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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	BLA 761121
Link to EDR	\\CDSESUB1\evsprod\BLA761121\0002
Submission Date	12/19/2018
Submission Type	<i>Original BLA (Priority Review)</i>
Brand Name	POLIVY®
Generic Name	Polatuzumab vedotin
Dosage Form and Strength	1.8 mg/kg (140 mg of lyophilized powder for reconstitution) (b) (4)
Route of Administration	Intravenous infusion
Proposed Indication	In combination with rituximab and bendamustine is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, after at least two prior therapies.
Applicant	Genentech, Inc.
Associated IND	IND 109409
OCP Review Team	Salaheldin S. Hamed, Ph.D. Justin Earp, Ph.D. Xinyuan Zhang Ph.D. Yuching Yang, Ph.D. Lian Ma, Ph.D. Guoxiang Shen, Ph.D.
OCP Final Signatory	NAM Atiqur Rahman, Ph.D.

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1. EXECUTIVE SUMMARY

Polatuzumab vedotin is an antibody drug conjugate consisting of a humanized monoclonal antibody targeting CD79b, which is a protein expressed on cells of B-cell origin. The antibody is linked to monomethyl auristatin E (MMAE) – an anti-microtubule small molecule that induces cell cycle arrest and apoptosis. The proposed indication for polatuzumab vedotin, in combination with bendamustine and rituximab, is the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL), not otherwise specified, after at least two prior therapies.

In a randomized, open-label, multicenter study that included 80 patients with relapsed or refractory DLBCL. Patients were randomized to receive either polatuzumab vedotin in combination bendamustine and rituximab or bendamustine and rituximab alone for six 21-day cycles. The complete response (CR) rate in the polatuzumab arm was 45% (95% CI: 29-62%) compared to a CR rate of 17.5% (95% CI: 7%-33%) in the control arm.

Doses ranging from 0.1-2.4 mg/kg were investigated in the dose escalation study; 1.8 mg/kg was selected for the registration trial. The 1.8 mg/kg starting dose was found acceptable based on an improved safety profile compared to 2.4 mg/kg. Exposure-safety analyses identified a relationship between polatuzumab vedotin exposure and the probability of Grade 2 or higher peripheral neuropathy and a relationship between unconjugated MMAE exposure and the probability of Grade 3 or higher anemia. Exposure-efficacy analysis supported the proposed dose compared to a lower dose; higher exposure was correlated with higher response in the supportive studies.

Population PK analysis indicated that patients with mild hepatic impairment had higher MMAE exposure (40% for AUC and 37% for C_{max}) compared to patients with normal function. However, no dose adjustment was necessary because the 40% increase in MMAE exposure is not clinically relevant and is not likely alter safety based on the established exposure-safety relationship. In addition, analysis of safety data suggested that the incidence of adverse events with comparable in patients with mild hepatic impairment and patients with normal hepatic function. Patients with moderate or severe hepatic impairment should avoid treatment with Polatuzumab vedotin. There were only two patients with moderate hepatic impairment and no information regarding severe hepatic impairment.

MMAE is a substrate and a time-dependent inhibitor of CYP3A enzymes in vitro. A physiologically-based pharmacokinetic model (PBPk) predicted that MMAE exposure would be increased by 45% when administered concomitantly with ketoconazole (a strong CYP3A inhibitor) and decreased by 63% when administered concomitantly with rifampin (a CYP3A inducer). Additionally, systemic MMAE (at the 1.8 mg/kg dose) did not affect midazolam (a sensitive CYP3A substrate) exposure, as predicted by the PBPk model. No dose adjustment is required for drug-drug interactions. Based on E-R relationships, 45% increase in MMAE exposure is not expected to substantially affect safety (similar to the observed exposure increase in patients with mild impairment) and 63% decrease in MMAE exposure is not likely to affect efficacy.

1.1 Recommendations

The Office of Clinical Pharmacology recommends the approval of BLA 761121 from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The effectiveness of polatuzumab vedotin was demonstrated in study GO29365. The CR rate in the polatuzumab (in combination with bendamustine and rituximab) arm was 40% (95% CI: 29%-62%) compared to a CR rate of 17.5% (95% CI: 7%-33%) in the control arm (bendamustine and rituximab alone). In the polatuzumab arm 70% of the patients who responded had a duration of response (DoR) of at least 6 months and 52% had a DoR of at least 12 months. In the control arm, 30% who responded had a DoR of at least 6 months and 20% had a DoR of at least 12 months.
General dosing instructions	The proposed dosing is 1.8 mg/kg administered on Day 1 of every 21-day treatment cycle for 6 cycles.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustments are necessary based on intrinsic or extrinsic factors.
Labeling	Labeling recommendations are generally adequate. See highlights in Section 2.4.
Bridge between the to-be-marketed and clinical trial formulations	The PK and safety of the lyophilized drug product (to-be-marketed) formulation was characterized in the Arm G (~40 patients) in study GO29365. Population PK analysis indicated that there is no difference in the PK between the lyophilized formulation and the solution formulation used in other clinical studies of polatuzumab.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action: Polatuzumab vedotin contains a humanized IgG1 monoclonal antibody that targets CD79b. The antibody portion is covalently linked to MMAE, the small molecule portion, via the protease cleavable linker mc-vc-PAB. Upon target binding, the MMAE is released due to degradation of the linker in lysosomes and binds to microtubules to induce cell cycle arrest and apoptosis.

Absorption: polatuzumab vedotin is administered as an intravenous (IV) infusion.

Distribution: The volume of distribution of polatuzumab vedotin is 3.15 L. The plasma protein binding of MMAE ranges from 71% to 77%.

Metabolism: MMAE, the small molecule portion of polatuzumab vedotin, is substrate of CYP3A enzymes.

Elimination: the terminal half-life of polatuzumab vedotin is approximately 12 days, and the elimination half-life of MMAE is approximately 4 days. The primary route of MMAE elimination is the biliary route.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dosage of polatuzumab vedotin is 1.8 mg/kg administered on Day 1 of every 21-day treatment cycle for 6 cycles.

2.2.2 Therapeutic individualization

No dose adjustments are recommended based intrinsic or extrinsic factors. Population PK analysis did not identify differences in polatuzumab vedotin PK due to age (20 to 89 years), sex, race/ethnicity (Asian and non-Asian), or renal impairment (mild and moderate).

Although patients with mild hepatic impairment had approximately 40% increase in MMAE exposure, no dose adjustment is recommended based on exposure-safety information. The effect of moderate and severe hepatic impairment on safety and PK of polatuzumab vedotin is unknown.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

Labeling recommendations are generally adequate and can be summarized as follows:

- No dose adjustment is required based on drug-drug interactions
- No dose adjustment is required based on renal impairment
- No dose adjustment is required in patients with mild hepatic impairment
- The administration of polatuzumab vedotin should be avoided in patients with moderate and severe hepatic impairment

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Polatuzumab vedotin was investigated under IND 109409. In September 2014, the IND was placed on partial clinical hold due to the increased toxicity, including deaths, at the 2.4 mg/kg dose. Clinical studies were conducted at 1.8 mg/kg dose. In December 2016, doses ranged from 0.1-2.4 mg/kg in the supportive studies and included only 1.8 mg/kg for the pivotal study. Polatuzumab vedotin received Orphan Drug Designation for the treatment of DLBCL. In September 2017, polatuzumab vedotin

received Breakthrough Therapy Designation for the treatment of adult patients with relapsed or refractory DLBCL who are not candidates for hematopoietic stem cell transplant.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Structure	Polatuzumab vedotin is an antibody drug conjugate composed a humanized IgG1 monoclonal antibody specific for human CD79b. The antibody is attached to the small molecule MMAE via the protease cleavable linker mc-vc-PAB.
Mechanism of Action	The monoclonal antibody binds to CD79b, a B-cell specific surface protein, which is expressed in more than 95% of DLBCL. Upon binding to CD79b, polatuzumab vedotin is internalized, and the linker is cleaved by lysosomal proteases to enable the delivery of MMAE. MMAE, subsequently, binds to microtubules and kills cells by inducing cell cycle arrest and apoptosis.
Proposed Dosing	The recommended dose of polatuzumab vedotin is 1.8 mg/kg administered on Day 1 of each 21-day treatment cycle for 6 cycles.
General Information	
Bioanalysis	Polatuzumab vedotin plasma concentrations were measured using an immunoaffinity liquid chromatography with tandem mass spectrometry (LC-MS/MS). Unconjugated MMAE plasma concentrations were measured using an LC-MS/MS assay.
Dose Proportionality	The plasma exposure of the ADC and unconjugated MMAE increased proportionally over a polatuzumab vedotin dose range of 0.1 to 2.4 mg/kg.
Accumulation	At Cycle 3, the AUC of the ADC was predicted to increase by approximately 30% compared to Cycle 1 and achieve more than 90% of the Cycle 6 AUC. The AUC and C _{max} of MMAE were predicted to decrease after repeat every-3-week dosing.
Variability	After the first dose, the coefficient of variation was 29% for the C _{max} of the ADC, 52% for the AUC of the ADC, 69% for the C _{max} of MMAE, and 34% for the AUC of MMAE.
Immunogenicity	The immunogenicity of polatuzumab vedotin was determined in 134 patients across all arms of study GO29365; 8 patients (6%) tested positive for antibodies against polatuzumab vedotin. Across clinical trials, 14/536 (2.6%) tested positive for polatuzumab vedotin antibodies.
QT Prolongation	The effect of polatuzumab vedotin (1.8 mg/kg) on the QTc interval was evaluated based on triplicate ECG data from two open-label studies in 209 patients with previously treated B-cell malignancies. The administration of platuzumab vedotin did not prolong the mean QTc interval by more than 20 ms from baseline. Small increases in the QTc interval (less than 10 ms) cannot be excluded because these studies did not include placebo arms or positive control arms.
Distribution	
Volume of Distribution	Based on population PK analysis, the estimated volume of distribution of the polatuzumab vedotin is 3.15 L. Based on in vitro studies, MMAE plasma protein binding is 71% to 77% and the blood-to-plasma ratio (b) (4).
Elimination	

Mean Terminal Half-Life	The terminal half-life of polatuzumab vedotin is approximately 12 days at Cycle 6. The unconjugated MMAE terminal half-life is approximately 4 days after the first dose.
Metabolism	
Primary Metabolic Pathways	Polatuzumab vedotin is thought to be catabolized into small peptides, amino acids, and unconjugated MMAE. MMAE is a CYP3A substrate.
DDI Potential	<u>PBPK:</u> - concomitant use of polatuzumab vedotin with ketoconazole (strong CYP3A inhibitor) is predicted to increase MMAE AUC by 45% - concomitant use of rifampin (strong CYP3A inducer) is predicted to decrease MMAE exposure by 63% - Concomitant use polatuzumab vedotin did not affect midazolam (sensitive CYP3A substrate) AUC <u>Population PK Analyses:</u> - Polatuzumab vedotin AUC increased by 24% and C_{max} increased by 5% in Cycle 6 when administered in combination with rituximab; however, MMAE AUC decreased by 37% and C_{max} decreased by 40% - Polatuzumab did not affect the exposure of rituximab or bendamustine <u>In vitro Studies:</u> - MMAE did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 - MMAE did not induce CYP450 enzymes - MMAE did not inhibit P-gp
Excretion	
Primary Excretion Pathway	Biliary excretion is the main route of elimination of MMAE.

3.3 Clinical Pharmacology Review Questions

3.3.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology program provides supportive evidence of effectiveness. The applicant submitted safety and efficacy results from Study GO29635 to support approval for the proposed indication in patients with DLBCL. Additionally, the applicant submitted data from a Phase I dose escalation study DCS4968g to support dose selection and data from studies GO27834 (ROMULUS) and GO29044 as supportive evidence of safety and efficacy of polatuzumab vedotin (**Table 1**).

Table 1: Clinical studies supporting polatuzumab vedotin safety and efficacy

Trial	Disease	Design	Regimen	Analysis Population
Registration Trial				
GO29365	Relapsed/refractory DLBCL or FL	Open label, multicenter, Phase 1b/2 study that includes: • Safety run-in	Pola 1.8 mg/kg + BR/BG q 21 days x 6 cycles (DLBCL) Pola 1.8 mg/kg + BR/BG q 28 days x 6 cycles (FL)	Efficacy in DLBCL: 80 patients randomized to pola + BR (n=40) vs BR (n=40)

		• Randomized Phase 2 (pola + BR vs BR) • Single arm expansion (pola + BG) • Single arm DLBCL cohort (Arm G) of lyophilized formulation		Safety: 141 pts treated with original-formulation pola 1.8 mg/kg + BR/BG including: Pola+BR: 89 treated – 45 with DLBCL (39 from randomized cohort), 44 with FL Pola+BG: 52 treated – 26 with DLBCL, 26 with FL Pola + BR/BG, q 21 day schedule: 71 (all DLBCL) BR alone: 80 treated (39 with DLBCL, 41 with FL) <u>New formulation (Arm G)</u> 32 evaluated
Supportive Studies				
DCS4968g	R/R B-NHL or CLL	Phase 2, open-label, multicenter study of pola +/- R	Pola monotherapy (0.1 – 2.4 mg/kg) q 21 days indefinitely Pola 2.4 mg/kg + R, q 21 days indefinitely	Total treated: 95 ^a Pola < 1.8 mg/kg: 30 Pola 1.8 mg/kg: 11 (4 DLBCL) Pola 2.4 mg/kg: 45 (27 DLBCL) Pola 2.4 mg/kg + R: 9
GO27834	R/R FL or DLBCL	Phase 2, open-label, multicenter study of pola + G or R	Pola 1.8 mg/kg + G, q 21 days x 8 cycles Pola 1.8 mg/kg or 2.4 mg/kg + R, q 21 days for up to 1 y	Total treated: 163 Pola 1.8 mg/kg + R: 20 (0 DLBCL) Pola 1.8 mg/kg + G: 84 (43 DLBCL) Pola 2.4 mg/kg + R: 59 (39 DLBCL)
GO29044	Newly diagnosed or R/R B-NHL		Pola 1.0 – 1.8 mg/g + R-CHP or G-CHP, q 21 days for 6 – 8 cycles	Includes 69 treated with pola 1.8 mg/kg + R/G-CHP (66 for 1L DLBCL)

Source: Clinical Review by Dr. Kasamon

B = bendamustine, G = obinutuzumab (Gazyva), R = rituximab

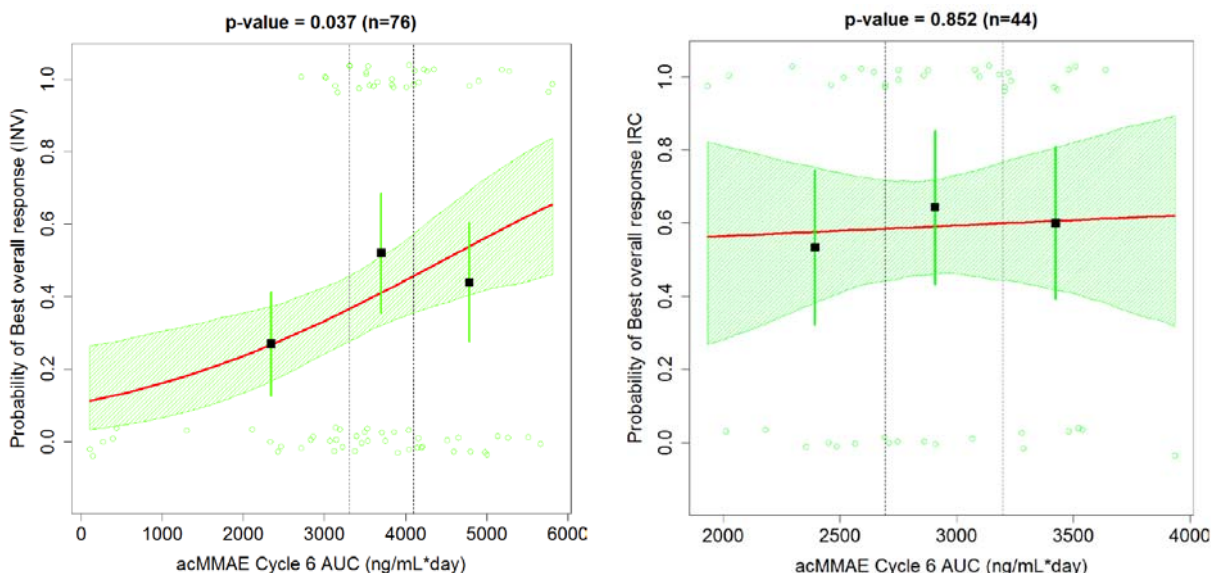
^a 40 DLBCL patients treated, 39 with pola monotherapy

Exposure-Efficacy Analyses

The applicant also submitted exposure-efficacy analyses based on data from both the pivotal and supportive studies as supportive evidence for effectiveness. Multivariate logistic regression analysis identified a positive E-R relationship for best overall response (**Figure 1**, left panel) in the supportive studies for polatuzumab vedotin. In the pivotal study, where only one dose level was evaluated, no E-R relationship for efficacy was identified (**Figure 1**, right panel). In addition to best overall response, the applicant also evaluated CR rate and overall response rate (ORR). The conclusions remain similar for these other endpoints for both analysis datasets. The applicant performed similar analyses for the unconjugated MMAE and no exposure-response for E-R relationship for efficacy was identified. No

baseline factors were identified as significant covariates in addition to PK. See Appendix 4.3 for further details regarding these analyses.

Figure 1: Exposure-Response relationship for best overall response in the supportive (left panel) and pivotal studies (right panel).



(Source: Applicant's Exposure-Safety & Exposure-Efficacy Report, Figure 67 and Figure 69)

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen with the option for dose modifications to mitigate adverse events is acceptable for the general patient population.

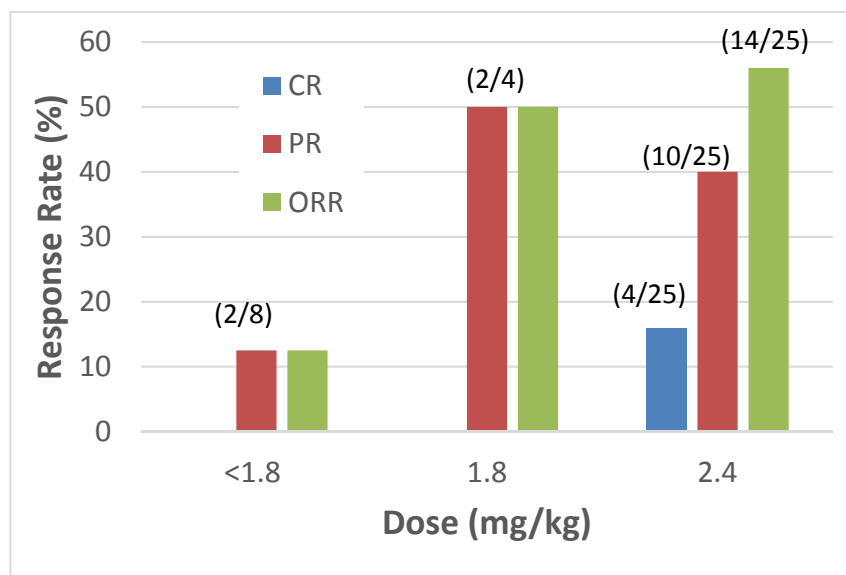
Dose Selection Rationale

Safety and efficacy data from trial DCS4968g – a Phase 1, multicenter, open-label, dose-escalation study supported polatuzumab vedotin dose selection. The study included a dose escalation phase and a dose expansion phase. The dose escalation phase was performed according to a standard 3+3 design.

The dose escalation started at a dose of 0.1 mg/kg in patients with non-Hodgkin's lymphoma (NHL). In the absence of dose limiting toxicities, dose escalation proceeded to the 2.4 mg/kg dose level. Of note, there was 1 Grade 4 neutropenia and 1 Grade 3 hypoxia in patients receiving 2.4 mg/kg. Even though no maximum tolerated dose (MTD) was identified, no further dose escalations were investigated.

A comparison of efficacy data across dose cohorts suggested that the 2.4 mg/kg exhibited the highest objective response rate (56%) compared to 1.8 mg/kg dose (50%); moreover, complete response (CR) was only achieved at the 2.4 mg/kg dose (**Figure 2**).

Figure 2: Polatuzumab vedotin efficacy in the dose escalation cohorts.



In the expansion phase, 2.4 mg/kg was investigated in combination with rituximab. Additionally, the 2.4 mg/kg dose was selected for Phase the Phase II study GO27834. Safety data collected from 144 patients across the development program suggested that there was a substantial increase in deaths when polatuzumab was administered at the 2.4 mg/kg dose in combination with rituximab (40%) compared to single agent polatuzumab vedotin (22%).

The frequency of adverse events was substantially lower at the 1.8 mg/kg dose compared to 2.4 mg/kg in patients with indolent non-Hodgkin's lymphoma (**Table 2**). Based on this safety information, the Agency recommended that clinical studies with polatuzumab vedotin should be conducted at doses lower than or equal to 1.8 mg/kg, and 1.8 mg/kg was chosen for further investigation.

Table 2: Overview of polatuzumab vedotin safety (1.8 mg/kg vs 2.4 mg/kg)

	All Follow-UP		Onset through Cycle 8	
	1.8 mg/kg (n=31)	2.4 mg/kg (n=113)	1.8 mg/kg (n=31)	2.4 mg/kg (n=113)
Death	2 (6.5%)	24 (21.2%)	2 (6.5%)	21 (18.5%)
Gr 5 AE	1 (3.2%)	8 (7.1%)	1 (3.2%)	7 (6.2%)
SAE	12 (39%)	43 (38%)	12 (39%)	40 (35%)
Gr 3+ AE	18 (58%)	80 (71%)	18 (58%)	78 (69%)
AE leading to study continuation	10 (32%)	52 (46%)	9 (29%)	32 (28%)
AEs of Special Interest				
Grade 2+ Peripheral Neuropathy	12 (39%)	54 (48%)	8 (26%)	34 (30%)
Grade 3+ Cytopenia	12 (39%)	44 (39%)	12 (39%)	43 (38%)
Grade 3+ infection Infestation	3 (10%)	12 (11%)	3 (10%)	11 (10%)

As detailed above, the 1.8 mg/kg dose was selected based on an improved safety profile compared to the 2.4 mg/kg and an improved CR and ORR compared to lower doses. To minimize the incidence of

peripheral neuropathy, polatuzumab vedotin treatment was limited to 6 cycles, as the risk of peripheral neuropathy was associated with prolonged exposure to polatuzumab vedotin.

In the pivotal study GO29365, the polatuzumab vedotin treatment arm in combination rituximab and bendamustine demonstrated a significant improvement in CR (45%, 95% CI: 29% - 62) compared to the rituximab and bendamustine (control) arm, where the CR rate was 17.5% (95%CI: 7.3% - 33%). In the polatuzumab arm 70% of the patients who responded had a DoR of at least 6 months and 52% had a DoR of at least 12 months. In the control arm, 30% who responded had a DoR of at least 6 months and 20% had a DoR of at least 12 months.

Exposure-Response for Efficacy and Safety

To further support the proposed dosing regimen and dose adjustment for specific population, the applicant conducted exposure-response analyses on efficacy and safety endpoints based on data from the supportive studies (DCS4968g and GO27834) and pivotal study GO29365, respectively. The E-R relationships for efficacy and safety in the supportive studies (dose ranges from 0.1 to 2.4 mg/kg) are generally consistent with the dose-response findings, suggesting that higher exposures are associated with higher CR and greater toxicity. In the pivotal study, which primarily evaluated the 1.8 mg/kg dose, no apparent E-R relationships were identified except for an association between unconjugated MMAE and anemia.

The applicant conducted multivariate logistic regression analyses to explore the relationship between polatuzumab vedotin, MMAE and multiple safety endpoints. Two E-R relationships were evident. **Figure 3** shows the relationship between polatuzumab vedotin AUC at cycle 6 and peripheral neuropathy, and **Figure 4** shows the relationship between MMAC AUC at cycle 6 and anemia. No baseline factors were identified as significant covariates in addition to PK.

Although the occurrence of Grade 3 or higher neutropenia, thrombocytopenia and infections/infestations were among the highest incidence observed for any AE, no E-R relationships with polatuzumab or MMAE were identified. See Appendix 4.3 for further details.

Figure 3: Exposure-safety relationships for peripheral neuropathy in the supportive (left panel) and pivotal studies (right panel).

