibitors [9].

Consistent with the legacy model, no relationship was observed between venetoclax CL/F and baseline characteristics, including body weight, age, sex, calculated CrCL, AST, ALT, bilirubin, albumin, and co-administration of P-glycoprotein inhibitors or weak CYP3A inhibitors. Patient population (R/R CLL vs. previously untreated unfit CLL vs. previously untreated CLL) and Binet stage had no appreciable influence on venetoclax steady-state PKs. Importantly, the current analysis suggested that venetoclax PKs in patients with mild or moderate hepatic or renal impairment are comparable with those with normal hepatic or renal function. There is therefore no evidence to support venetoclax dose adjustments in these subgroups.

Venetoclax $C_{meanSS,nominal}$ was estimated using a popPK modelling approach. We used $C_{meanSS,nominal}$ in the exposure–response analyses for efficacy, safety, and dose intensity rather than average plasma concentration to the time of the event, to avoid bias from correlations between time and response, and time and lower exposures after dose modifications, both of which are more likely the longer a patient is on

study. Moreover, $C_{meanSS,nominal}$ isolated the impact of steady-state exposure associated with the assigned target dose of venetoclax on safety and efficacy, and was not subject to confounding by complex interactions between time and treatment-/disease-related changes to venetoclax or obinutuzumab doses.

No significant relationships were observed between venetoclax exposure and obinutuzumab dose intensity, suggesting that venetoclax co-administration did not impact the dose intensity of obinutuzumab. Across the tertiles of venetoclax exposure (i.e., tertiles of $C_{meanSS,nominal}$), the mean and median dose intensity differences for obinutuzumab and venetoclax were similar. A trend toward a decline in the values of the first quartile of venetoclax dose intensity with increasing venetoclax $C_{meanSS,nominal}$ following the 400 mg QD dosing regimen was observed; however, there was no apparent correlation between venetoclax exposure and the dose intensity of either venetoclax or obinutuzumab in CLL14, suggesting that there were no significant changes in dose delays, reductions, or AE-related treatment discontinuations for venetoclax in patients with higher venetoclax exposures. This supports the tolerability of the combination.

In the CLL14 study, no statistically significant relationships between venetoclax exposure and the probability of developing grade $\geq$ 3 neutropenia, grade $\geq$ 3 thrombocytopenia, grade $\geq$ 3 infection, or SAEs were identified using logistic regression analysis. These results suggest that, over the range of exposures resulting from the 400 mg QD venetoclax target dose, no significant improvement in the safety profile would be expected at lower venetoclax exposures. Therefore, lowering the venetoclax target dose to yield lower exposures within this range is unlikely to markedly reduce these toxicities. In addition, graphical and Cox proportional analysis of the venetoclax-obinutuzumab arm from CLL14 showed no statistically significant relationship between venetoclax exposure and investigator- or IRC-assessed PFS, providing no evidence for improved efficacy with higher venetoclax exposure at the tested venetoclax dose.

A limitation of this study was that a single dose level of 400 mg of venetoclax was evaluated in combination with obinutuzumab in the phase 3 CLL14 trial in patients with previously untreated CLL and co-existing medical conditions. However, the justification of venetoclax dose and regimen (400 mg QD) is based upon efficacy, safety, tolerability, pharmacokinetics, and exposure-response data from the pivotal phase 3 CLL14 trial. These data along with the totality of the pharmacokinetics, efficacy, safety and exposure-response data from the supportive phase 1b GP28331 study, which tested a venetoclax dose range of 100–400 mg/day in patients with previously untreated and R/R CLL, were considered sufficient to justify the 400 mg QD dose of venetoclax in the previously untreated patients with CLL and co-existing medical conditions.

CONCLUSIONS

Collectively, the PKs, exposure-efficacy, exposure-safety, and exposure–tolerability analyses support the selected 400 mg QD venetoclax dose regimen in combination with obinutuzumab as 1L treatment in patients with CLL as appropriate for providing a positive benefit-risk profile, with highly favorable efficacy and a manageable safety profile.

ACKNOWLEDGEMENTS

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