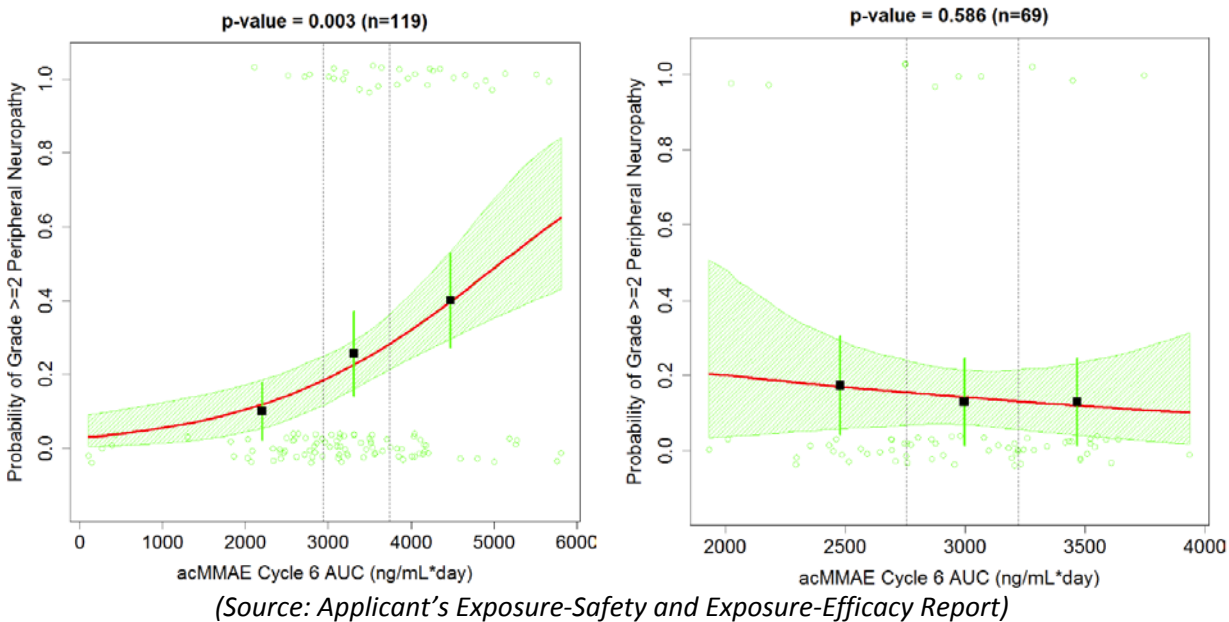
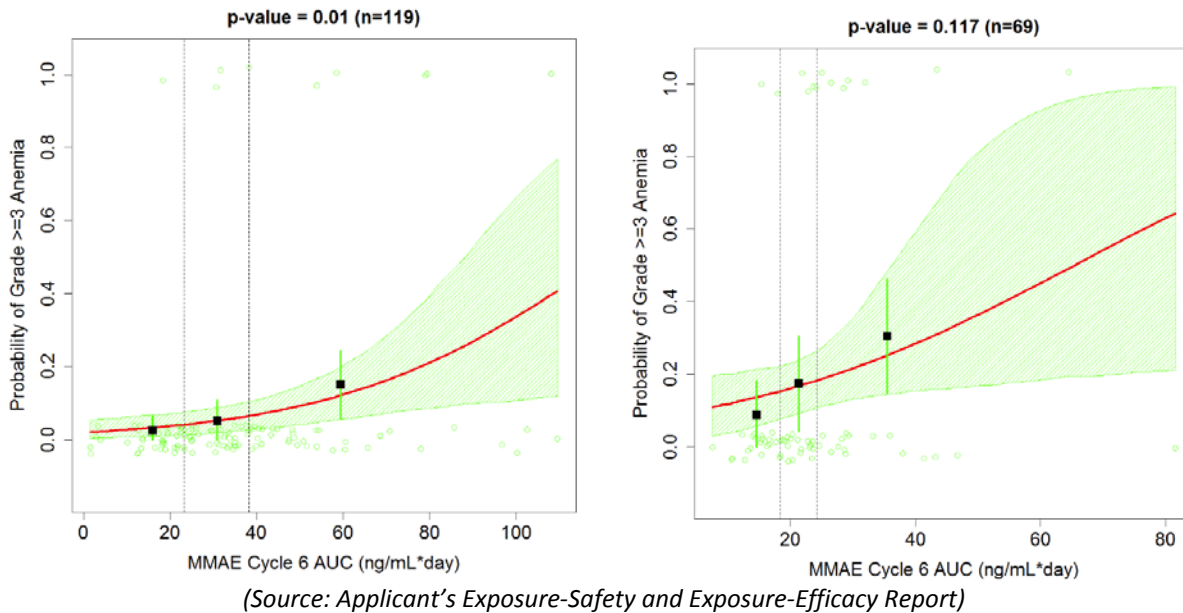


Figure 4: Exposure-safety relationships for anemia in the supportive (left panel) and pivotal studies (right panel).



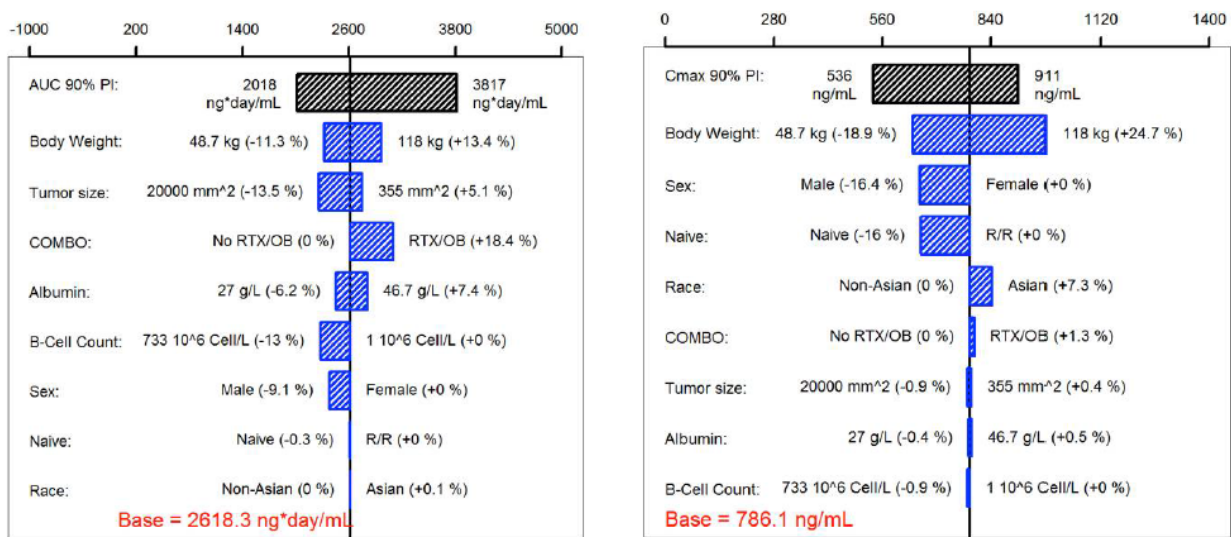
3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No, an alternative dosing regimen or management strategy is required based on age, sex, or race. Refer to Appendix 4.2 Population PK Analysis for a detailed discussion.

Bodyweight

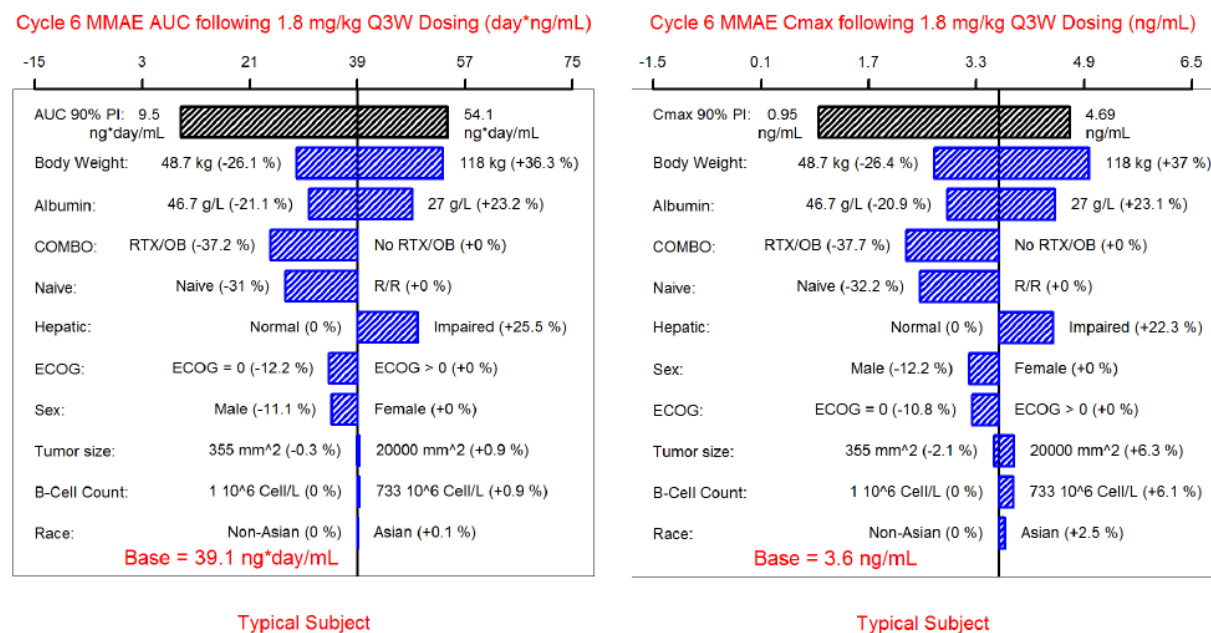
Population PK analysis identified bodyweight to be a statistically significant covariate on clearance and volume of the distribution on polatuzumab vedotin, which supports the bodyweight-based dosing regimen. Based on population PK analysis (Figure 5 and Figure 6), patients with bodyweight greater than 100 kg (n=59) are predicted to have an increase in polatuzumab vedotin exposure (8% for AUC and 17% for Cmax) and MMAE exposure (27% for AUC and Cmax) compared to patients with bodyweight less than 100 kg (n=401).

Figure 5: Final model covariate impact on platuzumab vetodin AUC (left panel) and C_{max} (right panel) following 1.8 mg/kg Q3 dosing



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

Figure 6: Final model covariate impact on MMAE AUC (left panel) and C_{max} (right panel) following 1.8 mg/kg Q3 dosing



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

In study GO29635, the frequency of adverse events was comparable between patients with bodyweight less than or equal 100 kg and those with bodyweight greater than 100 kg (**Table 3**). Based on population PK analysis and analysis of safety data, albeit limited, no dose capping is necessary for patients with high bodyweight.

Table 3: Frequency of adverse events in patients with bodyweight ≤ 100 kg and patients with bodyweight > 100 kg

	≤100 kg (n=128)*	>100 kg (n=13)*
Grade 5	14%	8%
Grade 3 – 4	84%	85%
Serious AE	60%	62%
Study withdrawal due to AE	23%	15%
Polatuzumab discontinuation	20%	23%
Polatuzumab delays/interruptions due to AE	41%	62%
Polatuzumab dose reductions	18%	23%
Any Grade Neutropenia	54%	54%
Any Grade peripheral neuropathy	44%	46%

*This population includes patients with DLBCL or follicular lymphoma who received polatuzumab vedotin in combination with bendamustine and rituximab or bendamustine and obinutuzumab.

Renal Impairment

No dose adjustment is required for patients with renal impairment. Population PK analysis included patients with mild (n=161) and moderate (n=109) renal impairment, in addition to patients with normal (n=185) renal function. Creatinine clearance was not identified as a statistically significant covariate of polatuzumab vedotin or unconjugated MMAE exposure. This is consistent with renal elimination not being a significant clearance pathway of polatuzumab vedotin or unconjugated MMAE.

Safety information from study GO29365 in patients with DLBCL suggests a slightly higher frequency of adverse of in patients with renal impairment; however, this effect is not consistent and does not seem to correlate with the degree of renal impairment (**Table 4**).

Table 4: Frequency of adverse events in patients with DLBCL in Study GO29365 who received polatuzumab vedotin

	Normal (n=19)	Mild (n=16)	Moderate (n=10)
Grade 5	11%	31%	20%
Grade 3 – 4	79%	88%	90%
Serious AE	68%	69%	50%
Study withdrawal due to AE	37%	31%	30%
Polatuzumab discontinuation	32%	25%	20%
Polatuzumab delays/interruptions due to AE	37%	63%	60%
Polatuzumab dose reductions	0	13%	0
Any Grade Neutropenia	42%	69%	80%
Any Grade peripheral neuropathy	32%	44%	50%

Hepatic Impairment

Polatuzumab vedotin clinical trials included patients with normal or mild hepatic function, according the NCI ODWG classification (i.e., ALT and AST less than 2.5 ULN and total bilirubin less than 1.5 ULN). The majority of patients included in the population of PK analysis had normal hepatic function (n =399) or mild hepatic impairment (n=54); only 2 patients had moderate hepatic impairment. Population PK analysis predicts that patients with mild hepatic impairment have similar polatuzumab vedotin exposure compared to patients with normal hepatic function; however, the exposure of unconjugated MMAE is predicted to be higher in patients with mild hepatic impairment (40% for AUC and 34% for C_{max}).

Analysis of safety information across polatuzumab vedotin studies suggested that the frequency of adverse is slightly higher in patients with mild hepatic impairment; however, there was no substantial difference in the tolerability of polatuzumab vedotin in patients with mild impairment (**Table 5**). Of note, the duration of treatment and the number of cycles of treatment was similar in patients with normal hepatic function and those with mild hepatic impairment.

Table 5: Adverse events in patients with normal hepatic function or mild hepatic impairment in polatuzumab vedotin trials

	GO29635		GO27834		GO29044	
	POLIVY + BR		POLIVY + G/R		POLIVY + R/G CHP	
	Normal (n=77)	Mild (n=8)	Normal (n=90)	Mild (n=10)	Normal (n=62)	Mild (n=6)
Median duration of treatment (months)	3.6	3.9	4.83	3.55	3.4	4.2
Median number of cycles	5	6	8	5.5	6	7
Median time to first dose reduction (months)	1.84	NE	2.86	1.38	3.6	NE
Grade 5	14.3%	0	2.2%	0	3.2%	0
Grade 3 – 4	80.5%	100%	53%	57%	63%	83%
Serious AE	61%	50%	31%	29%	37%	67%
Study withdrawal due to AE	23.4%	37.5%	11%	14%	5%	0
Pola discontinuation	18.2%	25%	20%	14%	11%	17%
Delays/interruptions due to AE	41.6%	50%	29%	36%	15%	17%
Dose reductions	3.9%	0	14%	21%	8%	0%
Any Grade peripheral neuropathy	40.3%	37.5%	49%	57%	42%	50%
Any Grade Hepatotoxicity	18.2%	25%	8%	14%	10%	0%

B = Bendamustine, R=rituximab, G= obinutuzumab, CHP= cyclophosphamide, doxorubicin, and prednisone.

Given that there is no substantial decrease in the tolerability of polatuzumab vedotin in patients with mild hepatic impairment, no dose adjustment is recommended for this population. Conceptually, lowering the dose of polatuzumab vedotin to match the exposure of MMAE may lead to lower ADC level, which is main driver of efficacy.

There is no experience in patients with moderate or severe hepatic impairment; only two patients with moderate hepatic impairment were enrolled in study GO29365. One patient received the study drug for 4 cycles and the other for 3 cycles; one patient died due to progressing disease and one patient discontinued treatment due to adverse events (peripheral neuropathy). Due to the limited number of patients, no associations between polatuzumab vedotin exposure and safety can be made. Based on

clinical experience with a similar class drug, there was a trend of increasing frequency of adverse events in patients with increasing level of hepatic impairment. As such, the recommendation to avoid polatuzumab vedotin administration in patients with moderate or severe hepatic impairment is reasonable.

3.3.4 Are there clinically relevant drug-drug interactions and what is the appropriate management strategy?

No, there are no clinically relevant drug-drug interactions anticipated. In vitro studies indicated that MMAE is a substrate of CYP3A. The applicant developed a physiologically-based PK (PBPK) model to investigate the effect of strong CYP3A inhibitor (ketoconazole) and strong CYP3A inducer (rifampin) on MMAE exposure. Refer to Appendix 4.4 for a detailed discussion.

The PBPK model predicted an increase in MMAE AUC (45%) and C_{max} (18%) with concomitant administration of ketoconazole, a magnitude similar to the increase due to mild hepatic impairment. Accordingly, a dose adjustment is not recommended for polatuzumab vedotin when co-administered with CYP3A inhibitors based on the expected minimal impact on safety.

Concomitant administration of rifampin, on the other hand, is predicted to result in 63% decrease in MMAE AUC and 41% decrease in MMAE C_{max} . This exposure is not likely to be clinically relevant as unconjugated MMAE is not a major driver of efficacy, based on the E-R relationships.

In vitro studies indicated that MMAE is a time-dependent inhibitor of CYP3A enzymes. The potential for MMAE to be a perpetrator was investigated using the PBPK model. Model predictions indicated that there is no change in midazolam exposure (a sensitive CYP3A substrate) with concomitant use of MMAE.

3.3.5 Are there clinically relevant differences in PK due to formulation change?

No, there are no clinically relevant differences in PK between the solution formulation and the lyophilized (to-be-marketed) powder formulation.

Except for Arm G in the registration trial GO29365, all clinical studies conducted during the polatuzumab vedotin program (**Table 1**) used a solution formulation (100 mg/10 mL). Patients enrolled in Arm G received the lyophilized drug product (140 mg/vial) that is intended for marketing.

Population PK analysis was used to assess the effect of formulation on the PK of polatuzumab vedotin and unconjugated MMAE. Observed concentrations obtained with the lyophilized product were compared to the model-predicted concentrations with the liquid product. Subsequently, individual exposure (based on Empirical Bayes Estimates) in Cycle 6 were compared for the lyophilized formulation and the solution formulation.

Polatuzumab vedotin exposure was slightly lower (5% for AUC and 6% for C_{max}) for the lyophilized drug product compared to the solution formulation. Similarly, MMAE exposure was lower for the lyophilized drug product (15% for AUC and 17% for C_{max}) compared to the solution formulation (**Table 6**). See appendix 4.2 for further details. Based on E-R relationships for safety and efficacy, these minor changes in polatuzumab vedotin and MMAE exposure are not predicted to have any clinical impact.

Table 6: Geometric Mean Ratio (90% CI) of PK Parameters of Lyophilized Formulation and Solution Formulation

	AUC	C_{max}	C_{trough}
ADC	0.95 (0.895 – 1.02)	0.94 (0.91 – 0.98)	0.99 (0.86 – 1.14)
Payload	0.854 (0.73 – 1.00)	0.89 (0.77 – 1.02)	0.82 (0.67 – 1.03)

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Polatuzumab Vedotin

Polatuzumab vedotin and ADC Internal Standard (b) (4) (b) (4) were both enriched from human plasma via IA capture using MabSelect beads (b) (6) (b) (6) in a 96-well filter plate. The immobilized ADCs were then digested with papain, releasing the free MMAE and MMAF IS analytes, which were subsequently eluted with 500 µL of 70:30 ethanol/water (v/v). The eluate was evaporated under a nitrogen stream at approximately 50 °C, and the remaining residue was reconstituted with 50µL of water. The sample then underwent a protein precipitation using 500 µL of 70:30 acetonitrile/methanol (v/v). The supernatant was evaporated under a nitrogen stream at approximately 50 °C, and the remaining residue was reconstituted with 250 µL of 50:50:0.1 methanol/water/formic acid (v/v/v). The final extract was analyzed via LC-MS/MS using positive ion electrospray. Transition 718.7/152.2 was monitored for MMAE and transition 732.7/170.2 was monitored for MMAF IS.

Table 7: Immunoaffinity LC/MS-MS Method Validation Summary for Polatuzumab Vedotin

Parameter	Details
Method	HPLC/MS-MS
Analyte	Polatuzumab vedotin (Anti-CD79b-vc-MMAE)
Internal Standard	(b) (6)
Calibration Range	0.5 to 50.0 nM
VQC Concentrations	0.5, 1.00, 5.00, 12.0, and 39.0 nM
Intra-Batch Precision (%CV)	LLOQ QC: <10.4%; remaining QC samples: < 5.66%
Intra-Batch Accuracy (%RE)	LLOQ QC: -6.23% to 6.19%; remaining QC samples: -2.3% to 5.04%
Inter-Batch Precision (%CV)	LLOQ QC: 15.6%; remaining QC samples: 3.4% to 8.82%
Inter-Batch Accuracy (%RE)	LLOQ QC: -2.24%; remaining QC samples: -2.1% to 0.1%
Parallelism	QCs (n=6) containing 5.00 nM ADC with two-fold dilution and 8000 nM with 1000-fold dilution. Precision: 5.77% and 8.13% Accuracy: 1.96 and -2.61
Analyte Recovery	104%-116% across low, mid, high VQC
IS Recovery	45%-49% across low, mid, high IS
Selectivity	No significant peaks noted in blank samples
Stability	
IS Stock Solution	Demonstrated for 368 days at -20 °C for 100.00 mg/mL
Frozen Storage Matrix Stability	40 days at -20 °C and at -70 °C
Extract Stability	263 hours at 2 to 8 °C
Freeze/Thaw Matrix Stability	Demonstrated for 5 cycles at -20 °C and at -70 °C
Re-injection Reproducibility	Demonstrated for 48 hours at 2 to 8 °C in reconstitution solution. precision was less than 5% and accuracy ranged from -0.84% to -4.95%

Unconjugated MMAE

The unconjugated MMAE concentrations in human plasma samples containing lithium heparin were quantified using a validated LC-MS/MS method. Samples were fortified with IS (b) (6) and analytes were isolated through protein precipitation. A portion of the supernatant was evaporated under a nitrogen stream at approximately 40°C, and the remaining residue was reconstituted with 100:0.1 water/formic acid (v/v). The final extract was analyzed via LC-MS/MS using positive ion electrospray. Transition 718.6/152.2 was monitored for MMAE and transition 726.6/152.2 was monitored for MMAE-d8.

Table 8: LC/MS-MS Method Parameters and Validation Summary for MMAE

Parameter	Details
Method	HPLC/MS-MS
Analyte	Monomethyl Auristatin E (MMAE)
Internal Standard	(b) (6)
Calibration Range	0.0359, 0.0718, 0.359, 1.79, 3.59, 8.97, 16.2, and 17.9 ng/mL
VQC Concentrations	0.0359, 0.108, 7.18, and 14.4 ng/mL
Intra-Batch Precision (%CV)	8 to 8.3% for LLOQ and narrower ranges for low, median and high QCs.
Intra-Batch Accuracy (%RE)	-0.8 to 10.9%
Inter-Batch Precision (%CV)	5.4% for LLOQ and narrower ranges for low, median and high QCs.
Inter-Batch Accuracy (%RE)	3.3% for LLOQ and narrower ranges for low, median and high QCs.
Dilution Factor	Demonstrated for 10-fold
Analyte Recovery	84.1% to 87.8% average across low, mid, high VQC
IS Recovery	67.7%
Selectivity	No significant interference at the retention times of analyte and IS.
Stability	
Primary Stock Solution	17 hours at room temperature in DMF.
Ambient Temperature Matrix Stability	6 hours at room temperature
Frozen Storage Matrix Stability	117 days at -20 °C and 36 days at -70 °C
Freeze/Thaw Matrix Stability	Demonstrated for 4 cycles at -20 °C
Re-injection Reproducibility	Demonstrated for 93 hours at room temperature

4.2 Population PK Analysis

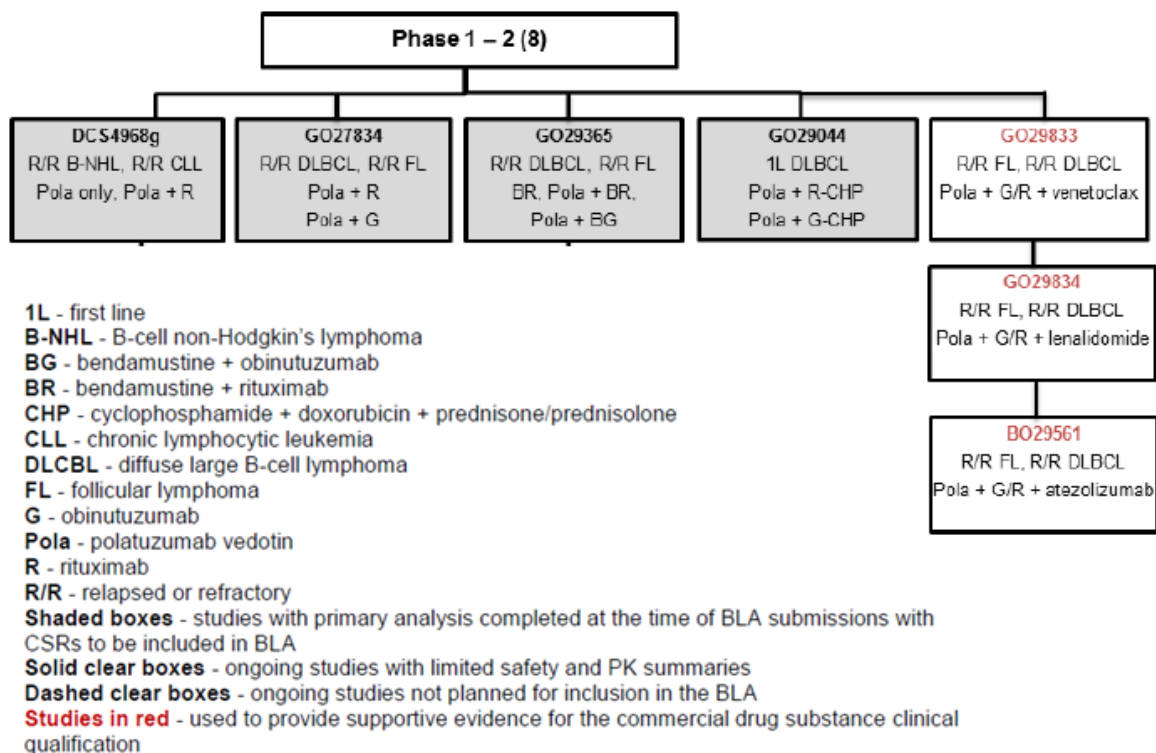
Part 1: Analysis with the Liquid DP Formulation

The applicant developed their primary structural model, performed the covariate evaluation and established the final integrated population PK model for both acMMAE and unconjugated MMAE first with the data from administration of the liquid DP formulation, known as Part 1 data.

A brief overview of the studies included in the analysis and treatment per studies are shown in Figure 7.

A total of 4194 observations from 460 patients were included in the analysis from the part 1 database. An overview of the observation records by study is shown in Table 9. Summaries of the covariates evaluated in the population PK analysis are shown in Table 10 and Table 11. A description of the magnitude of renal and hepatic impairment in the part 1 database is shown in **Table 12** and **Table 13**.

Figure 7: Completed and ongoing clinical studies of polatuzumab vedotin used in the population PK analysis



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

Table 9: Summary of PK data in studies with the liquid DP formulation (Part 1).

Description	Total	DCS4968g	GO27834	GO29044	GO29365
Patients Included in the Analysis	460	77	162	82	139
Summary of acMMAE concentration values					
Excluded pre-dose observations	456	79	164	82	131
Total post-dose observations	4719	1738	1556	812	613
Observations included in the analysis	4215	1585	1332	724	574
Excluded post-dose positive observations	289	56	162	43	28
Excluded post-dose BLQ observations	215	97	62	45	11
Summary of unconjugated MMAE concentration values					
Excluded pre-dose observations	448	76	158	81	133
Total post-dose observations	4707	1725	1566	811	605
Observations included in the analysis	4194	1597	1349	715	533
Excluded post-dose positive observations	79	15	46	9	9
Excluded post-dose BLQ observations	434	113	171	87	63

(Source: Applicant's Population PK Report, Table 18)

Table 10: Summary of continuous covariates (Mean[SD]), Part 1 data.

Covariate	Description	Total	DCS4968g	GO29044	GO27834	GO29365
Number of Patients		460	77	82	162	139
BAGE	Age (years)	65.1 (11.6)	65.8 (10.9)	66.9 (9.92)	64.8 (12.9)	64 (11.4)
BWT	Weight (kg)	80 (18.6)	79.2 (19.1)	79.6 (17.8)	81.9 (19.7)	78.4 (17.4)
BBSA	Body Surface Area (m ²)	1.9 (0.249)	1.91 (0.255)	1.89 (0.244)	1.92 (0.251)	1.88 (0.248)
BBMI	Body Mass Index(kg/m ²)	27.9 (5.42)	27 (5.03)	28.1 (5.42)	28.5 (5.79)	27.5 (5.13)
BLBWT	Lean Body Weight (kg)	55.9 (11.1)	57.4 (11.1)	54.5 (10.5)	56.5 (11.2)	55.3 (11.1)
BHT	Height (cm)	169 (10.9)	171 (9.98)	168 (10.3)	169 (10.7)	169 (11.8)
BALBUM	Albumin (g/L)	38.4 (5.02)	37.5 (5.27)	37.1 (5.58)	38.8 (4.5)	39.1 (4.95)
BTPROT	Total Protein (g/L)	64.9 (6.47)	63.8 (6.2)	67.4 (7.57)	64.9 (5.29)	64.1 (6.83)
BALP	Alkaline Phosphatase (u/L)	89.5 (46.8)	94.4 (46.5)	78.1 (23.3)	83.4 (27.7)	101 (67.9)
BALT	Alanine Aminotransferase (u/L)	25.4 (18.3)	25.4 (19.2)	25.3 (17)	26.5 (15.5)	24.2 (21.5)
BAST	Aspartate Aminotransferase (u/L)	27.1 (17.7)	32.6 (25.4)	23.9 (9.34)	26.7 (15.8)	26.4 (17.8)
BBILI	Bilirubin (umol/L)	11 (10.5)	15.4 (18.6)	8.12 (4.02)	10.8 (9.93)	10.6 (6.43)
HGB	Hemoglobin (g/L)	121 (18.8)	117 (19.3)	126 (19.1)	121 (17.8)	122 (19)
BLDH	Lactate Dehydrogenase (u/L)	428 (718)	-	407 (442)	479 (974)	381 (450)
BSCR	Serum Creatinine (umol/L)	82.4 (25)	84.4 (27.1)	77.4 (24.2)	83.7 (25.4)	82.8 (23.8)
BCRCL	Creatinine Clearance (ml/min)	90.9 (36.8)	90.7 (40.1)	92 (32.7)	92.1 (38.4)	89.1 (35.7)
BBCC	Absolute B Cell Count (10 ⁶ /L)	915 (10700)	4430 (25300)	416 (2210)	125 (711)	67.6 (114)
LogBBCC	Log of BBCC (10 ⁶ /L)	2.66 (2.44)	2.79 (3.02)	4.41 (1.46)	2.04 (2.3)	2.43 (2.2)
BTMBD	Tumor SPD (mm ²)	4730 (5320)	5260 (5430)	5850 (6090)	4380 (4920)	4170 (5150)

(Source: Applicant's Population PK Report, Table 19)

Table 11: Summary of categorical covariates (Part 1)

Covariate	Level	Total	DCS4968g	GO29044	GO27834	GO29365
N (%)		460 (100%)	77 (16.7%)	82 (17.8%)	162 (35.2%)	139 (30.2%)
Race (RACE)	White	385 (83.7%)	63 (81.8%)	72 (87.8%)	140 (86.4%)	110 (79.1%)
	Asian	18 (3.9%)	1 (1.3%)	-	2 (1.2%)	15 (10.8%)
	Other	57 (12.4%)	13 (16.9%)	10 (12.2%)	20 (12.3%)	14 (10.1%)
Gender (SEX)	Female	188 (40.9%)	23 (29.9%)	39 (47.6%)	67 (41.4%)	59 (42.4%)
	Male	272 (59.1%)	54 (70.1%)	43 (52.4%)	95 (58.6%)	80 (57.6%)
Region	West. Europe	110 (23.9%)	25 (32.5%)	30 (36.6%)	25 (15.4%)	30 (21.6%)
	East. Europe	17 (3.7%)	-	-	-	17 (12.2%)
	North America	317 (68.9%)	52 (67.5%)	52 (63.4%)	134 (82.7%)	79 (56.8%)
	Asia/Pacific	13 (2.8%)	-	-	-	13 (9.4%)
	Other	3 (0.7%)	-	-	3 (1.9%)	-
Histology (TUMOR)	DLBCL	266 (57.8%)	40 (51.9%)	75 (91.5%)	82 (50.6%)	69 (49.6%)
	FL	176 (38.3%)	22 (28.6%)	4 (4.9%)	80 (49.4%)	70 (50.4%)
	MCL	9 (2%)	7 (9.1%)	2 (2.4%)	-	-
	Other NHL	9 (2%)	8 (10.4%)	1 (1.2%)	-	-
Prior Exposure (RRFN)	Naive	80 (17.4%)	-	80 (97.6%)	-	-
	R/R	380 (82.6%)	77 (100%)	2 (2.4%)	162 (100%)	139 (100%)
ECOG Status (BECOG)	0	179 (38.9%)	26 (33.8%)	31 (37.8%)	64 (39.5%)	58 (41.7%)
	1	228 (49.6%)	38 (49.4%)	31 (37.8%)	91 (56.2%)	68 (48.9%)
	2	53 (11.5%)	13 (16.9%)	20 (24.4%)	7 (4.3%)	13 (9.4%)
Bulky Disease (BBULKY)	Missing	167 (36.3%)	-	56 (68.3%)	-	111 (79.9%)
	Absent	187 (40.7%)	57 (74%)	-	130 (80.2%)	-
	Present	106 (23%)	20 (26%)	26 (31.7%)	32 (19.8%)	28 (20.1%)
Combination Therapy (COMBO)	Monotherapy	68 (14.8%)	68 (88.3%)	-	-	-
	Rituximab	229 (49.8%)	9 (11.7%)	53 (64.6%)	79 (48.8%)	88 (63.3%)
	Obinutuzumab	163 (35.4%)	-	29 (35.4%)	83 (51.2%)	51 (36.7%)
Bendamustine (BENDA)	Not used	321 (69.8%)	77 (100%)	82 (100%)	162 (100%)	-
	Used	139 (30.2%)	-	-	-	139 (100%)

Covariate	Level	Total	DCS4968g	GO29044	GO27834	GO29365
CHOP Chemo (CHOP)	Not Used	378 (82.2%)	77 (100%)	-	162 (100%)	139 (100%)
	Used	82 (17.8%)	-	82 (100%)	-	-
Computed Hepatic Impairment (HEPA)	Missing	7 (1.5%)	-	1 (1.2%)	-	6 (4.3%)
	Normal	399 (86.7%)	60 (77.9%)	75 (91.5%)	141 (87%)	123 (88.5%)
	Mild	54 (11.7%)	17 (22.1%)	6 (7.3%)	21 (13%)	10 (7.2%)
	Moderate	5 (1.1%)	-	-	-	5 (3.6%)
Renal Impairment (RENAL)	Missing	2 (0.4%)	1 (1.3%)	1 (1.2%)	-	-
	Normal	185 (40.2%)	29 (37.7%)	35 (42.7%)	61 (37.7%)	60 (43.2%)
	Mild	161 (35%)	26 (33.8%)	34 (41.5%)	51 (31.5%)	50 (36%)
	Moderate	109 (23.7%)	20 (26%)	12 (14.6%)	48 (29.6%)	29 (20.9%)
	Severe	3 (0.7%)	1 (1.3%)	-	2 (1.2%)	-
ADA Status (ATAP)	Missing	38 (8.3%)	2 (2.6%)	19 (23.2%)	11 (6.8%)	6 (4.3%)
	Present	12 (2.6%)	4 (5.2%)	-	-	8 (5.8%)
	Absent	410 (89.1%)	71 (92.2%)	63 (76.8%)	151 (93.2%)	125 (89.9%)
Nominal Dose Cohort (DOSET)	0.1 mg/kg	4 (0.9%)	4 (5.2%)	-	-	-
	0.25 mg/kg	3 (0.7%)	3 (3.9%)	-	-	-
	0.5 mg/kg	6 (1.3%)	6 (7.8%)	-	-	-
	1 mg/kg	7 (1.5%)	4 (5.2%)	3 (3.7%)	-	-
	1.4 mg/kg	9 (2%)	-	9 (11%)	-	-
	1.8 mg/kg	318 (69.1%)	6 (7.8%)	70 (85.4%)	103 (63.6%)	139 (100%)
	2.4 mg/kg	113 (24.6%)	54 (70.1%)	-	59 (36.4%)	-

(Source: Applicant's Population PK Report, Table 21)

Table 12: Summary of creatinine clearance by renal impairment category in studies with liquid DP formulation, part 1 data.

Renal Function	Number of patients	Creatinine Clearance (mL/min)	
		Mean (SD)	Median (range)
Normal	N=185	114 (24.3)	107 (90.3-270)
Mild Impairment	N=161	75.1 (8.5)	75.7 (60.4-90)
Moderate Impairment	N=109	49.9 (8.19)	52.3 (30.1-60)
Severe Impairment	N=3	28.9 (0.591)	28.7 (28.4-29.5)

(Source: Applicant's Table 23)

Table 13: Summary of hepatic markers by hepatic impairment category in studies with the liquid DP formulation, Part 1 data.

Hepatic Function	Number of patients	Mean (SD)	Median (range)
Bilirubin (umol/L)			
Normal	N=396	10.4(10.4)	8.55 [2.91-87.7]
Mild Impairment 1	N=44	11(7.4)	8.78 [3.42-51.3]
Mild Impairment 2	N=9	22(4.97)	22 [16.1-32.5]
Moderate Impairment	N=5	36.4(5.98)	37 [27.4-42]
Ratio of Bilirubin to Upper limit of normal			
Normal	N=396	0.441(0.177)	0.4 [0.142-1]
Mild Impairment 1	N=44	0.491(0.192)	0.423 [0.154-1]
Mild Impairment 2	N=9	1.14(0.133)	1.1 [1.04-1.46]
Moderate Impairment	N=5	1.89(0.235)	2.02 [1.6-2.1]
AST (U/L)			
Normal	N=399	22.9(7.4)	22 [10-52]
Mild Impairment 1	N=45	59(32.8)	47 [31-198]
Mild Impairment 2	N=9	42.2(42.9)	22 [17-148]
Moderate Impairment	N=5	41.8(30.4)	21 [19-79]
Ratio of AST to Upper limit of normal			
Normal	N=399	0.567(0.177)	0.543 [0.236-1]
Mild Impairment 1	N=45	1.53(0.896)	1.24 [1-5.82]*
Mild Impairment 2	N=9	0.953(0.746)	0.561 [0.4-2.51]
Moderate Impairment	N=5	1.09(0.838)	0.514 [0.422-2.14]
ALT (U/L)			
Normal	N=399	22.7(13)	20 [5-131]
Mild Impairment 1	N=45	46.7(35.6)	35 [11-209]
Mild Impairment 2	N=9	27.3(18.1)	14 [11-60]
Moderate Impairment	N=5	43(27.4)	29 [20-83]
Ratio of ALT to Upper limit of normal			
Normal	N=399	0.486(0.286)	0.423 [0.104-2.65]
Mild Impairment 1	N=45	1.02(0.919)	0.75 [0.167-5.65]*
Mild Impairment 2	N=9	0.597(0.387)	0.424 [0.204-1.23]
Moderate Impairment	N=5	0.87(0.478)	0.725 [0.444-1.62]

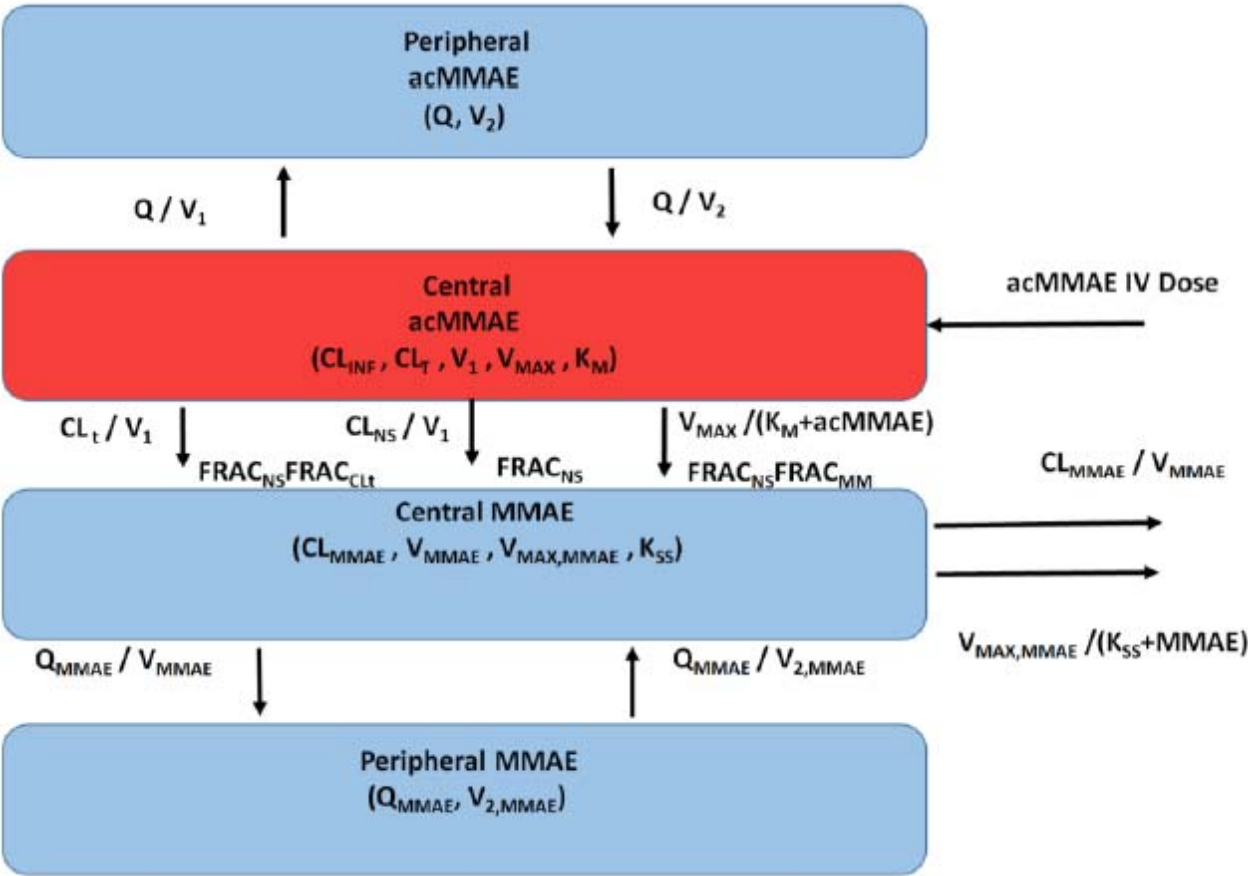
Source file: CovSummaryHepatic.csv (BLA_Report.R)

*Subject (b) (6) from DCS4968g study has ratio of AST to ULN of 5.82; Subject (b) (6) from GO29365 study has ratio of ALT to ULN of 5.65 and AST to ULN of 4.86; when both subjects were removed, the range of AST ratio to ULN is [1-2.22 ULN], the range of ALT ratio to ULN is [0.167-2.46 ULN]

(Source: Applicant's Population PK Report, Table 24)

The applicant's final integrated population model is depicted in **Figure 8**. This model is termed integrated as it includes a simultaneous fitting of both the acMMAE and unconjugated MMAE moieties. The model building sequence started with data from acMMAE only and prior knowledge of MMAE PK from the Brentuximab-MMAE antibody drug conjugate PK properties.

Figure 8: Schematic representation of structural acMMAE-MMAE model



(Source: Applicant's Population PK Report, Figure 3)

The final integrated model parameters and goodness of fit plots are shown in **Table 14**, **Table 15**,

Table 16, **Figure 9**, and **Figure 10**. A visual predictive check for dose-normalized concentrations is shown **Figure 11**. Final model covariate effects are described in **Figure 5**, **Table 16**, and **Table 17**.

Table 14: Estimates of structural fixed-effect parameters for the final integrated model

Parameter		Description	Value	RSE%	95% CI
acMMAE parameters					
k_{des} (1/hr)	θ_1	rate constant of CL_t decrease	0.0046	7.95	0.00389-0.00532
CL_T (L/hr)	θ_2	initial time-dependent CL	0.00623	19.6	0.00383-0.00862
CL_{INF} (L/hr)	θ_3	non-specific linear clearance after repeated dosing	0.0344	3.6	0.032 - 0.0368
V_1 (L)	θ_4	central volume	3.15	1.58	3.05 - 3.25
V_2 (L)	θ_5	peripheral volume	3.98	2.92	3.75 - 4.2
Q (L/hr)	θ_6	inter-compartment rate	0.0145	2.53	0.0138-0.0153
V_{max} (ng/mL/hr)	θ_7	maximum MM elimination	0.0203	14.3	0.0146 - 0.026
K_M (ng/mL)	θ_8	MM constant	0.604	36.2	0.175 - 1.03
$CL_{INF,MAX}$	θ_9	maximum effect of time on CL_{NS}	0.223	8.6	0.185 - 0.261
T_{50} (month)	θ_{10}	time of the half-effect of $CL_{INF,MAX}$	3.53	6.77	3.07 - 4
γ	θ_{11}	Sigmoidicity of $CL_{NS}(t)$ function	2.27	12.5	1.71 - 2.82
Unconjugated MMAE parameters					
V_{MMAE} (L)	θ_{12}	unconjugated MMAE apparent central volume	82.2	8.15	69.1 - 95.4
CL_{MMAE} (L/hr)	θ_{13}	unconjugated MMAE apparent clearance	1.89	8.14	1.59 - 2.2
Q_{MMAE} (L/hr)	θ_{14}	unconjugated MMAE apparent inter-compartment clearance	36.3	12.3	27.5 - 45.1
$V_{2,MMAE}$ (L)	θ_{15}	unconjugated MMAE apparent peripheral volume	200	6.13	176 - 224
$V_{MAX,MMAE}$ (ng/mL/hr)	θ_{16}	maximum MM elimination	0.0307	9.17	0.0252 - 0.0362
K_{SS} (ng/mL)	θ_{17}	MM constant	0.581	10.5	0.461 - 0.701
$FRAC_{CLT}$	θ_{18}	factor for relative conversion fraction of CL_t pathway	3.70	3.11	3.48 - 3.93
$FRAC_{MM}$	θ_{19}	factor for relative conversion fraction of MM pathway	2.72	9.45	2.21 - 3.22
$ALPH$ (1/month)	θ_{20}	rate constant of $FRAC_t$ decrease	0.167	38.5	0.0411 - 0.293
$FRAC_T$	θ_{21}	initial time-dependent part of $FRAC_{NS}$	0.139	21.0	0.0816 - 0.196

SE: Standard Error; PE: Parameter Estimate; **RSE%**: Relative Standard Error = 100·SE/PE; **95% CI**: 95% confidence interval
Source: 201ParEst.csv (BLA_DiagnosticPlots_Integrated.R)

(Source: Applicant's Population PK Report, Table 38)

Table 15: Estimates of covariate fixed-effect parameters in the final integrated model

Parameter		Description	Value	RSE%	95% CI
Effects on acMMAE Model Parameters					
CL _{INF, WT}	θ ₂₂	Weight effect on CL _{INF}	0.73	8.18	0.613 - 0.848
V _{1, WT} ; V _{2, WT} ; Q _{WT}	θ ₂₃	Weight effect on V ₁ , V ₂ and Q	0.50	6.24	0.439 - 0.561
V _{1, males}	θ ₂₄	Male vs. female effect on V ₁	1.20	1.83	1.16 - 1.24
V _{1, ASIAN}	θ ₂₅	Asian race effect on V ₁	0.929	4.18	0.852 - 1
V _{1, NAIVE}	θ ₂₆	Treatment-naive effect on V ₁	1.2	1.96	1.16 - 1.25
CL _{INF, SEX}	θ ₂₇	Gender effect on CL _{INF}	1.1	2.66	1.04 - 1.15
CL _{INF, ALBUM}	θ ₂₈	Albumin effect on CL _{INF}	-0.247	36.3	-0.423 - -0.0712
CL _{INF, RTX, Ob}	θ ₂₉	Combination therapy effect on CL _{INF}	0.844	2.95	0.795 - 0.892
CL _{INF, B-cells}	θ ₃₀	B-cell count effect on CL _{INF}	0.0212	17.9	0.0138 - 0.0286
CL _{INF, TMBD}	θ ₃₁	Tumor SPD effect on CL _{INF}	0.0521	27.4	0.0241 - 0.0801
k _{des, NAIVE}	θ ₃₂	Prior treatment effect on k _{des}	3.38	12.7	2.54 - 4.22
K _{DES, RTX, Ob}	θ ₃₃	Combination therapy effect on k _{des}	0.932	11.2	0.727 - 1.14
CL _{T, NAIVE}	θ ₃₄	Treatment-naive effect on CL _T	3.53	34.7	1.13 - 5.93
CL _{T, TMBD}	θ ₃₅	Tumor SPD of 50% effect on CL _T	1150	46.0	114 - 2190
CL _{T, Threshold}	θ ₃₆	Threshold of B-cells on CL _T	121	46.0	11.9 - 229
CL _{T, B-cells}	θ ₃₇	B-cell count effect on CL _T	0.578	24.6	0.3 - 0.856
Effects on acMMAE-MMAE relative conversion fraction					
FRAC _{WT}	θ ₃₈	Weight effect on FRAC _{NS}	-0.467	23.1	-0.679 - -0.256
FRAC _{SEX}	θ ₃₉	Gender effect on FRAC _{NS}	0.911	4.72	0.827 - 0.995
FRAC _{NAIVE}	θ ₄₀	Treatment-naive status effect on FRAC _{NS}	0.756	5.95	0.668 - 0.844
FRAC _{RTX, Ob}	θ ₄₁	Combination therapy effect on FRAC _{NS}	0.709	5.54	0.632 - 0.786
FRAC _{HEPA}	θ ₄₂	Hepatic Impairment on FRAC _{NS}	1.19	5.58	1.06 - 1.32
FRAC _{ECOG}	θ ₄₃	ECOG (=0) effect on FRAC _{NS}	0.905	4.34	0.828 - 0.982
FRAC _{ALB}	θ ₄₄	Albumin effect on FRAC _{NS}	-0.613	23.2	-0.892 - -0.334

SE: Standard Error; PE: Parameter Estimate; RSE%: Relative Standard Error = 100·SE/PE; 95% CI: 95% confidence interval.
Source: 201ParEst.csv (BLA_DiagnosticPlots_Integrated.R)

(Source: Applicant's Population PK Report, Table 39)

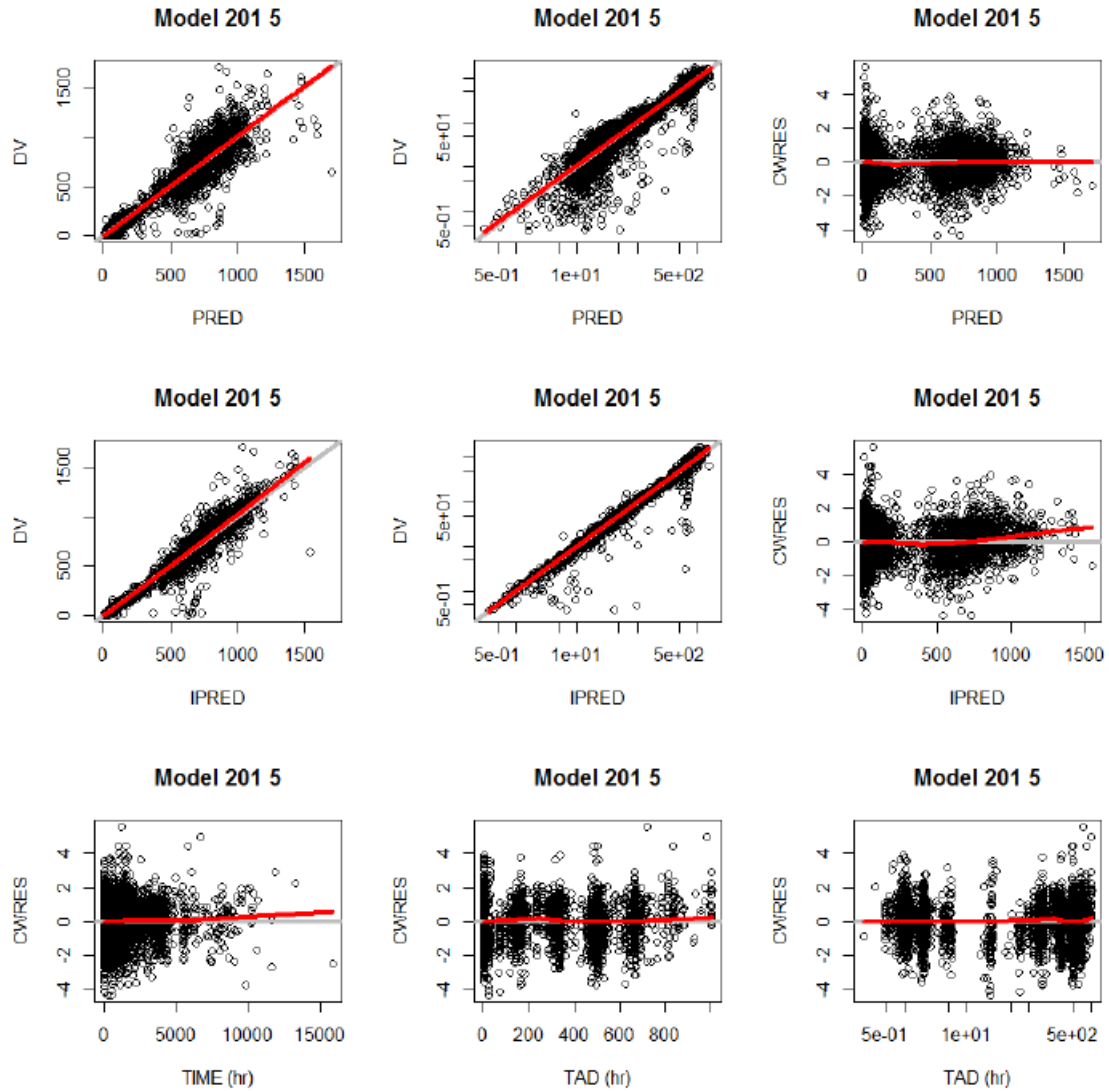
Table 16: Estimates of variance parameters for the final integrated model

Parameter		Description	Value	RSE%	95% CI	CV	Shrinkage
ω^2_{CLT}	Ω_{11}	Random effect on CL_T	1.89	9.96	1.52 - 2.26	1.38	17.4%
ω^2_{CLINF}	Ω_{22}	Random effect on CL_{INF}	0.0376	6.83	0.0325 - 0.0426	0.194	8.1%
ω^2_{V1}	Ω_{33}	Random effect on V_1	0.0151	9.98	0.0122 - 0.0181	0.123	11.8%
ω^2_{V2}	Ω_{44}	Random effect on V_2	0.107	9.94	0.0859 - 0.127	0.327	21.6%
ω^2_Q	Ω_{55}	Random effect on Q	0.0538	13.3	0.0398 - 0.0678	0.232	30.6%
ω^2_{VMAX}	Ω_{66}	Random effect on V_{MAX}	0.462	19.8	0.283 - 0.641	0.679	33.4%
ω^2_{FRACNS}	Ω_{77}	Random effect on conversion fraction	0.0972	9.63	0.0788 - 0.115	0.312	11.1%
ω^2_{CLMMAE}	Ω_{88}	Random effect on CL_{MMAE}	0.115	11.9	0.088 - 0.141	0.339	21.5%
$\omega^2_{V2,MMAE}$	Ω_{99}	Random effect on $V_{2,MMAE}$	0.0422	24.5	0.0219 - 0.0625	0.205	48.5%
$\omega^2_{\sigma_{acMMAE}}$	$\Omega_{10,10}$	Random effect on σ_{acMMAE}	0.0521	9.08	0.0428 - 0.0614	0.228	-2.7%
$R_{\omega_{\sigma_{acMMAE}} \omega_{\sigma_{MMAE}}}$	$\Omega_{11,10}$	σ_{acMMAE} - σ_{MMAE} Correlation	0.038	9.32	0.0311 - 0.045	0.806	-
$\omega^2_{\sigma_{MMAE}}$	$\Omega_{11,11}$	Random effect on σ_{MMAE}	0.0427	12.2	0.0325 - 0.0529	0.207	0.1%
σ^2_{acMMAE}	Σ_{11}	Residual error for acMMAE	0.0254	4.1	0.0233 - 0.0274	0.159	9.2%
σ^2_{MMAE}	Σ_{22}	Residual error for unconjugated MMAE	0.0726	3.86	0.0671 - 0.0781	0.27	6.4%

ω^2 and σ^2 : variances of inter-individual and residual variability, respectively, R: correlation coefficient, SE: standard error; PE: parameter estimate; RSE (%): relative standard error = 100·SE/PE; 95% CI: 95% confidence interval, CV: coefficient of variation

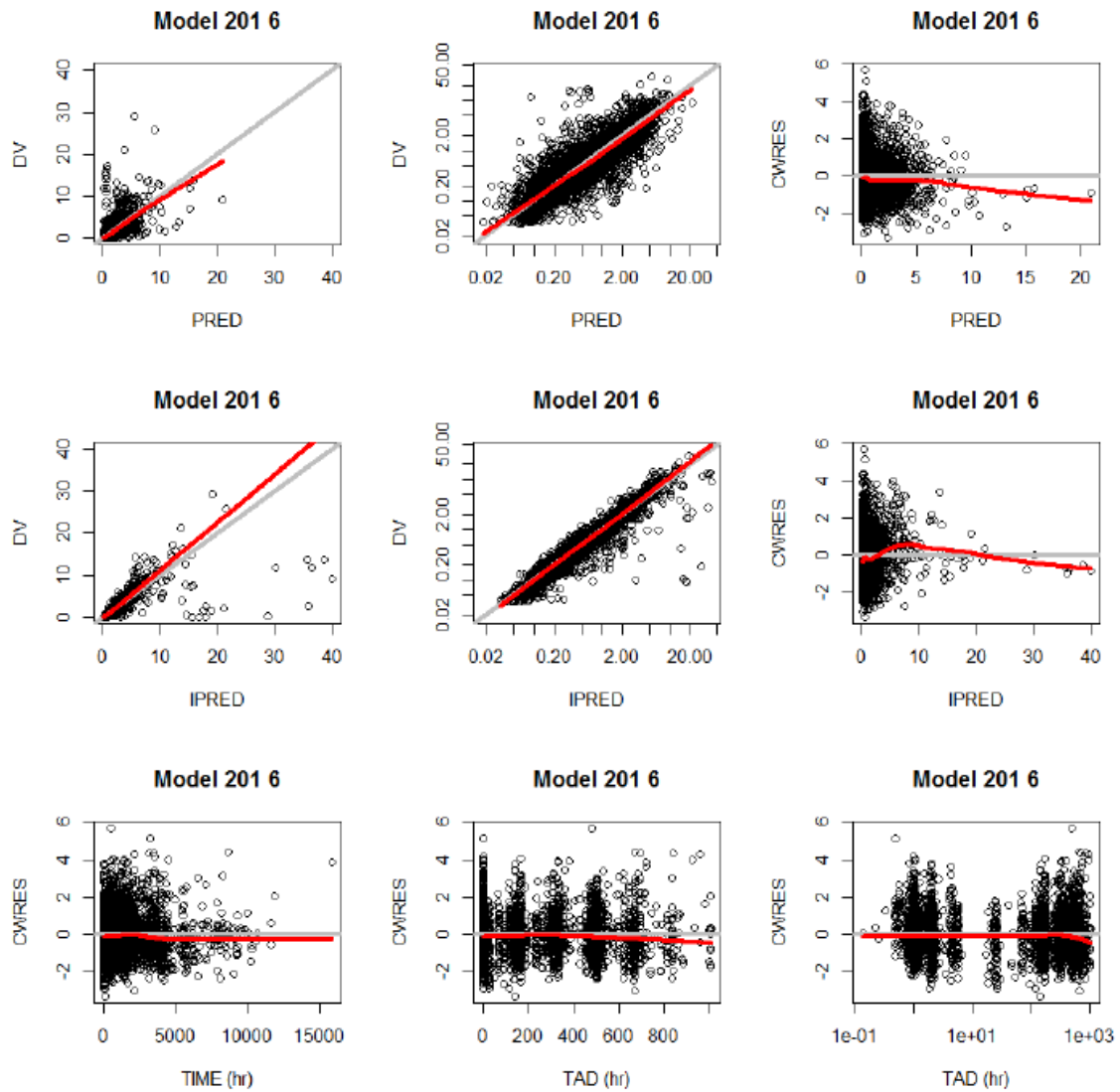
(Source: Applicant's Population PK Report, Table 40)

Figure 9: Goodness-of-fit for the final integrated model for acMMAE



(Source: Applicant's Population PK Report, Figure 97)

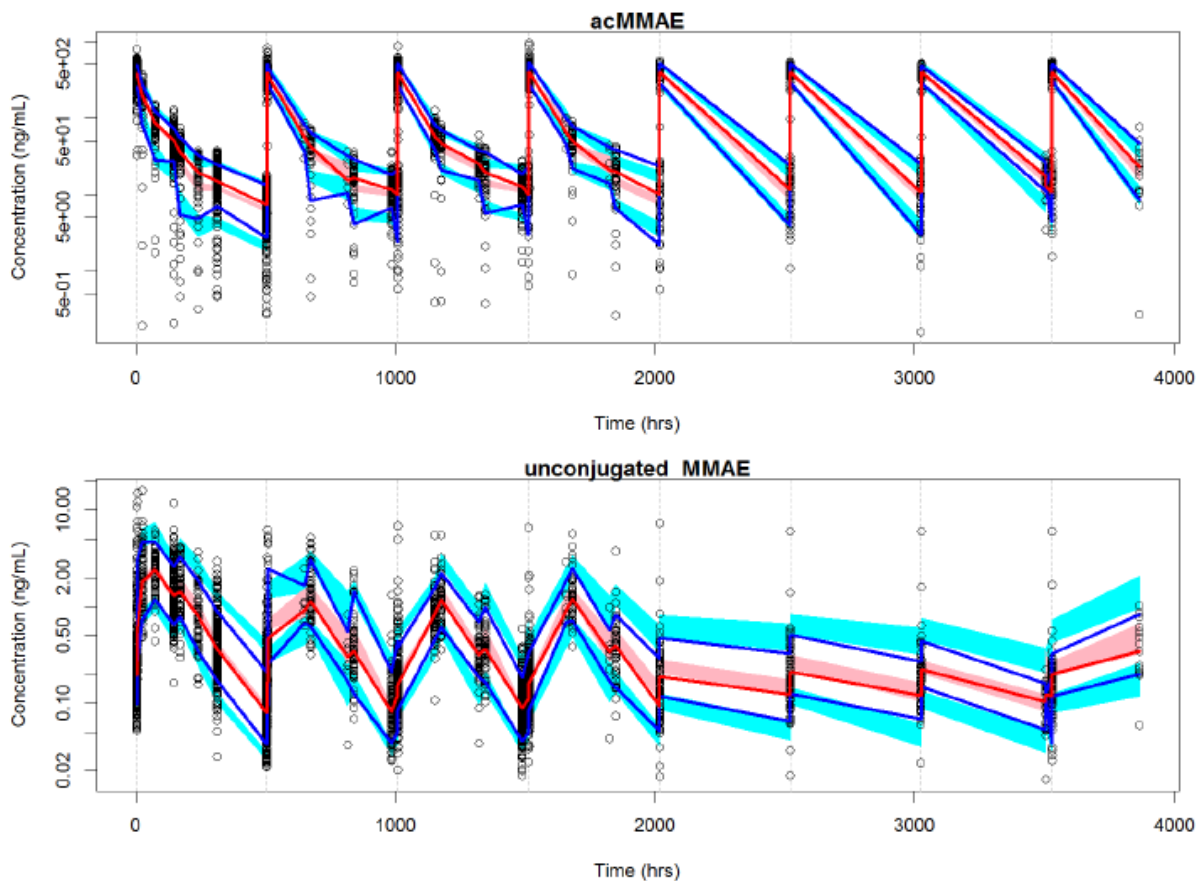
Figure 10: Goodness-of-fit for the final integrated model for MMAE



(Source: Applicant's Population PK Report, Figure 98)

Figure 11: Visual predictive check for dose-normalized concentrations following Q3 dosing for the final integrated model

The lines show median (red), and the 10th and 90th percentiles (blue) of the dose-normalized concentrations plotted versus time. The shaded regions show the 80% confidence intervals 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.



(Source: Applicant's Population PK Report, Figure 139)

Table 17: Covariate effects for the final integrated model

Parameter	Covariate	Reference Value	Covariate Value ^a	Effect Value [95%CI](%)
k_{des}	Prior treatment	Relapsed/refractory	Treatment-naive	238.4 [154.3; 322.4]
	Therapy	Monotherapy	With RTX/Obinutuzumab	-6.8 [-27.3; 13.7]
CL_T	Prior treatment	Relapsed/refractory	Treatment-naive	253.1 [13.2; 492.9]
	Tumor SPD	5000 mm ²	355 mm ²	-71 [-82.9; -6.8]
			20,000 mm ²	16.4 [10.9; 22.4]
	B-cell count	< 121*10 ⁶ cell/L	733*10 ⁶ cell/L	183.9 [71.8; 369.2]
CL_{INF}	Weight	75 kg	48.7 kg	-27.1 [-30.6; -23.3]
			118.0 kg	39.2 [32; 46.8]
	Gender	Female	Male	9.8 [4; 15.5]
	Serum Albumin	35.0 g/L	27.0 g/L	6.6 [1.9; 11.6]
			46.7 g/L	-6.9 [-11.5; -2]
	Therapy	Monotherapy	With RTX/Obinutuzumab	-15.6 [-20.5; -10.8]
	Tumor SPD	5000 mm ²	355 mm ²	-4.8 [-7.4; -2.2]
			20,000 mm ²	15.6 [7.2; 24]
	B-cell count	≤1*10 ⁶ cells/L	733*10 ⁶ cell/L	15.0 [9.5; 20.8]
V_1, V_2, Q	Weight	75 kg	48.7 kg	-19.4 [-21.5; -17.3]
			118.0 kg	25.4 [22; 28.9]
V_1	Gender	Female	Male	20.0 [15.7; 24.3]
	Race	Non- Asian	Asian	-7.1 [-14.8; 0.5]
	Prior treatment	Relapsed/refractory	Treatment-naive	20.3 [15.6; 24.9]
FRAC	Weight	75 kg	48.7 kg	22.4 [11.7; 34.1]
			118.0 kg	-19.1 [-26.5; -10.9]
	Gender	Female	Male	-8.9 [-17.3; -0.5]
	Prior Treatment	Prior Treatment	Naive	-24.4 [-33.2; -15.6]
	Therapy	Monotherapy	With RTX/Obinutuzumab	-29.1 [-36.8; -21.4]
	Hepatic function	Normal	Mild/Moderate Impairment	19.2 [6.2; 32.2]
	ECOG Score	ECOG = 1 or 2	ECOG=0	-9.5 [-17.2; -1.8]
	Serum Albumin	35.0 g/L	27.0 g/L	17.2 [9; 26]
			46.7 g/L	-16.2 [-22.7; -9.2]

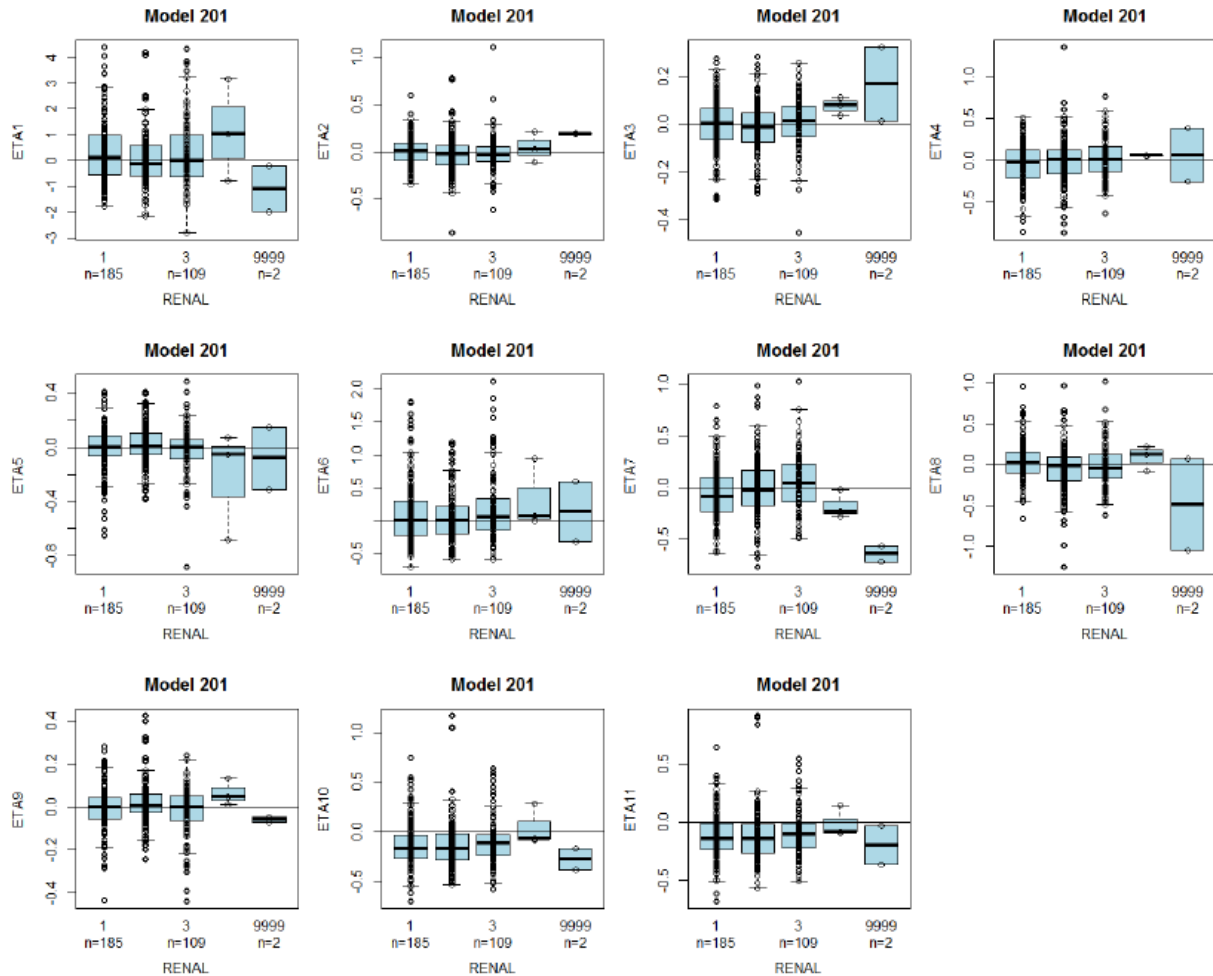
^a The values of the continuous covariates represent 2.5th and 97.5th percentiles of the values in the analysis dataset.
Source: 201covEffects.csv (BLA_201CovEffects_Integrated.R)

(Source: Applicant's Population PK Report, Table 41)

The applicant further evaluated the potential for further unexplained effects for renal and hepatic impairment by plotting ETA distributions against the renal or hepatic impairment category (**Figure 12** and **Figure 13**).

Figure 12: Relationships between the inter-individual random effects and renal impairment for the final integrated model

ETA1: the random effect on CL_T ; **ETA2**: the random effect on CL_{LINF} ; **ETA3**: the random effect on V_1 ; **ETA4**: the random effect on V_2 ; **ETA5**: the random effect on Q ; **ETA6**: the random effect on V_{MAX} ; **ETA7**: the random effect on $FRAC$; **ETA8**: the random effect on CL_{MMAE} ; **ETA9**: the random effect on $V_{2,MMAE}$; **ETA10**: the random effect on the magnitude of the acMMAE residual error; **ETA11**: the random effect on the magnitude of the unconjugated MMAE residual error. **RENAL**: 1 - no impairment; 2 - mild; 3 - moderate; 4 - severe; 9999=missing.

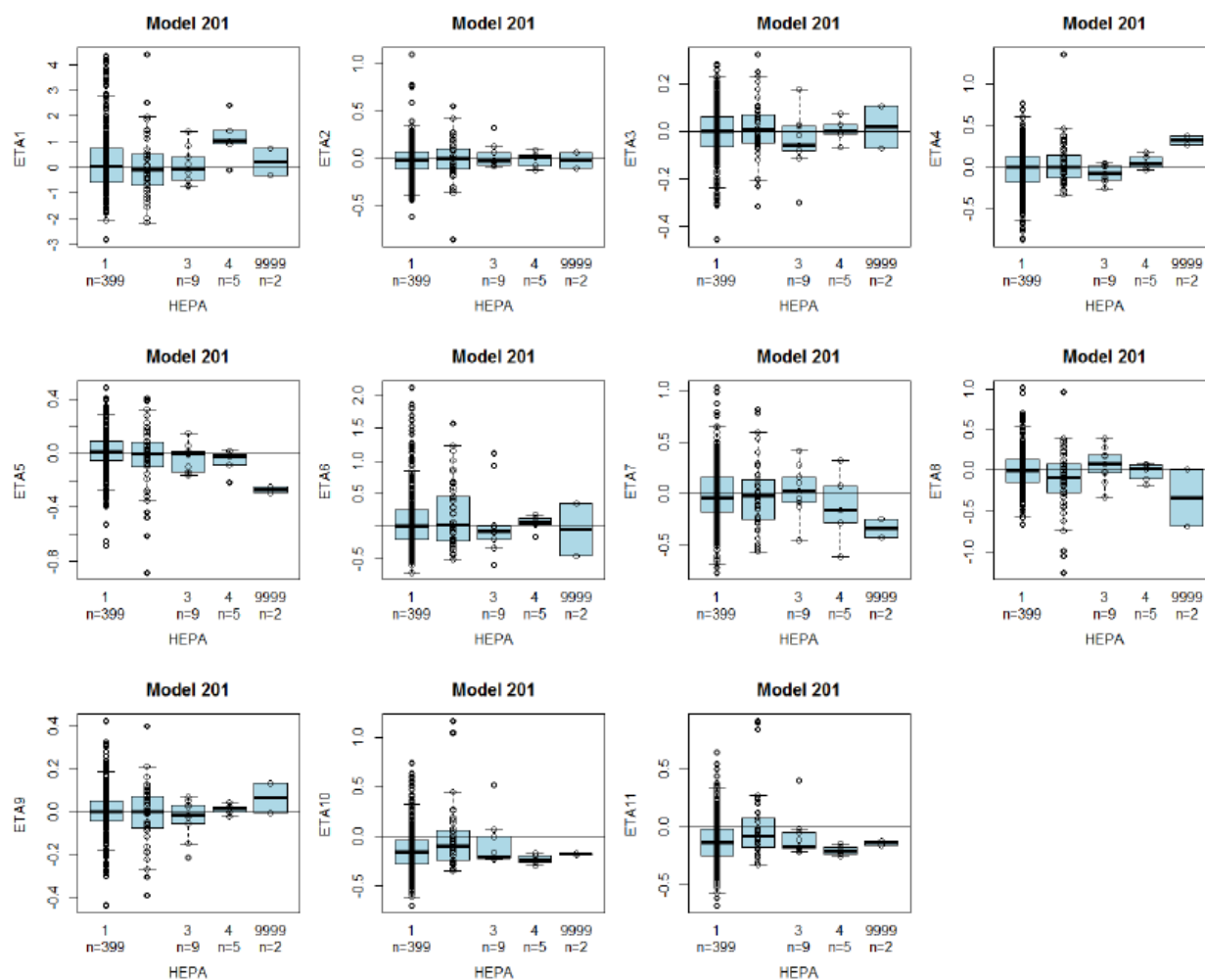


Source: 201ETA11vsCaiRENAL.png

(Source: Applicant's Population PK Report, Figure 134)

Figure 13: Relationship between the inter-individual random effects and hepatic impairment for the final integrated model

ETA1: the random effect on CL_T ; **ETA2:** the random effect on CL_{LINF} ; **ETA3:** the random effect on V_1 ; **ETA4:** the random effect on V_2 ; **ETA5:** the random effect on Q ; **ETA6:** the random effect on V_{MAX} ; **ETA7:** the random effect on $FRAC$; **ETA8:** the random effect on CL_{MMAE} ; **ETA9:** the random effect on $V_{2,MMAE}$; **ETA10:** the random effect on the magnitude of the acMMAE residual error; **ETA11:** the random effect on the magnitude of the unconjugated MMAE residual error. **HEPA:** 1 = no impairment; 2 = mild; 3 = moderate; 4 = severe; 9999=missing.



(Source: Applicant's Population PK Report, Figure 133)

Reviewer's Comments:

The applicant's population PK model is acceptable for describing the PK characteristics for the label and providing individual post hoc estimates of AUC and C_{max} of acMMAE and unconjugated MMAE for the exposure-response analyses. There appear to be sufficient data to make claims regarding mild and moderate renal impairment with numbers of subjects in both these categories greater than 100. While there were only 3 subjects with severe renal impairment from the part 1 dataset, conclusions regarding the PK may be unreliable based on the small number of subjects with PK data in this category. For hepatic

impairment there were 54 subjects with mild impairment while there were 5 with moderate impairment and none with severe impairment. Conclusions regarding mild hepatic impairment are reasonable based on the available data. Estimates of shrinkage were reasonable given the number of clearance parameters in the integrated model (CL_{inf} , CLT , V_{max} , and CL_{MMAE}). CL_{inf} and CLT had estimates of shrinkage below 20% while V_{max} had an eta shrinkage of 33% and CL_{MMAE} had an eta shrinkage of about 22%. Given V_{max} does not change the magnitude of CL at complete saturation the current model appears acceptable. The allometric exponent is 0.73 for clearance and 0.5 for volume of distribution which supports use of bodyweight dosing.

Part 2: Analysis with the Lyophilized Powder Formulation

Characteristics of the part 2 dataset for the lyophilized powder formulation are presented in

Table 18 - Table 20.

Table 18: Summary of data in studies with Lyophilized DP, Part 2 data

Description	Total	BO29561	GO29833	GO29834
Patients Included in the Analysis	106	34	27	45
Summary of acMMAE concentration values				
Excluded pre-dose observations	116	35	36	45
Total post-dose observations	628	185	185	258
Observations included in the analysis	573	174	173	226
Excluded post-dose positive observations	34	7	6	21
Excluded post-dose BLQ observations	21	4	6	11
Summary of unconjugated MMAE concentration values				
Excluded pre-dose observations	116	35	36	45
Total post-dose observations	632	184	185	263
Observations included in the analysis	557	180	179	198
Excluded post-dose positive observations	7	0	0	7
Excluded post-dose BLQ observations	68	4	6	58

(Source: Applicant's Population PK Report, Table 25)

Table 19: Summary of continuous covariates (Mean[SD]), Part 2 data

Covariate	Description	Total	BO29561	GO29833	GO29834
N	Number of Patients	106	34	27	45
BAGE	Age (years)	61.1 (11.4)	62 (14.8)	60.6 (9.2)	60.6 (9.88)
BWT	Weight (kg)	83.4 (21.8)	86.1 (19.6)	83.7 (15.2)	81.2 (26.5)
BBSA	Body Surface Area (m ²)	1.95 (0.255)	1.98 (0.219)	1.94 (0.184)	1.92 (0.312)
BBMI	Body Mass Index(kg/m ²)	28.5 (6.05)	29.1 (6.11)	29.4 (5.38)	27.4 (6.34)
BLBWT	Lean Body Weight (kg)	57.2 (10.2)	58.4 (8.94)	56.7 (9.26)	56.5 (11.6)
BHT	Height (cm)	171 (9.85)	172 (9.29)	169 (9.13)	171 (10.7)
BALBUM	Albumin (g/L)	39.4 (5.56)	40.1 (5.04)	37.7 (5.69)	40 (5.74)
BTPROT	Total Protein (g/L)	63.4 (6.53)	63.8 (4.96)	60.5 (6.68)	64.9 (7.01)
BALP	Alkaline Phosphatase (u/L)	97.9 (57.2)	89.7 (33.2)	92.6 (41)	107 (76.3)
BALT	Alanine Aminotransferase (u/L)	29.8 (31)	20.9 (7.66)	34.8 (35.2)	33.2 (37.4)
BAST	Aspartate Aminotransferase (u/L)	29.9 (25)	22.5 (5.42)	38.9 (37.7)	30 (22.9)
BBILI	Bilirubin (umol/L)	8.66 (5.32)	8.93 (3.82)	8.21 (4.87)	8.71 (6.56)
HGB	Hemoglobin (g/L)	122 (19.2)	120 (19.7)	123 (20.1)	122 (18.7)
BLDH	Lactate Dehydrogenase (u/L)	377 (249)	352 (235)	347 (252)	414 (257)
BSCR	Serum Creatinine (umol/L)	83.3 (20.1)	89.1 (26)	82.5 (14.9)	79.6 (17.4)
BCRCL	Creatinine Clearance (ml/min)	97 (42.3)	95.7 (46)	94.7 (23.3)	99.5 (49.3)
BBCC	B Cell Count (10 ⁹ /L)	865 (5040)	64.6 (104)	1980 (8410)	719 (3770)
LogBBCC	Log of BBCC (10 ⁹ /L)	2.81 (2.49)	2.51 (2.15)	3.62 (2.81)	2.49 (2.45)
BTMBD	Tumor SPD (mm ²)	4860 (5880)	6450 (8050)	3990 (5620)	4190 (3510)

(Source: Applicant's Population PK Report, Table 26)

Table 20: Summary of categorical covariates, Part 2 data

Covariate	Level	Total	BO29561	GO29833	GO29834
N (%)		106 (100%)	34 (32.1%)	27 (25.5%)	45 (42.5%)
Race (RACE)	White	100 (94.3%)	31 (91.2%)	25 (92.6%)	44 (97.8%)
	Asian	1 (0.9%)	-	1 (3.7%)	-
	Other	5 (4.7%)	3 (8.8%)	1 (3.7%)	1 (2.2%)
Gender (SEX)	Female	42 (39.6%)	12 (35.3%)	11 (40.7%)	19 (42.2%)
	Male	64 (60.4%)	22 (64.7%)	16 (59.3%)	26 (57.8%)
Region	West. Europe	42 (39.6%)	9 (26.5%)	4 (14.8%)	29 (64.4%)
	East. Europe	14 (13.2%)	14 (41.2%)	-	-
	North. Amer.	41 (38.7%)	11 (32.4%)	14 (51.9%)	16 (35.6%)
	Asia/Pacific	9 (8.5%)	-	9 (33.3%)	-
Histology (TUMOR)	DLBCL	35 (33%)	21 (61.8%)	5 (18.5%)	9 (20%)
	FL	71 (67%)	13 (38.2%)	22 (81.5%)	36 (80%)
Prior Exposure (PRIOR)	R/R	106 (100%)	34 (100%)	27 (100%)	45 (100%)
ECOG Status (BECOG)	0	51 (48.1%)	15 (44.1%)	15 (55.6%)	21 (46.7%)
	1	51 (48.1%)	16 (47.1%)	12 (44.4%)	23 (51.1%)
	2	4 (3.8%)	3 (8.8%)	-	1 (2.2%)
Bulky Disease (BBULKY)	Missing	72 (67.9%)	-	27 (100%)	45 (100%)
	Absent	21 (19.8%)	21 (61.8%)	-	-
	Present	13 (12.3%)	13 (38.2%)	-	-
Combination Therapy (COMBO)	RTX	35 (33%)	21 (61.8%)	5 (18.5%)	9 (20%)
	GA101	71 (67%)	13 (38.2%)	22 (81.5%)	36 (80%)
Bendamustine (BENDA)	Not used	106 (100%)	34 (100%)	27 (100%)	45 (100%)
CHOP Chemo (CHOP)	Not Used	106 (100%)	34 (100%)	27 (100%)	45 (100%)
Computed Hepatic Impairment (HEPA)	Missing	1 (0.9%)	1 (2.9%)	-	-
	Normal	90 (84.9%)	32 (94.1%)	20 (74.1%)	38 (84.4%)
	Mild	14 (13.2%)	1 (2.9%)	7 (25.9%)	6 (13.3%)
	Moderate	1 (0.9%)	-	-	1 (2.2%)
Renal Impairment (RENAL)	Missing	4 (3.8%)	4 (11.8%)	-	-
	Normal	50 (47.2%)	14 (41.2%)	13 (48.1%)	23 (51.1%)
	Mild	42 (39.6%)	10 (29.4%)	12 (44.4%)	20 (44.4%)
	Moderate	10 (9.4%)	6 (17.6%)	2 (7.4%)	2 (4.4%)
ATA Status (ATAP)	Missing	11 (10.4%)	3 (8.8%)	1 (3.7%)	7 (15.6%)
	Detected	1 (0.9%)	-	1 (3.7%)	-
	Not detected	94 (88.7%)	31 (91.2%)	25 (92.6%)	38 (84.4%)
Nominal Dose Cohort(DOSET)	1.4 mg/kg	48 (45.3%)	3 (8.8%)	13 (48.1%)	32 (71.1%)
	1.8 mg/kg	58 (54.7%)	31 (91.2%)	14 (51.9%)	13 (28.9%)

(Source: Applicant's Population PK Report, Table 28)

The final integrated Model with fixed parameters was applied to Part 2 data (3 studies with lyophilized DP) to obtain individual post-hoc parameters and predictions. The applicant concluded: that the goodness-of-fit plots for three studies together (**Figure 14 - Figure 15**) showed no obvious deficiencies, although trend lines for CWRES versus time after dose (TAD) are lower than zero at lower values of TAD for both acMMAE and unconjugated MMAE indicating possible overestimation of C_{max} values. Distributions of the random effect for CL_T (ETA1) indicated slightly higher CL_T for the Part 2 data.

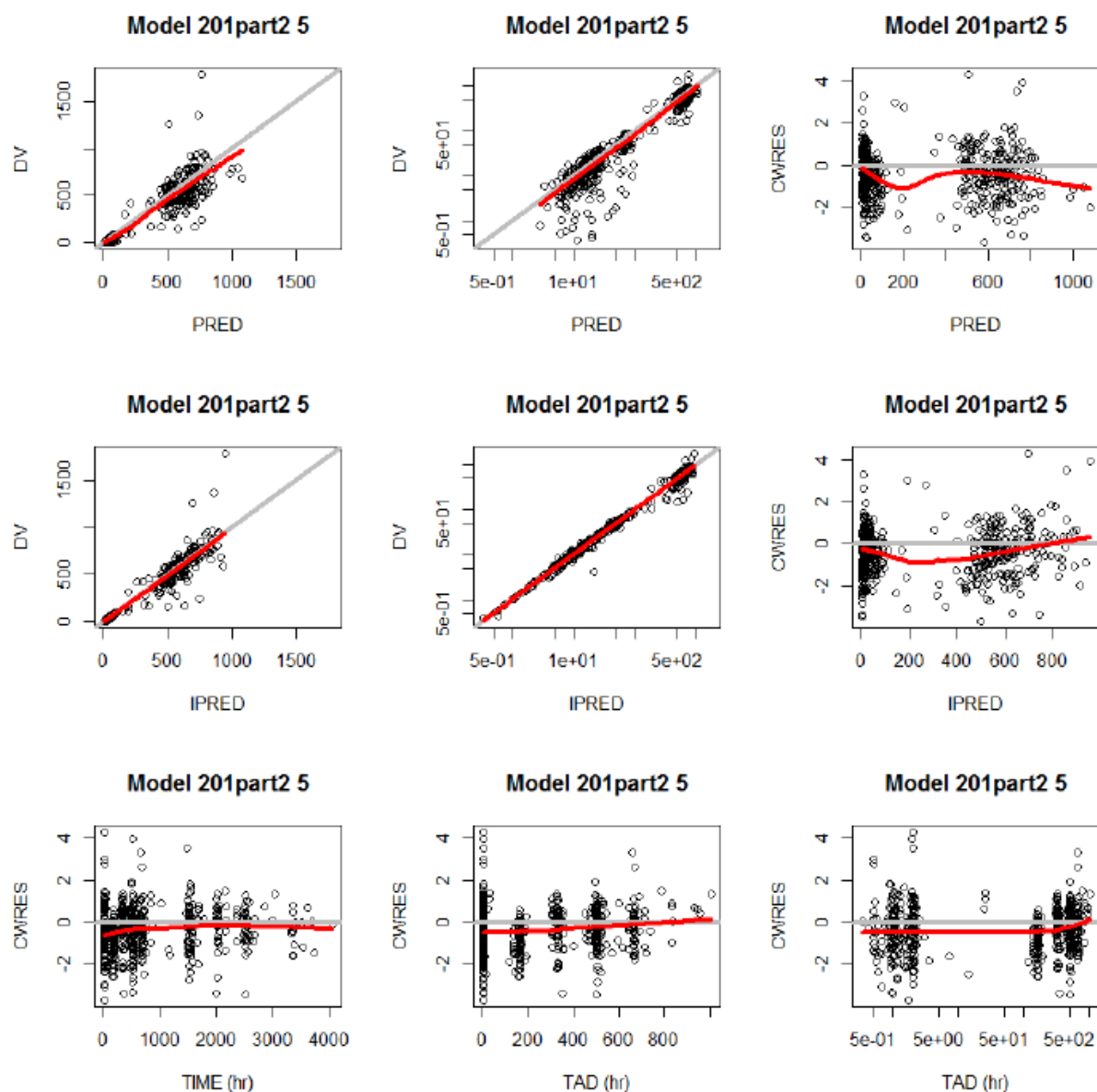
Evaluation of the model using NPDE techniques is illustrated in **Figure 16** -

Figure 19, separately for acMMAE and unconjugated MMAE. The applicant concluded: The NPDE plots for all data (**Figure 16 - Figure 17**) and only for Cycle ≥ 3 (**Figure 18**-

Figure 19) show trend of increasing NPDE values with increasing time after dose for both analytes. The NPDE analysis for acMMAE steady state PK data ($\geq$ Cycle 3) suggested that 50% of the observation is above the 50th percentile of a standard normal distribution $N(0,1)$, 5% of the observation is above the 90th percentile, and 9% of the observation is below the 10th percentile.

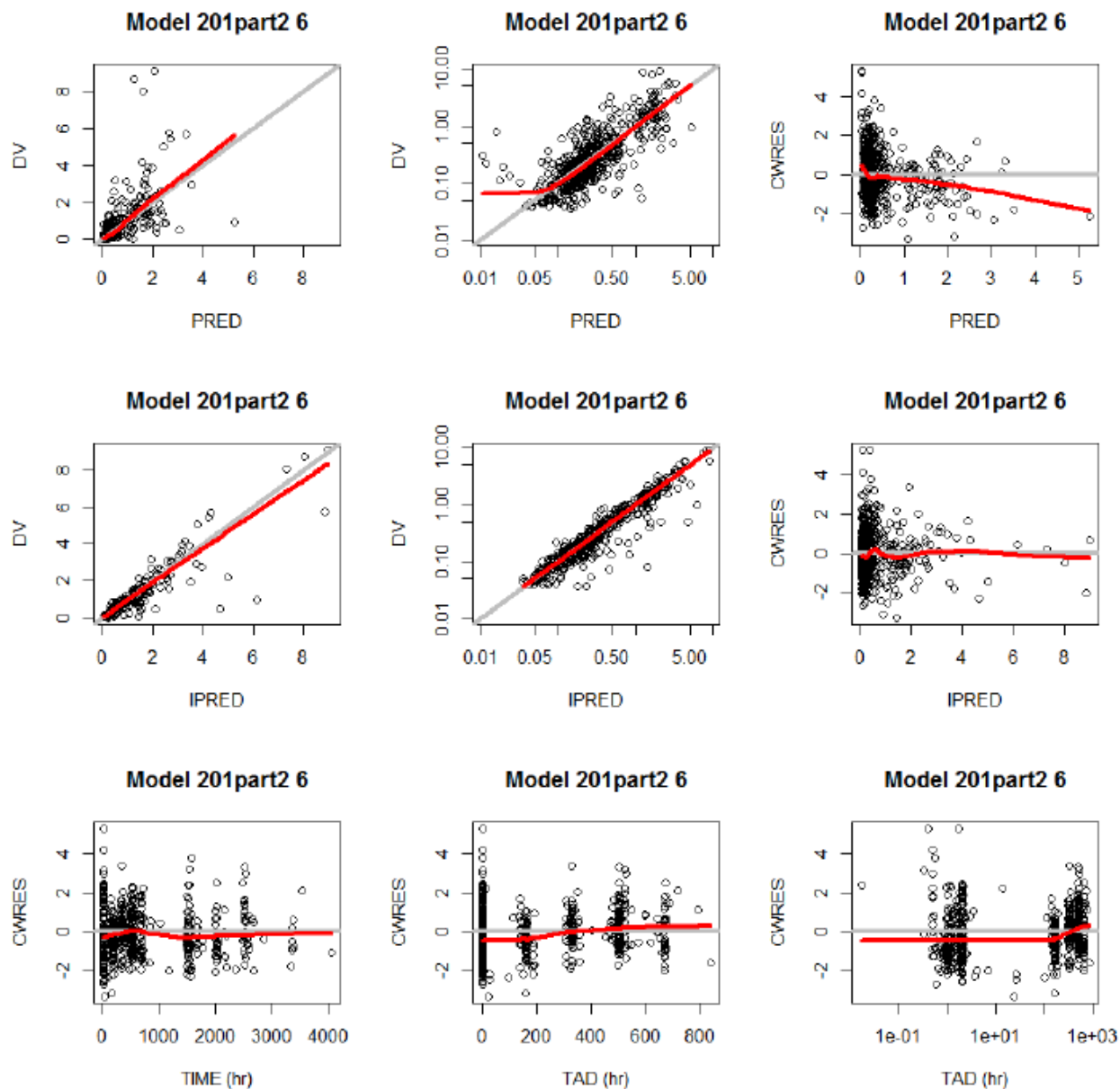
Simulated covariate-corrected (using cCC procedure) individual exposure parameters for patients with lyophilized DP and liquid DP were compared in **Table 21**. acMMAE exposures (AUC and C_{max}) in patients receiving lyophilized DP are similar (8.6% lower for AUC, 6.9% lower for C_{max}) to those receiving liquid DP, while unconjugated MMAE exposures are mildly lower (11.4% for AUC and 9.6% for C_{max}).

Figure 14: Goodness-of-fit for acMMAE and Part 2 data for the final integrated model



(Source: Applicant's Population PK Report, Figure 164)

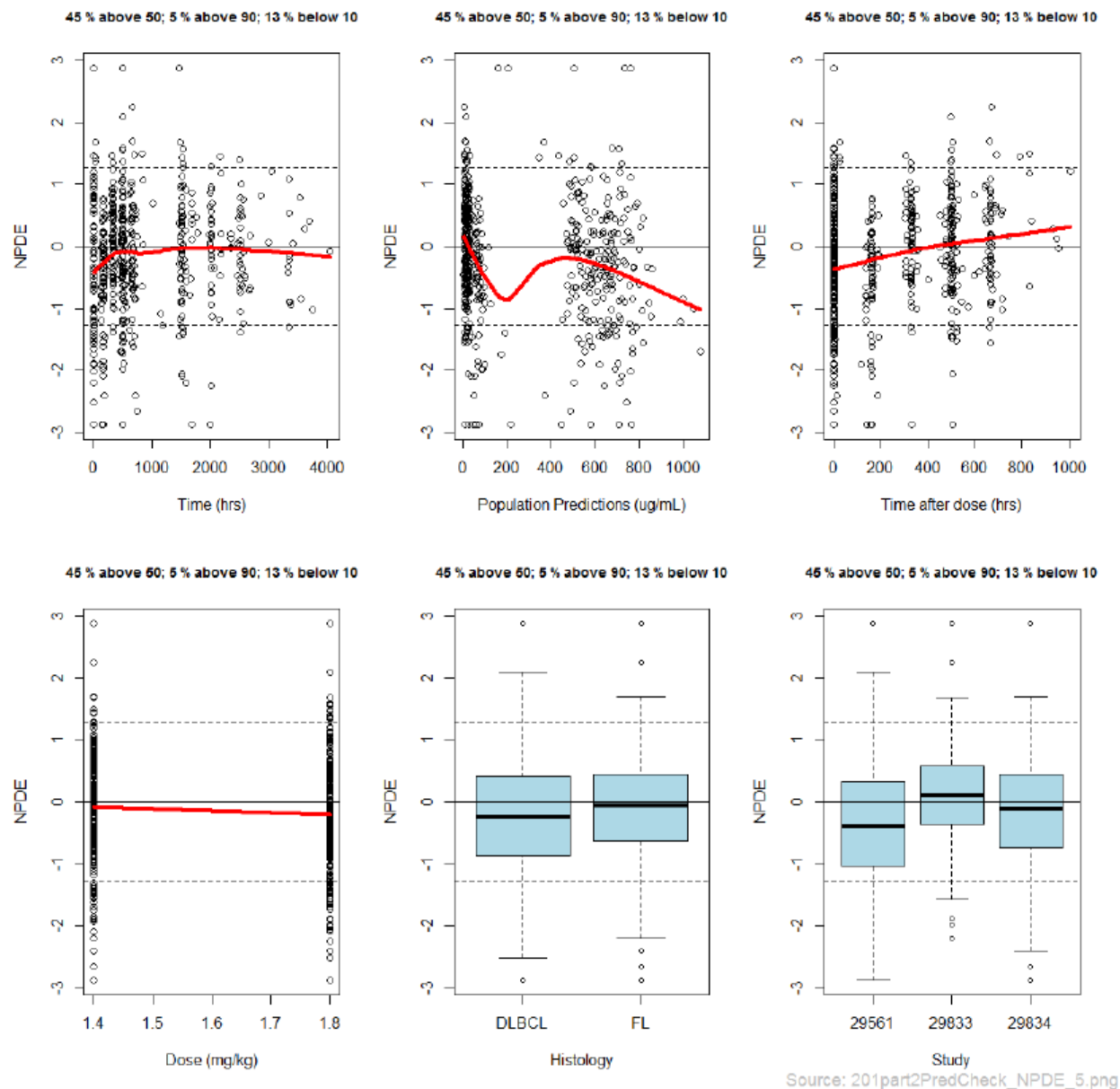
Figure 15: Goodness-of-Fit for unconjugated MMAE and Part 2 Data for the final integrated model



(Source: Applicant's Population PK Report, Figure 165)

Figure 16: NPDE plots for the final integrated model applied to part 2 data for acMMAE

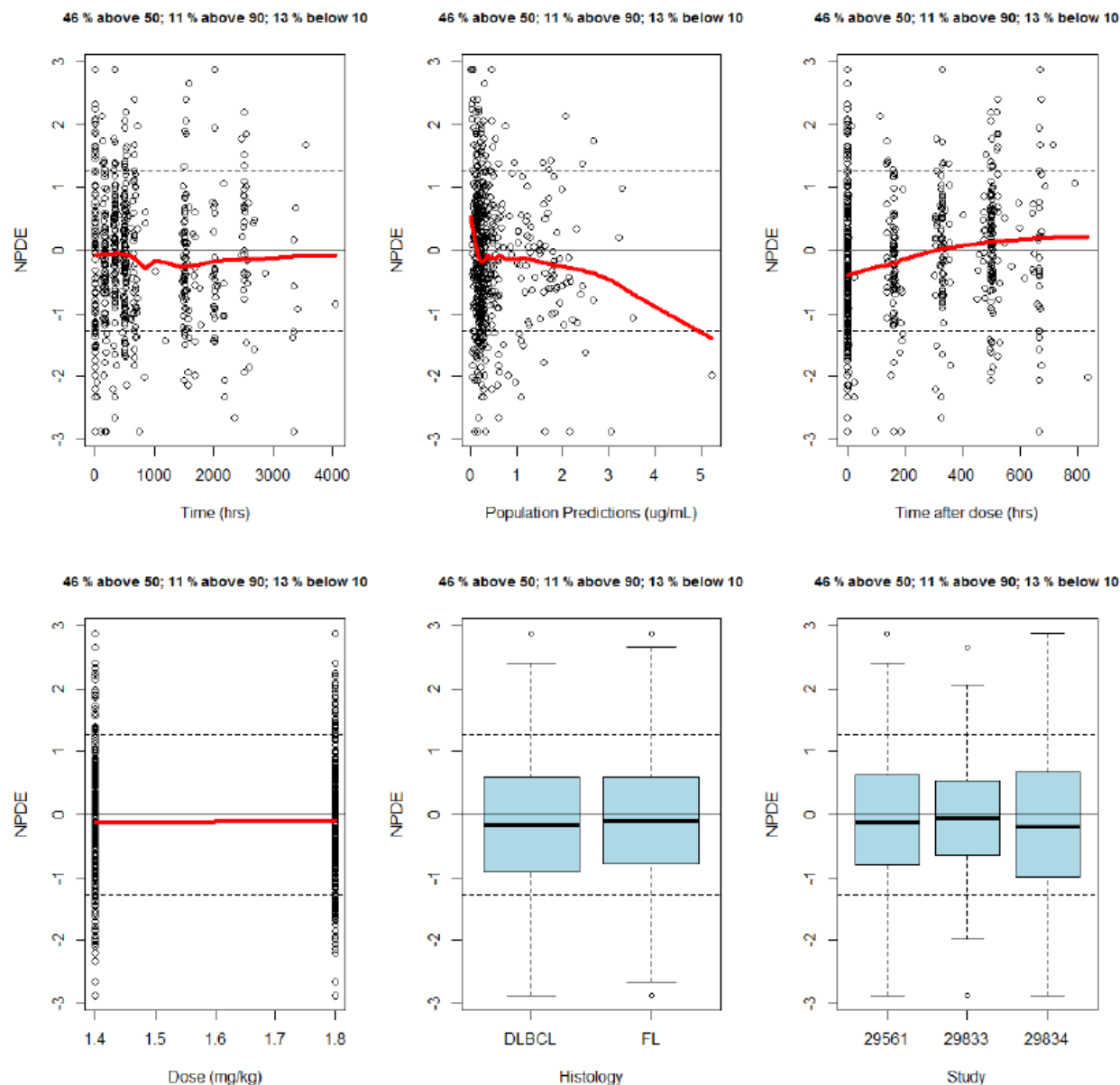
Circles correspond to NPDE of observations in the distribution of 500 simulated values. Lines at $y=0$ correspond to median, and dashed lines show the 10th and 90th percentiles. Percentages of points below 10th percentile and above 50th and 90th percentiles are reported. Red lines show the lowest trend lines.



(Source: Applicant's Population PK Report, Figure 173)

Figure 17: NPDE plots for the final integrated model applied to part 2 data for unconjugated MMAE

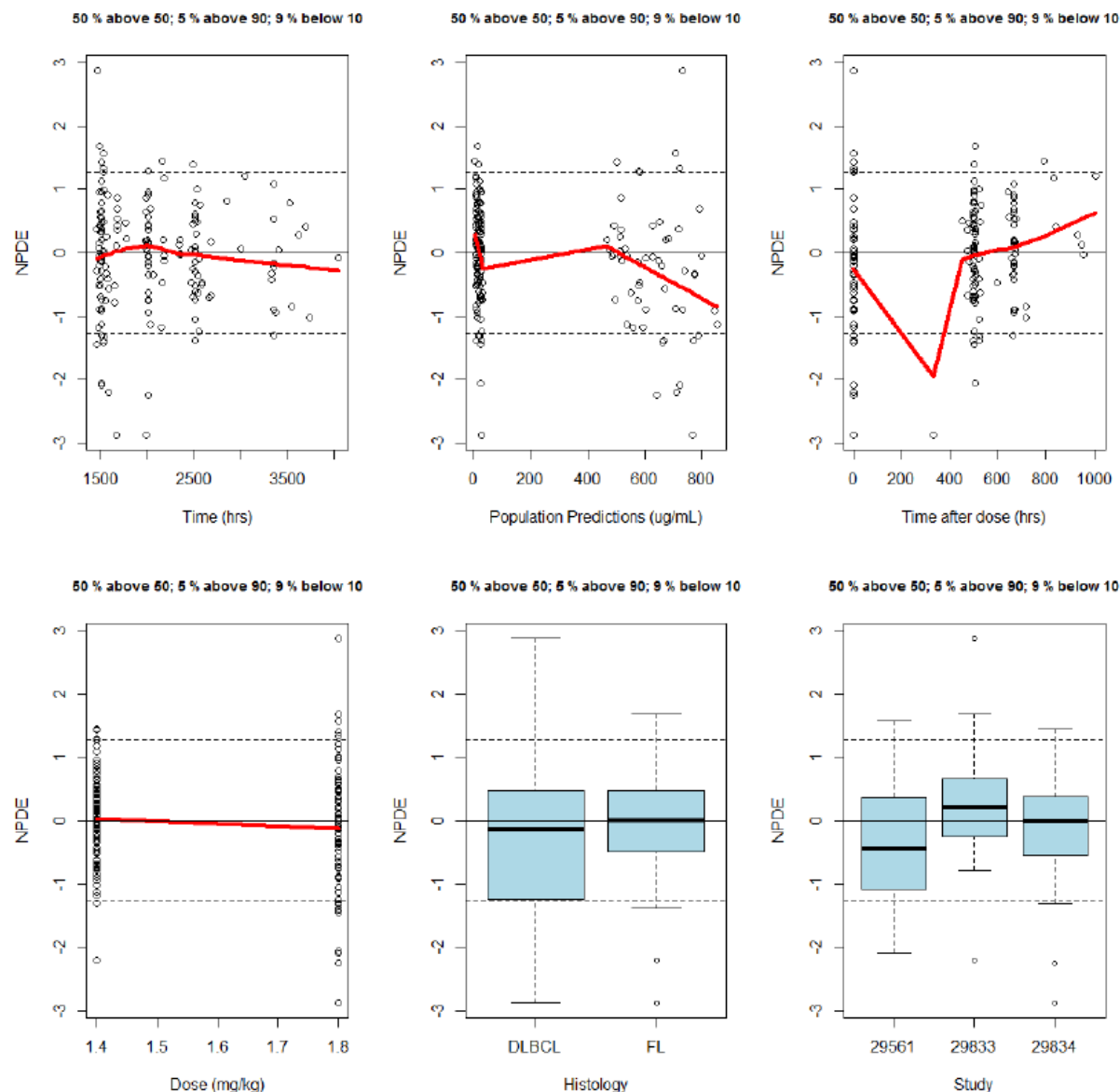
Circles correspond to NPDE of observations in the distribution of 500 simulated values. Lines at $y=0$ correspond to median, and dashed lines show the 10th and 90th percentiles. Percentages of points below 10th percentile and above 50th and 90th percentiles are reported. Red lines show the lowest trend lines.



(Source: Applicant's Population PK Report, Figure 174)

Figure 18: NPDE plots for the final integrated model applied to part 2 data for acMMAE, Cycle ≥ 3 (Steady-State)

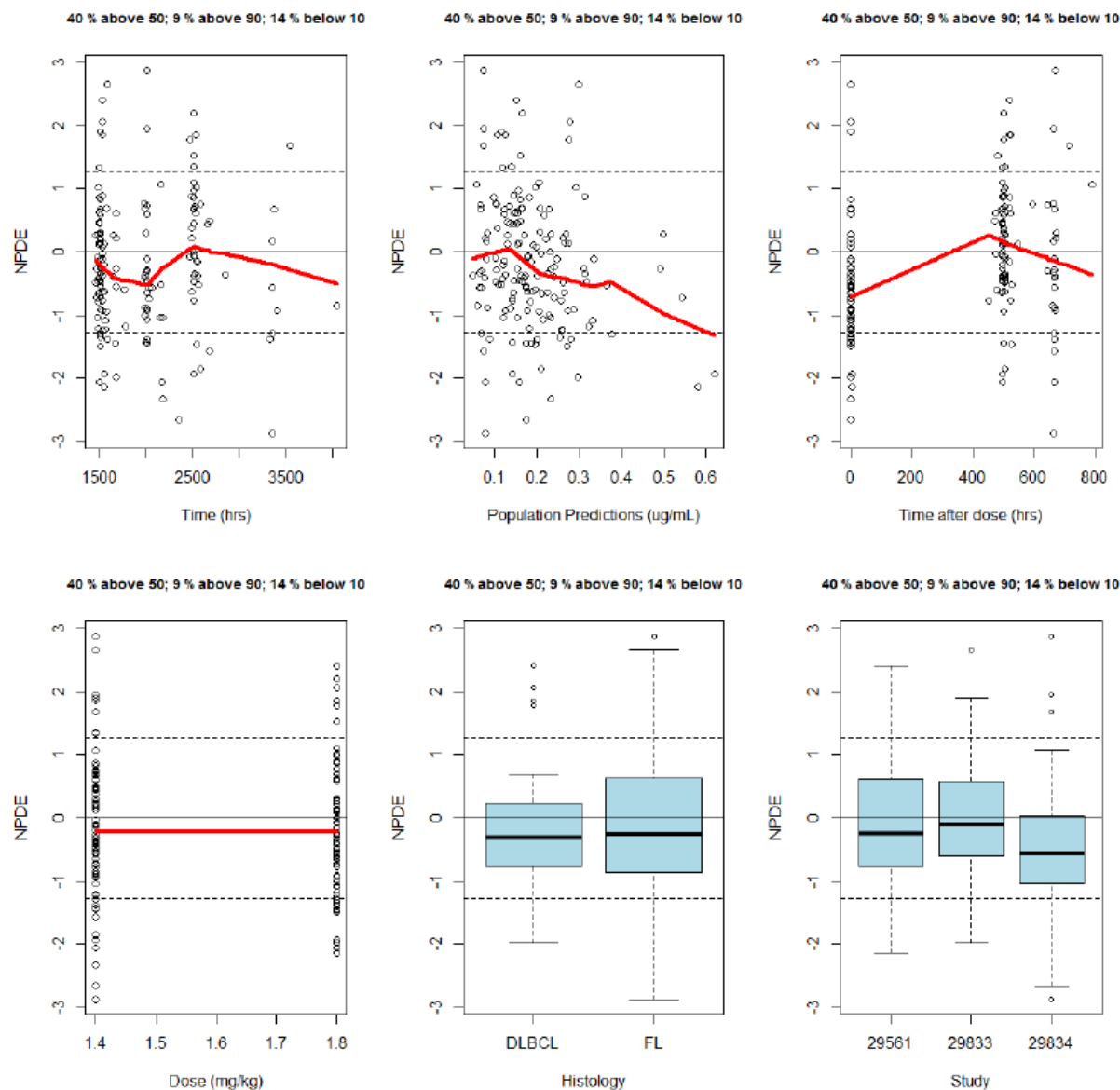
Circles correspond to NPDE of observations in the distribution of 500 simulated values. Lines at $y=0$ correspond to median, and dashed lines show the 10th and 90th percentiles. Percentages of points below 10th percentile and above 50th and 90th percentiles are reported. Red lines show the lowest trend lines.



(Source: Applicant's Population PK Report, Figure 175)

Figure 19: NPDE plots for the final integrated model applied to part 2 data for unconjugated MMAE, Cycle ≥ 3 (steady-state)

Circles correspond to NPDE of observations in the distribution of 500 simulated values. Lines at $y=0$ correspond to median, and dashed lines show the 10th and 90th percentiles. Percentages of points below 10th percentile and above 50th and 90th percentiles are reported. Red lines show the lowest trend lines.



(Source: Applicant's Population PK Report, Figure 176)

Table 21: Comparison of complete covariate-corrected exposures by study material

Individual exposures were computed for all patients from Part 1 (v0.1-derived liquid DP) and Part 2 (v1.0-derived lyophilized DP) following 1.8 mg/kg Q3W dosing for 6 cycles using cCC procedure, based on covariate-corrected empirical Bayes estimates of individual PK parameters. CV was computed as standard deviation of a log-transformed variable.

Exposure	Statistics	Liquid	Lyophilized
	N	460	106
acMMAE AUC (ng*day/mL)	Geometric Mean (CV%)	3140 (18%)	2870 (14%)
	Geometric Mean Ratio (90% CI)	1	0.914 (0.89-0.938)
acMMAE C _{max} (ng/mL)	Geometric Mean (CV%)	801 (11%)	746 (12%)
	Geometric Mean Ratio (90% CI)	1	0.931 (0.912-0.951)
acMMAE C _{trough} (ng/mL)	Geometric Mean (CV%)	32 (43%)	27.4 (38%)
	Geometric Mean Ratio (90% CI)	1	0.858 (0.801-0.921)
MMAE AUC (ng*day/mL)	Geometric Mean (CV%)	24.1 (43%)	21.4 (44%)
	Geometric Mean Ratio (90% CI)	1	0.886 (0.82-0.958)
MMAE C _{max} (ng/mL)	Geometric Mean (CV%)	2.21 (38%)	1.99 (39%)
	Geometric Mean Ratio (90% CI)	1	0.904 (0.843-0.968)
MMAE C _{trough} (ng/mL)	Geometric Mean (CV%)	0.269 (59%)	0.232 (55%)
	Geometric Mean Ratio (90% CI)	1	0.863 (0.782-0.953)

(Source: Applicant's Population PK Report, Table 66)

Reviewer's Comments:

The applicant's approach to evaluate whether the lyophilized powder formulation PK is different from the liquid DP formulation is acceptable. Model post hoc estimates from the final model conditioned on part 1 did not show bias in the goodness of fit plots with the part 2 data. However, the estimated geometric mean ratios suggested that concentrations of acMMAE and unconjugated MMAE may be slightly lower with the lyophilized powder.

Part 3: Analysis with Arm G of Study GO29365

The applicant submitted an additional analysis in support of PK for the lyophilized powder formulation with data from Arm G of Study GO29365.

All patients from Arm G who had at least one quantifiable acMMAE or unconjugated MMAE plasma concentration value post-treatment by the data cut-off date (05/29/2018, N=29) were included in the analysis. To evaluate the effect of drug product (DP) change on acMMAE and unconjugated MMAE PK, the final population PK model (developed for Studies GO29365 (Arms A-F), GO29044, GO27834, and DCS4968g) was used to evaluate the data from Arm G of Study GO29365 graphically by prediction corrected – visual predictive check (pc-VPC) and numerically by normalized prediction distribution error (NPDE) assessment.

Then, individual covariate-corrected exposures (AUC and C_{max} in Cycle 6 at 1.8 mg/kg Q3W) were computed using the final model and the individual empirical Bayes estimates (EBE) of PK parameters. The exposure measures were summarized and compared for patients administered v0.1-derived liquid DP and v1.0-derived lyophilized DP. The summary statistics included geometric mean and CV% as well as

geometric mean ratio of the population means (v1.0-derived lyophilized DP/v0.1-derived liquid DP) and 90% confidence interval.

Characteristics of the Arm G dataset are described in Table 22 - Table 24.

Table 22: Summary of data in Arm G of study GO29365

Description	acMMAE	MMAE
Total post-dose observations	175	174
Observations included in the analysis	170	170
Excluded post-dose non-BQL observations	4	4
Excluded post-dose BLQ observations	1	0

(Source: Applicant's Population PK Report for Arm G of GO29365, Table 3)

Table 23: Summary of continuous covariates in Arm G of study GO29365

Covariate	Description	Mean[SD]	Median [Range]
BAGE	Age (years)	60.5 (13.1)	64 [27-83]
BWT	Weight (kg)	78.2 (17.6)	76.3 [41.9-118]
BBSA	Body Surface Area (m ²)	1.89 (0.249)	1.88 [1.38-2.4]
BBMI	Body Mass Index(kg/m ²)	27.1 (5.05)	26.2 [17-42.2]
BLBWT	Lean Body Weight (kg)	55.1 (11.2)	55.3 [34.3-78.6]
BHT	Height (cm)	169 (11)	169 [150-192]
BALBUM	Albumin (g/L)	35.5 (6.7)	36.2 [20-45]
BTPROT	Total Protein (g/L)	60.2 (6.56)	62 [48-72]
BALP	Alkaline Phosphatase (u/L)	110 (78.1)	92 [52-398]
BALT	Alanine Aminotransferase (u/L)	20.7 (12.5)	16 [6-53]
BAST	Aspartate Aminotransferase (u/L)	29.9 (15.7)	27 [11-76]
BBILI	Bilirubin (umol/L)	10.8 (7.64)	8.55 [3.59-41.6]
HGB	Hemoglobin (g/L)	114 (17.6)	114 [85-168]
BLDH	Lactate Dehydrogenase (u/L)	654 (663)	329 [159-3070]
BSCR	Serum Creatinine (umol/L)	77.5 (30.4)	70.7 [35.4-167]
BCRCL	Creatinine Clearance (ml/min)	102 (43.2)	99.4 [37-193]
BBCC	B Cell Count (10 ⁹ /L)	19.8 (69.6)	0 [0-338]
LogBBCC	Log of BBCC (10 ⁹ /L)	0.842 (1.57)	0 [0-5.82]
BTMBD	Tumor SPD (mm ²)	7650 (8920)	5950 [341-44600]

(Source: Applicant's Population PK Report for Arm G of GO29365, Table 4)

Table 24: Summary of categorical covariates in Arm G of study GO29365

Covariate	Level	Total
N (%)		29
Race (RACE)	White	24 (82.8%)
	Asian	1 (3.4%)
	Other	4 (13.8%)
Gender (SEX)	Female	14 (48.3%)
	Male	15 (51.7%)
Region	West. Europe	10 (34.5%)
	Eeast. Europe	5 (17.2%)
	North. Amer.	7 (24.1%)
	Asia/Pacific	7 (24.1%)
Histology (TUMOR)	DLBCL	28 (96.6%)
	Other	1 (3.4%)
ECOG Status (BECOG)	0	6 (20.7%)
	1	21 (72.4%)
	2	2 (6.9%)
Bulky Disease (BBULKY)	Missing	20 (69%)
	Present	9 (31%)
Computed Hepatic Impairment (HEPA)	Normal	23 (79.3%)
	Mild	5 (17.2%)
	Moderate	1 (3.4%)
Renal Impairment (RENAL)	Normal	16 (55.2%)
	Mild	9 (31%)
	Moderate	4 (13.8%)

(Source: Applicant's Population PK Report for Arm G of GO29365, Table 5)

The applicant utilized the approach for the part 2 dataset for the Arm G data to evaluate whether the lyophilized powder PK was different from the liquid DP formulation.

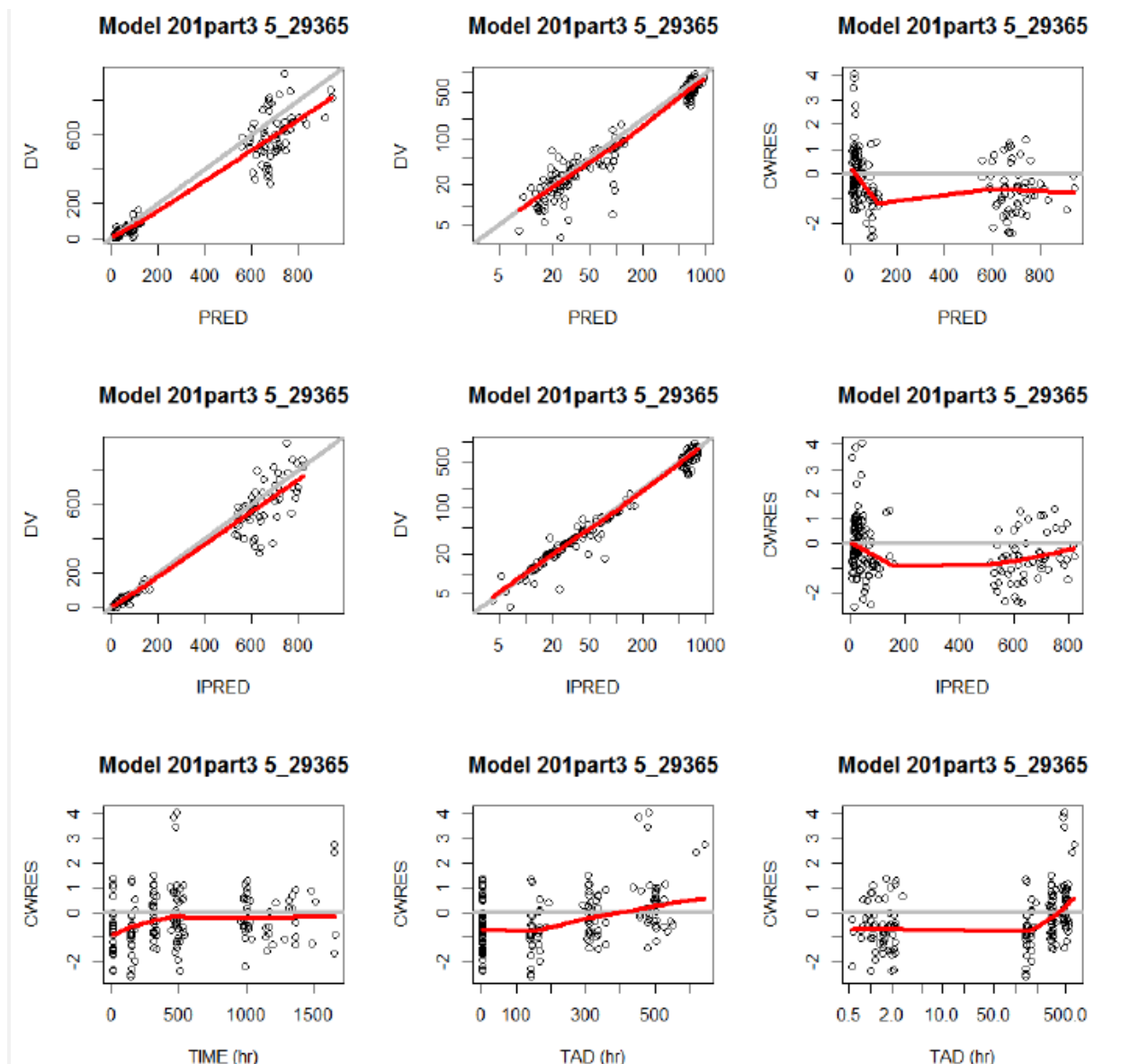
Goodness of fit plots are shown in Figure 20 and Figure 21. These plots in general indicate a slight trend for lower unconjugated MMAE values compared to the liquid DP formulation. Similar results were found with the NPDE plots shown in **Figure 22 - Figure 25**.

Simulated covariate-corrected individual exposure parameters for R/R DLBCL patients in Arm G with lyophilized DP (n=29) and all patients with liquid DP (n=460; patients from DCS4968g, GO27834, GO29044 and Cohort A-F of GO29365 studies) are compared in **Table 25**. Based on the comparison of geometric mean values of PK exposures, the acMMAE exposures (AUC and Cmax in cycle 6) in patients receiving lyophilized DP are similar (5.6% lower for AUC, 8.5% lower for Cmax) to those receiving liquid DP, while unconjugated MMAE exposures are also similar (11.6% for AUC and 10.4% for Cmax). The magnitude of difference is smaller than the IIV of 36-43% of unconjugated MMAE exposures.

Simulated covariate-corrected individual exposure parameters for R/R DLBCL patients in Arm G lyophilized DP (n=29) and DLBCL RR patients in Cohort A-F of study 29365 with liquid DP (n=44) are compared in **Table 26**. Based on the comparison of geometric mean values of PK exposures, the acMMAE exposures (AUC and Cmax) in patients receiving lyophilized DP are similar (4.5% lower for AUC, 6.1% lower for Cmax) to

those receiving liquid DP, while unconjugated MMAE exposures are also similar (14.6% for AUC and 11.3% for C_{max}). The magnitude of difference is smaller than the IIV of 36-43% of unconjugated MMAE exposures.

Figure 20: Goodness-of-fit for acMMAE in Arm G of study GO29365.



(Source: Applicant's Population PK Report for Arm G of GO29365, Figure 9)

Figure 21: Goodness-of-fit for unconjugated MMAE in Arm G of study GO29365

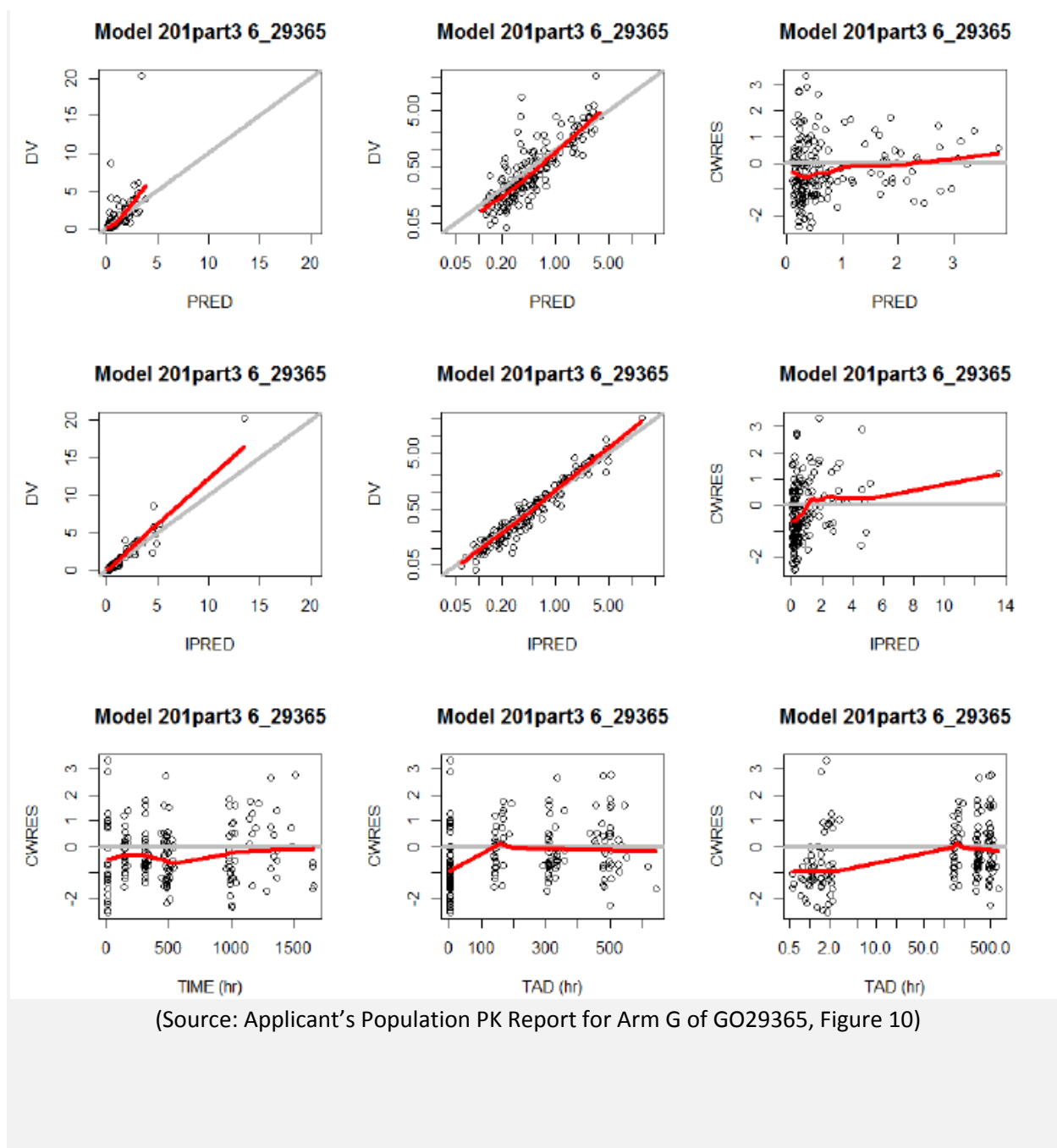
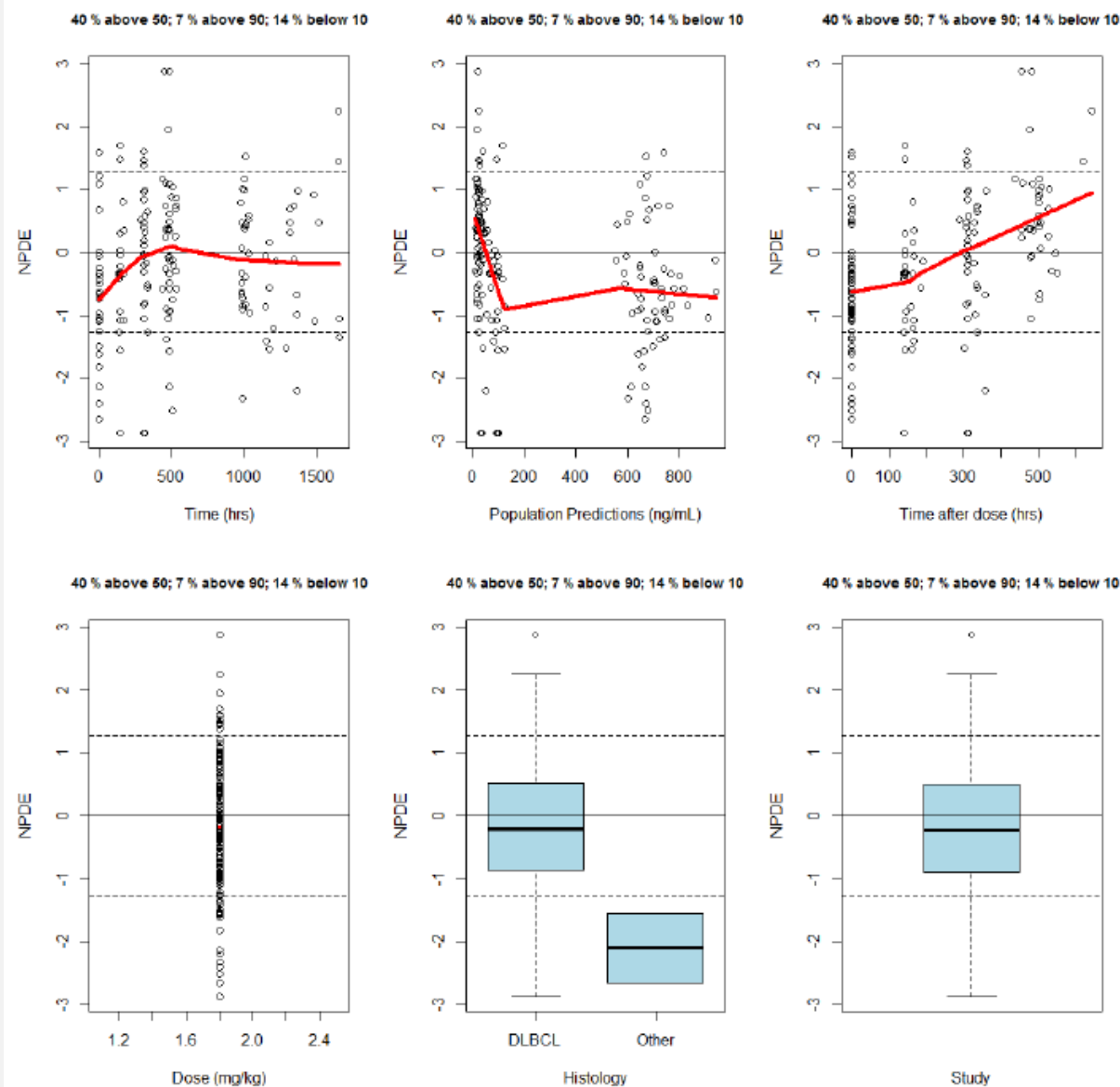


Figure 22: NPDE plots for acMMAE in Arm G of study GO29365

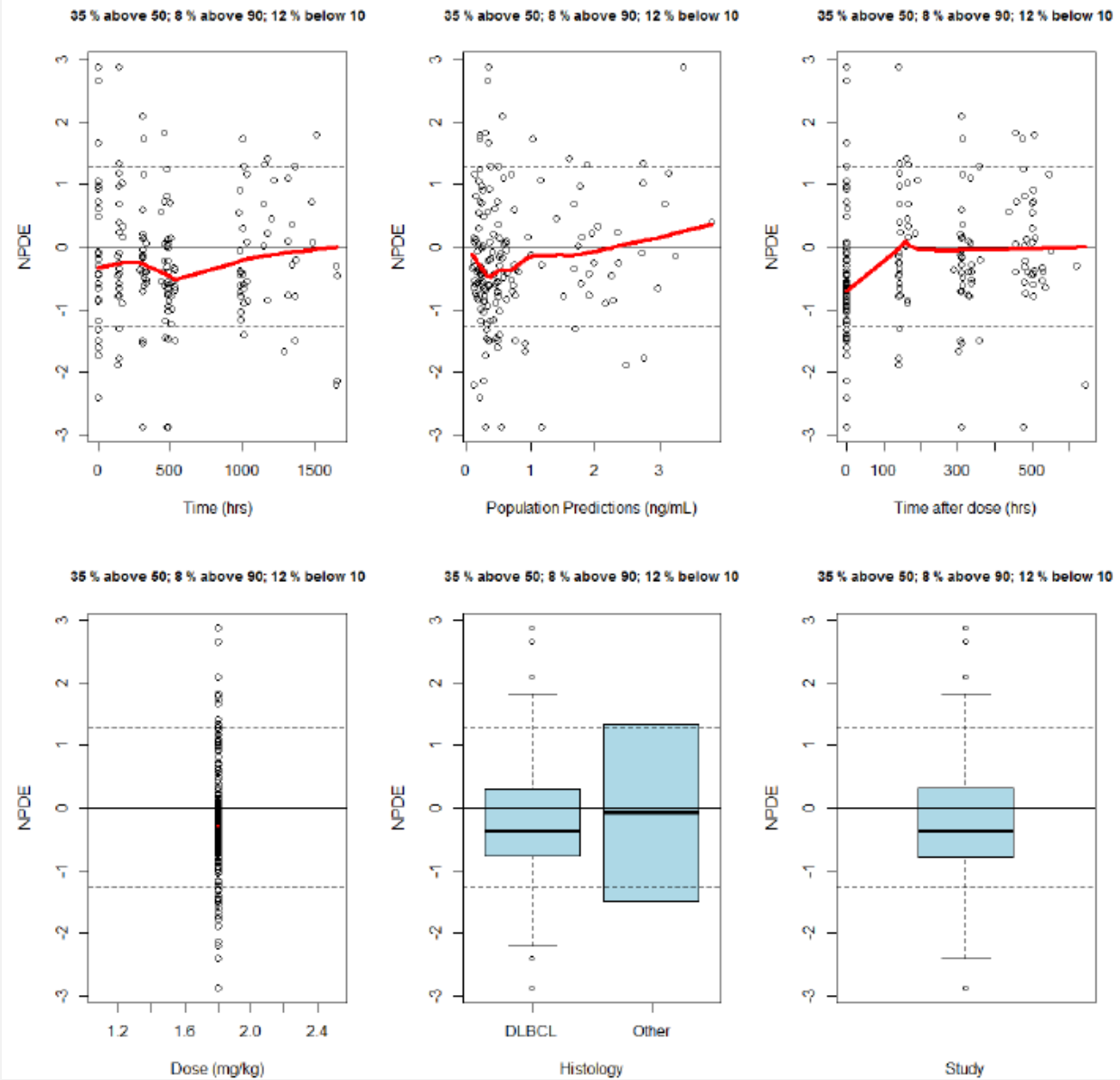
Circles correspond to NPDE of observations in the distribution of 500 simulated values. Lines at $y=0$ correspond to median, and dashed lines show the 10th and 90th percentiles. Percentages of points below 10th percentile and above 50th and 90th percentiles are reported. Red lines show the lowest trend lines.



(Source: Applicant's Population PK Report for Arm G of GO29365, Figure 12)

Figure 23: NPDE plots for unconjugated MMAE in Arm G of study GO29365

Circles correspond to NPDE of observations in the distribution of 500 simulated values. Lines at $y=0$ correspond to median, and dashed lines show the 10th and 90th percentiles. Percentages of points below 10th percentile and above 50th and 90th percentiles are reported. Red lines show the lowest trend lines.



(Source: Applicant's Population PK Report for Arm G of GO29365, Figure 13)

Figure 24: NPDE plots for acMMAE in Arm G of study GO29365, Cycle ≥ 3 (steady-state)

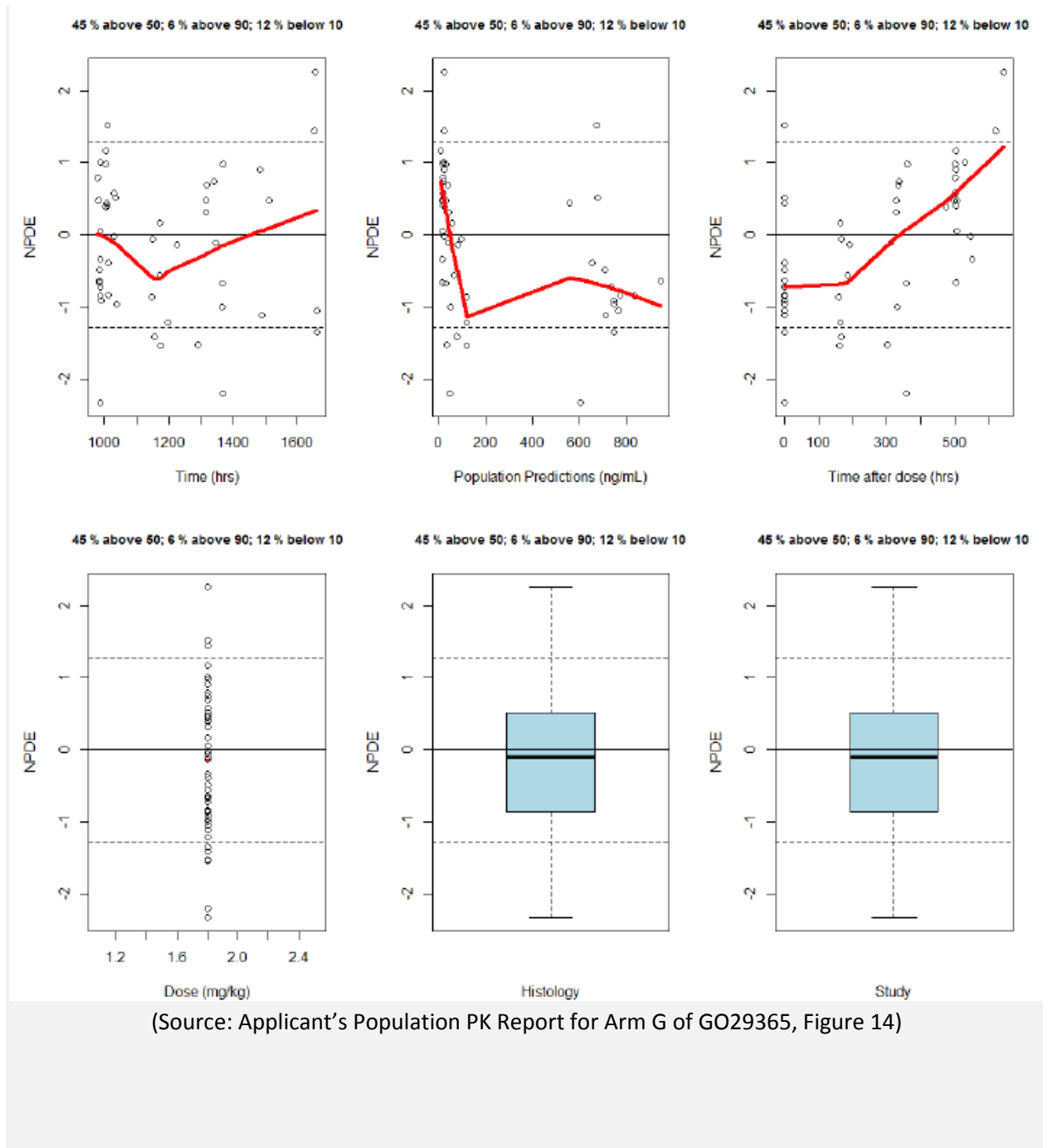
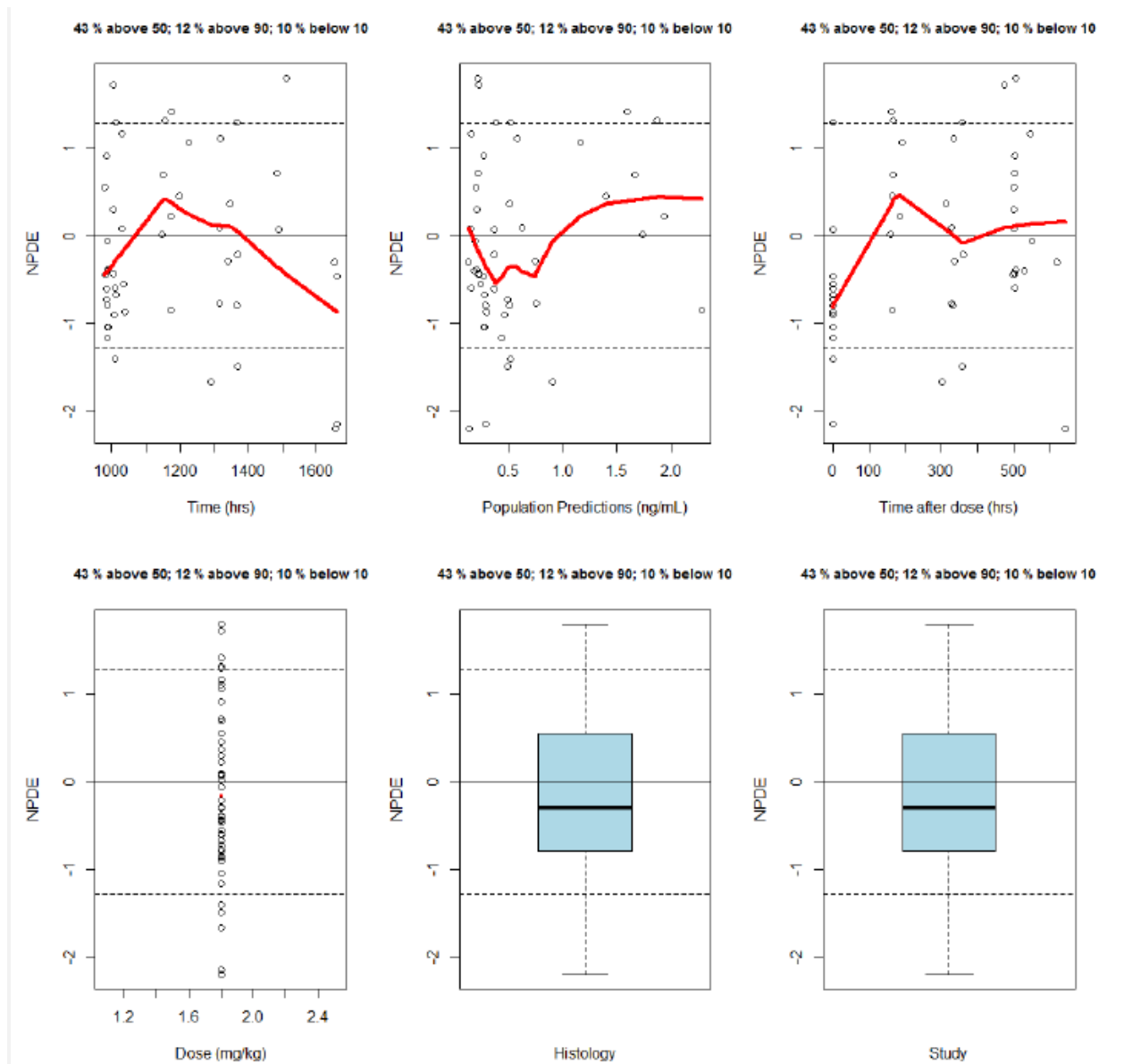


Figure 25: NPDE plots for MMAE in Arm G of study GO29365, Cycle ≥ 3 (steady-state)



(Source: Applicant's Population PK Report for Arm G of GO29365, Figure 15)

Table 25: Comparison of covariate-corrected exposures, Arm G versus all patients with liquid DP formulation

Exposure	Statistics	Liquid	Lyophilized
	N	460	29
acMMAE AUC (ng*day/mL)	Geometric Mean (CV%)	3140 (18%)	2970 (18%)
	Geometric Mean Ratio (90% CI)	1	0.944 (0.891-1)
acMMAE C _{max} (ng/mL)	Geometric Mean (CV%)	801 (11%)	733 (10%)
	Geometric Mean Ratio (90% CI)	1	0.915 (0.887-0.945)
acMMAE C _{trough} (ng/mL)	Geometric Mean (CV%)	32 (43%)	32.3 (38%)
	Geometric Mean Ratio (90% CI)	1	1.01 (0.891-1.14)
MMAE AUC (ng*day/mL)	Geometric Mean (CV%)	24.1 (43%)	21.3 (42%)
	Geometric Mean Ratio (90% CI)	1	0.884 (0.77-1.01)
MMAE C _{max} (ng/mL)	Geometric Mean (CV%)	2.21 (38%)	1.98 (36%)
	Geometric Mean Ratio (90% CI)	1	0.896 (0.796-1.01)
MMAE C _{trough} (ng/mL)	Geometric Mean (CV%)	0.269 (59%)	0.236 (57%)
	Geometric Mean Ratio (90% CI)	1	0.878 (0.73-1.05)

(Source: Applicant's Population PK Report for Arm G of GO29365, Table 7)

Table 26: Comparison of covariate-corrected exposures, Arm G versus R/R DLBCL patients with lyophilized DP from study GO29365 administered polatuzumab in combination with rituximab.

Exposure	Statistics	v0.1 Liquid	v1.0 Lyophilized
	N	44	29
acMMAE AUC (ng*day/mL)	Geometric Mean (CV%)	3110 (13%)	2970 (18%)
	Geometric Mean Ratio (90% CI)	1	0.955 (0.895-1.02)
acMMAE C _{max} (ng/mL)	Geometric Mean (CV%)	781 (9%)	733 (10%)
	Geometric Mean Ratio (90% CI)	1	0.939 (0.905-0.975)
acMMAE C _{trough} (ng/mL)	Geometric Mean (CV%)	32.7 (31%)	32.3 (38%)
	Geometric Mean Ratio (90% CI)	1	0.986 (0.855-1.14)
MMAE AUC (ng*day/mL)	Geometric Mean (CV%)	25 (36%)	21.3 (42%)
	Geometric Mean Ratio (90% CI)	1	0.854 (0.728-1)
MMAE C _{max} (ng/mL)	Geometric Mean (CV%)	2.23 (30%)	1.98 (36%)
	Geometric Mean Ratio (90% CI)	1	0.887 (0.774-1.02)
MMAE C _{trough} (ng/mL)	Geometric Mean (CV%)	0.285 (51%)	0.236 (57%)
	Geometric Mean Ratio (90% CI)	1	0.828 (0.667-1.03)

(Source: Applicant's Population PK Report for Arm G of GO29365, Table 8)

Reviewer's Comments:

There appears to be a consistent shift to slightly lower acMMAE and unconjugated MMAE concentrations with the lyophilized powder PK data. While this was also observed with the same analysis on the Part 2 data, the magnitude of difference was relatively small, a 5 – 15% reduction.

4.3 Exposure-Response Analyses

The applicant's analysis investigated the exposure-safety and exposure-efficacy relationships for patients with R/R DLBCL in the pivotal and supportive studies separately.

The analysis was based on the pivotal study GO29365 and was performed in the R/R DLBCL population to assess the exposure-response relationship at the proposed label dose of 1.8 mg/kg Q3W of up to 6 cycles given in combination with bendamustine/rituximab.

Studies DCS4968g and GO27834 are supportive Phase 1b/II open label studies evaluating the safety, tolerability, and anti-tumor activity of polatuzumab monotherapy or polatuzumab in combination with rituximab (polatuzumab + R) or obinutuzumab (polatuzumab +G) in patients with R/R DLBCL, FL, and other NHL subtypes (patients with CLL included in Study DCS4968g were not used in the analyses). In these supportive studies, a range of polatuzumab doses (0.1-2.4 mg/kg) were administered Q3W up to disease progression or unacceptable toxicity as monotherapy or in combination with rituximab. Also, in Study GO27834, 1.8 mg/kg polatuzumab doses were administered Q3W for up to 8 cycles in combination with obinutuzumab. Different treatment durations for the supportive and pivotal studies may lead to different safety and efficacy profiles. To use the risk-benefit profile from the supportive studies to justify the dose and regimen in the pivotal study, the safety and efficacy data for supportive studies were cut to 8-cycle landmark (cycle 9 day 1) if patients were treated beyond 8 cycles. The cutoff of 8-cycle was selected to include the tumor assessment scheduled at the end of cycle 8 for studies DCS4968g and GO27834, so that same cutoff for safety and efficacy can be applied.

OBJECTIVES

Analysis of Exposure Safety Relationships:

The exposure-safety analysis was conducted for the 119 R/R DLBCL patients from the supportive studies DCS4968g (polatuzumab monotherapy and polatuzumab + R arms) and GO27834 (polatuzumab + R and polatuzumab +G arms); and for the 69 R/R DLBCL patients from the pivotal study GO29365 (polatuzumab + BR and polatuzumab + BG arms):

- To investigate the relationships between polatuzumab exposure (defined as the cycle 6 AUC and Cmax for antibody-conjugated MMAE [acMMAE]) and unconjugated MMAE simulated based on nominal polatuzumab dosing) and the probability of treatment emergent adverse events (Grade $\geq$ 3 Neutropenia, Grade $\geq$ 2 Peripheral Neuropathy, Grade $\geq$ 3 Infections and Infestations, Grade $\geq$ 3 Anemia; Grade $\geq$ 3 Thrombocytopenia, Grade $\geq$ 3 Diarrhea, Grade $\geq$ 3 AST increase, Grade $\geq$ 3 ALT increase, and Grade $\geq$ 3 bilirubin increase);
- To investigate the relationships between polatuzumab exposure and time to the first polatuzumab dose modification (including reduction, delay, or discontinuation) due to AE.
- To assess the relationship between polatuzumab exposure and the dose intensity for polatuzumab, rituximab, and bendamustine (pivotal study only), accounting for dose reduction [if allowed] and dose delay.

Analysis of Exposure Efficacy Relationships

The exposure-efficacy analysis was conducted for the 76 R/R DLBCL patients from the supportive studies DCS4968g (polatuzumab monotherapy and polatuzumab + R arms) and GO27834 (polatuzumab + R arms):

- To assess the relationships between polatuzumab exposure (cycle 6 AUC for acMMAE) and probability of Investigator-assessed (INV) complete or partial response up to cycle 8 landmark by PET-CT or CT (INV-BOR);

- To assess the relationships between polatuzumab exposure and probability of INV-assessed complete or partial response at Cycle-8 landmark by PET-CT or CT (INV- OR).

The exposure-efficacy analysis was conducted for the 44 R/R DLBCL patients from the polatuzumab+BR arm of pivotal study GO29365, with an additional 40 R/R DLBCL patients from BR control arm for the Kaplan-Meier analysis only:

- To assess the relationships between polatuzumab exposure and probability of independent review committee (IRC)-assessed complete response (IRC-CR), defined as complete response at primary response assessment (PRA) by PETCT only;
- To assess the relationships between polatuzumab exposure and probability of IRC-assessed overall response (IRC-OR), defined as complete or partial response at primary response assessment by PET-CT only;
- To assess the relationships between polatuzumab exposure and probability of IRC-assessed best overall response (IRC-BOR), defined as complete or partial response by PET-CT or CT;
- To assess the relationships between polatuzumab exposure and IRC-assessed duration of response (IRC-DOR) for patients with response by PET-CT or CT;
- To assess the relationships between polatuzumab exposure and IRC-assessed progression-free survival (IRC-PFS);
- To assess the relationships between polatuzumab exposure and overall survival (OS).

In the pivotal study GO29365, both IRC and investigator-assessed efficacy endpoints, including BOR, CR at PRA, OR at PRA, time to relapse (DOR), and PFS showed consistently significant benefit favoring pola + BR in r/r DLBCL patients. Concordance rates were high between the investigator- and IRC-assessed efficacy endpoints. Since IRC assessment was the primary assessment, for exposure-efficacy analysis of the pivotal study GO29365, only IRC assessed efficacy endpoints were evaluated.

METHODOLOGY

The individual empirical Bayes estimates of polatuzumab PK parameters estimated using the population PK model were used to obtain the individual exposure measures of polatuzumab, defined as Cycle 6 AUC and Cmax for acMMAE and unconjugated MMAE based on nominal dose (i.e., assuming that the subject received the planned doses according to cohort assignment during the entire study). The AUC and Cmax for both acMMAE and unconjugated MMAE were used for the exposure-safety analysis; Only AUC for acMMAE was used for the exposure efficacy analysis.

Exposure-safety analyses:

The same safety endpoints were investigated for patients from the supportive studies DCS4968g and GO27834 and the pivotal study GO29365. The following key adverse events of special interest (AESI) were investigated in the analysis: Grade $\geq$ 3 Neutropenia, Grade $\geq$ 2 Peripheral Neuropathy, Grade $\geq$ 3 Infections and Infestations, Grade $\geq$ 3 Anemia, Grade $\geq$ 3 Thrombocytopenia, Grade $\geq$ 3 Diarrhea, Grade $\geq$ 3 AST increase, Grade $\geq$ 3 ALT increase, and Grade $\geq$ 3 bilirubin increase.

For each AE type with more than 5% frequency and more than 5 events, logistic regression models were implemented to assess the correlation of the probability of AE occurrence and the exposure of acMMAE and unconjugated MMAE (AUC and Cmax). If a statistically significant effect of exposure was observed, a covariate analysis was conducted.

Association of the probability of dose modification (including reduction, delay, or discontinuation) due to any AE with exposure was investigated using logistic regression models. Association of time to the first dose modification due to any AE with exposure was investigated using survival analyses methods (Kaplan-Meier plots and Cox proportional hazards [CPH] models). If a statistically significant effect of exposure was observed, a covariate analysis was conducted.

The covariate analysis for exposure-safety relationship was conducted using a forward addition - backward elimination procedure, for the following list of variables: demographics (body weight, sex, age, race), geographic region, baseline laboratory measurements (LDH, serum albumin, neutrophil count [only for neutropenia], hemoglobin level [only for anemia], platelet count [only for thrombocytopenia]), baseline disease characteristics (relapsed or refractory status, ECOG score, bulky disease, prior stem cell transplant, lines of prior anti-lymphoma chemotherapy, peripheral neuropathy history [only for peripheral neuropathy], peripheral neuropathy status at baseline [only for peripheral neuropathy]), and concomitant therapy with rituximab or obinutuzumab and polatuzumab ADA status.

Association of dose intensity of polatuzumab, rituximab, and bendamustine (for pivotal study only) with polatuzumab exposure was explored graphically, by linear regression, and summarized by exposure tertiles.

Exposure-efficacy analyses:

The efficacy endpoints investigated for patients from supportive studies DCS4968g and GO27834 were INV-BOR and INV-OR.

Efficacy endpoints investigated for patients from Pivotal Study GO29365 were IRC-BOR, IRC-CR, IRC-OR, DOR, IRC-PFS, and OS.

For each binary efficacy endpoint (INV-BOR, INV-OR, IRC-BOR, and IRC-OR), logistic regression models were implemented to assess relationships of probability of response and acMMAE AUC. If a statistically significant effect of exposure was observed, a covariate analysis was conducted. For each time-to-event endpoint (DOR, IRC-PFS, and OS), Kaplan-Meier plots stratified by categories of exposure (acMMAE AUC) and CPH modeling were conducted. If a statistically significant effect of exposure was observed, a covariate analysis was conducted.

The covariate analysis for exposure-efficacy relationship was conducted using a forward addition - backward elimination procedure, for all the covariate listed in the exposure-safety analysis, except for those only tested for safety endpoints (neutrophil count, hemoglobin level, platelet count, peripheral neuropathy history, and peripheral neuropathy status at baseline), and except for concomitant therapy with obinutuzumab. The following baseline covariates were included only in the exposure-efficacy

analyses as they were not expected to affect safety: B-cell (CD19) count, β 2-microglobulin, Neutrophil-to-lymphocyte ratio, tumor SPD, Ann Arbor stage, DLBCL genetic subgroup, IPI, refractory status to the last prior anti-cancer therapy, duration of response to prior anti-lymphoma therapy and extra nodal involvement.

RESULTS:

The overall summaries of the results for the exposure-safety (Table 27) and exposure-efficacy (Table 28) analyses were summarized below.

Exposure-safety analysis:

- The analysis based on supportive studies suggested that higher acMMAE exposures (AUC, Cmax) were significantly correlated with higher incidence of Grade ≥ 2 peripheral neuropathy. The covariate analysis was performed only for the acMMAE AUC model. The forward inclusion identified LDH as the significant covariate at $\alpha = 0.01$ level. The exposure-response relationship remained significant in the presence of LDH in the model. No covariate was retained in the final model at $\alpha = 0.001$ level during the backward elimination. Higher unconjugated MMAE exposures (AUC, Cmax) were significantly correlated with higher incidence of Grade ≥ 3 anemia. The covariate analysis was performed only for the unconjugated MMAE AUC model. The forward inclusion identified North America region as significant covariate at $\alpha = 0.01$ level. The exposure-response relationship remained significant in the presence of North America region in the model; No covariate was retained in the final model at $\alpha = 0.001$ level during the backward elimination. Higher unconjugated MMAE exposures (AUC, Cmax) were also significantly correlated with earlier time to first dose modification due to AE. The covariate analysis was performed only for the unconjugated MMAE AUC model. No covariates were identified at $\alpha = 0.01$ level during the forward inclusion. Although significant relationship was identified for unconjugated MMAE exposures and the time to first dose modification due to AE, the relationship between unconjugated MMAE exposures and the probability of dose modification due to AE was found not significant. There was a statistically significant correlation between acMMAE exposures (AUC, Cmax) and the dose intensity of polatuzumab. However, given an overall high dose intensity (>89%) across each tertile of the acMMAE exposure, this statistical significance was not clinically relevant. For all other safety endpoints assessed, there were no statistically significant correlations with the exposure of acMMAE or unconjugated MMAE.
- The analysis based on the pivotal study suggested that higher acMMAE Cmax was significantly associated with earlier time to first dose modification due to AE. No covariates were identified at $\alpha = 0.01$ level during the forward inclusion. There was no significant relationship between acMMAE Cmax and the probability of dose modification due to AE. All other analysis was not statistically significant. It is acknowledged that the analysis can be limited by the data from a single dose level of 1.8 mg/kg, given the relatively narrow range of exposures.

Table 27: Summary of the results for exposure-safety analysis

Adverse Event	Analysis Type	N	N (%) with Event	p-value			
				acMMAE		unconjugated MMAE	
				AUC	Cmax	AUC	Cmax
Analysis based on the supportive studies							
Grade ≥3 Neutropenia	Logistic regression	119	39 (32.8%)	0.091	0.157	0.338	0.339
Grade ≥2 Peripheral Neuropathy		119	30 (25.2%)	0.003	0.011	0.571	0.755
Grade ≥3 Infections and Infestations		119	12 (10.1%)	0.615	0.631	0.066	0.101
Grade ≥3 Anemia		119	9 (7.6%)	0.866	0.964	0.010	0.015
Grade ≥3 Thrombocytopenia		119	6 (5.0%)	0.638	0.928	0.327	0.221
Dose Modification due to AE		119	32 (26.9%)	0.340	0.256	0.455	0.325
Time to the First Dose Modification due to AE	Cox PH model	119	32 (26.9%)	0.359	0.601	0.004	0.002
Pola Dose intensity	Linear regression	119	-	0.030	0.026	0.128	0.114
Rituximab Dose intensity		40	-	0.544	0.986	0.725	0.560
Analysis based on the pivotal study							
Grade ≥3 Neutropenia	Logistic regression	69	35 (50.7%)	0.649	0.269	0.810	0.993
Grade ≥2 Peripheral Neuropathy		69	10 (14.5%)	0.586	0.965	0.309	0.226
Grade ≥3 Infections and Infestations		69	20 (29.0%)	0.376	0.879	0.765	0.930
Grade ≥3 Anemia		69	13 (18.8%)	0.888	0.390	0.117	0.119
Grade ≥3 Thrombocytopenia		69	24 (34.8%)	0.781	0.780	0.253	0.253
Dose Modification due to AE		69	40 (58.0%)	0.100	0.062	0.448	0.465
Time to the First Dose Modification due to AE	Cox PH model	69	40 (58.0%)	0.145	0.009	0.639	0.541
Pola Dose intensity	Linear regression	69	-	0.099	0.555	0.984	0.953
Bendamustine Dose intensity		69	-	0.339	0.192	0.118	0.242
Rituximab Dose intensity		44	-	0.070	0.232	0.296	0.186

(Source: Applicant's Exposure-Safety and Exposure-Efficacy Report, Table A)

Exposure-efficacy analysis:

- The analysis based on the supportive studies over a polatuzumab dose range of 0.1-2.4 mg/kg Q3W treatment up to 8-cycles suggested that higher acMMAE AUC were significantly correlated with higher tumor response rate by investigator assessment, including INV-BOR up to 8-cycle treatment and INV-OR at the end of cycle 8 landmark. Refractory to prior anti-lymphoma treatment and ECOG status equal to 0 (versus greater than 0) were the significant covariate at $\alpha = 0.01$ level for INV-OR during the forward inclusion. The exposure-response relationship remained significant in the presence of those two covariates in the model; No covariate was retained in the final model at $\alpha = 0.001$ level during the backward elimination. Refractory to prior anti-lymphoma treatment was the significant covariate at $\alpha = 0.01$ level for INV-BOR during the forward inclusion. The exposure-response relationship remained significant in the presence of this covariate in the model. No covariate was retained in the final model at $\alpha = 0.001$ level during the backward elimination.
- The analysis based on the pivotal study of polatuzumab dose of 1.8 mg/kg Q3W for up to 6 cycles in combination with rituximab and bendamustine suggested a borderline significant correlation ($p = 0.048$ by cox regression) between acMMAE AUC and OS, i.e. higher acMMAE AUC may be correlated with longer OS. The forward inclusion identified baseline B cell count, Ann Arbor criteria equal to 4 (versus less than 4), and ECOG status equal to 0 (versus greater than 0) as significant covariates on OS at $\alpha = 0.01$ level. The exposure-response relationship remained significant in the presence of those covariates in the model. No covariates were retained in the

final model at $\alpha = 0.001$ level during the backward elimination. The analysis can be limited by the data from a single dose level of 1.8 mg/kg, given the relatively narrow range of exposures.

Table 28: Summary of the Results for Exposure-Efficacy Analysis.

Endpoint	Analysis Type	N Evaluable	N (%) with Event	p-value
Analysis based on the supportive studies				
BOR (INV)	Logistic regression	76	31 (40.8%)	0.037
OR at Cycle 8 (INV)		76	23 (30.3%)	0.014
Analysis based on the pivotal study				
BOR (IRC)	Logistic regression	44	26 (59.1%)	0.852
CR at primary assessments (IRC)		44	19 (43.2%)	0.521
OR at primary assessments (IRC)		44	21 (47.7%)	0.956
Time to Relapse	Cox PH model	26	11 (42.3%)	0.057
PFS		44	26 (59.1%)	0.102
OS		44	24 (54.5%)	0.048

(Source: Applicant's Exposure-Safety and Exposure-Efficacy Report, Table B)

APPLICANT'S CONCLUSIONS

Exposure-safety analyses were performed using data collected in the supportive studies (R/R DLBCL patients in pooled DCS4968g and GO27834 studies up to 8 cycles of treatment, with polatuzumab doses of 0.1-2.4 mg/kg Q3W as a single agent or in combination with rituximab or obinutuzumab) and in the pivotal study (R/R DLBCL patients in GO29365 study for up to 6 cycles of treatment, with polatuzumab dose of 1.8 mg/kg Q3W in combination with bendamustine and rituximab or obinutuzumab). Exposure-efficacy analyses were performed using the above described studies except that the obinutuzumab combination data were not included.

The exposure-response analysis results based on supportive studies suggested that the dose increase may be associated with potentially higher toxicity for some safety endpoints, and the dose decrease may be associated with lower efficacy. The results based on pivotal study indicated that within the exposure range of 1.8 mg/kg there was no apparent exposure safety relationship. An early dose modification due to AE with increased acMMAE C_{max} was identified in the pivotal study, but the probability of dose modification due to AE was not significantly impacted. For exposure-efficacy analysis of the pivotal study, increased acMMAE AUC may be associated with longer OS. It is acknowledged that the analysis of pivotal study is limited by the data from a single dose level of 1.8 mg/kg, given the relative narrow exposure range.

Overall, the exposure-response analysis results and the favorable benefit-risk profile of 1.8 mg/kg polatuzumab up to 6 cycles in combination with rituximab and bendamustine for treating R/R DLBCL patients supported the proposed dosing regimen.

Exposure – Safety Analysis Plots:

Graphical presentation of the exposure-safety relationships that were significant are presented. The relationship between peripheral neuropathy and acMMAE is depicted in **Figure 3**. **Figure 4** shows the relationship for anemia with the unconjugated MMAE.

The remaining significant exposure-safety relationships determined are with changes to the dosing regimen because of an AE or the magnitude of the dose intensity. The applicant's cox proportional hazards analysis indicated significant trends for time to first dose modification with unconjugated MMAE AUC and Cmax in the supportive studies (**Table 29**) and for acMMAE Cmax in the pivotal study (**Table 30**). Multivariate analysis did not indicate any other significant covariates.

Table 29: Analysis based on the supportive studies: base models for time to the first dose modification due to AE.

Model description	β	SE	RSE (%)	HR	HR95CI	p-value
acMMAE AUC	-0.00018	0.000195	108.91	0.9998	0.9994-1	0.359
acMMAE Cmax	-0.00053	0.001008	191.02	0.9995	0.9975-1.001	0.601
MMAE AUC	0.02824	0.009677	34.27	1.029	1.009-1.048	0.004
MMAE Cmax	0.4002	0.1318	32.94	1.492	1.152-1.932	0.002

Source: Supp_ACMMAEAUType_1_baseModelTableTTE.csv, Supp_ACMMAECAUType_1_baseModelTableTTE.csv, Supp_MMMAEUAUType_1_baseModelTableTTE.csv, Supp_MMMAECAUType_1_baseModelTableTTE.csv, (BLA_ER_AE_Supp.R)
 β = estimate for exposure parameter(s); SE = standard error of β estimate; RSE = relative standard error of β estimate (%); HR = hazard ratio computed as $\exp(\beta)$; HR95CI = 95% confidence intervals on hazard ratio.

(Source: Applicant's Exposure-Safety and Exposure-Efficacy Report, Table 27)

Table 30: Analysis based on the pivotal study: base models for time to the first dose modification due to AE.

Model description	β	SE	RSE (%)	HR	HR95CI	p-value
acMMAE AUC	0.000547	0.000376	68.7	1.001	0.9998-1.001	0.145
acMMAE Cmax	0.004701	0.001805	38.4	1.005	1.001-1.008	0.009
MMAE AUC	0.00548	0.01168	213.17	1.005	0.9827-1.029	0.639
MMAE Cmax	0.09536	0.1562	163.76	1.1	0.81-1.494	0.541

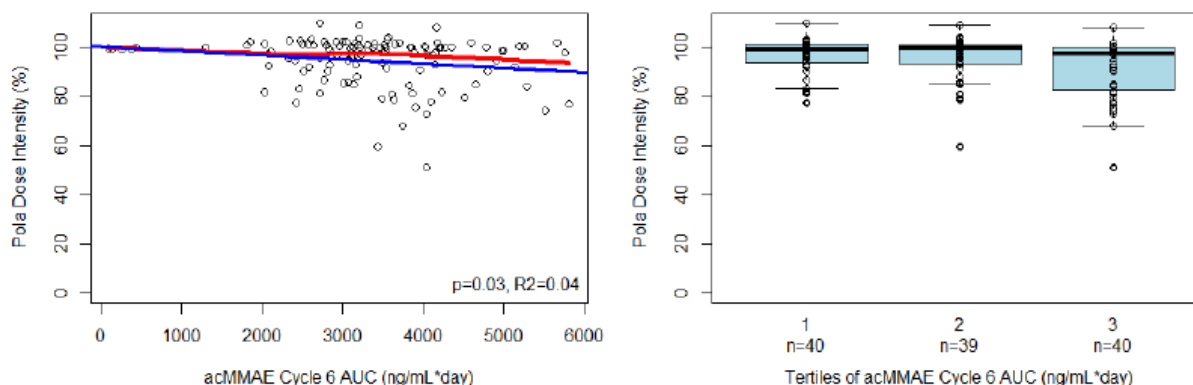
Source: Main_ACMMAEAUType_1_baseModelTableTTE.csv, Main_ACMMAECAUType_1_baseModelTableTTE.csv, Main_MMMAEUAUType_1_baseModelTableTTE.csv, Main_MMMAECAUType_1_baseModelTableTTE.csv (BLA_ER_AE_Main.R)
 β = estimate for exposure parameter(s); SE = standard error of β estimate; RSE = relative standard error of β estimate (%); HR = hazard ratio computed as $\exp(\beta)$; HR95CI = 95% confidence intervals on hazard ratio.

(Source: Applicant's Exposure-Safety and Exposure-Efficacy Report, Table 29)

Relationships between dose intensity and exposure were evaluated with linear regression and significant relationships were observed in the supportive studies for acMMAE AUC (**Figure 26**) and Cmax (**Figure 27**).

Figure 26: Analysis based on the supportive studies: dose intensity, acMMAE AUC.

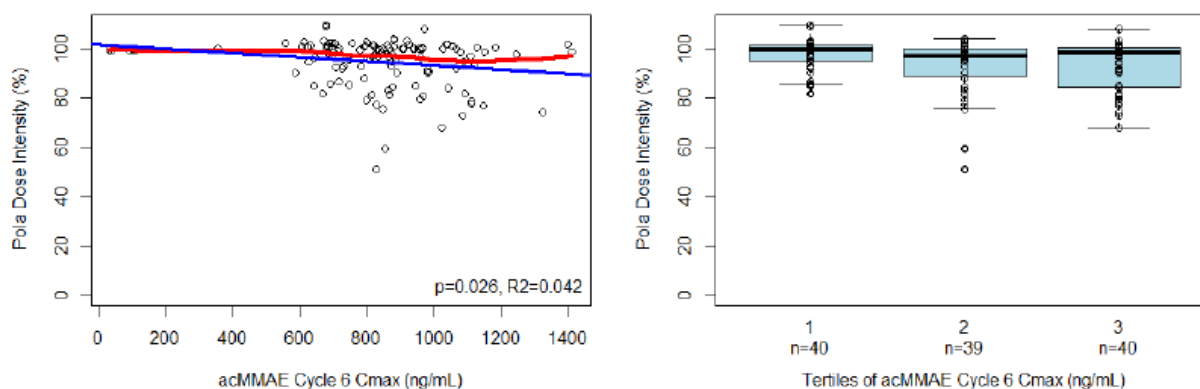
Red line: lowess trend line; blue line: linear regression: R^2 and p-values for the linear regression are listed on the plot.



(Source: Applicant's Exposure-Safety and Exposure-Efficacy Report, Figure 59)

Figure 27. Analysis based on the supportive studies: dose intensity, acMMAE Cmax.

Red line: lowess trend line; blue line: linear regression: R^2 and p-values for the linear regression are listed on the plot.

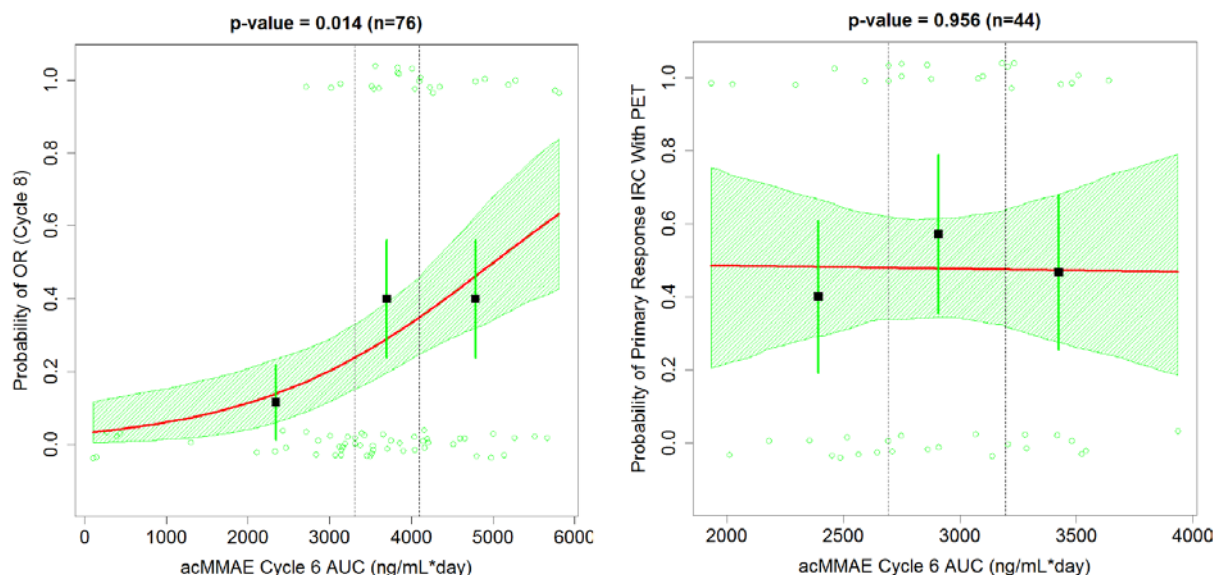


(Source: Applicant's Exposure-Safety and Exposure-Efficacy Report, Figure 60)

Exposure – Efficacy Analysis Plots

The relationship for the investigator best overall response in both the supportive and pivotal studies is shown in *Figure 1*. The relationship for investigator adjudicated overall response is depicted below in *Figure 28*. The cox-proportional hazards model for OS is shown in *Table 31*. Multivariate analysis identified three other factors that may be of relevance. The applicant excluded them based on their backward elimination criteria alpha of 0.001. In all models did the applicant prioritize keeping exposure in the model while other covariates were eliminated first regardless of the magnitude of the p-value for exposure relative to the other covariates being tested.

Figure 28: Exposure-response relationship for OR at cycle 8 in the supportive studies (left panel) and pivotal study (right panel).



(Source: Applicant's Exposure-Safety and Exposure-Efficacy Report, Figures 68 and 71)

Table 31: Multivariate cox proportional hazards model for overall survival utilizing data from the pivotal study

Parameters	β	SE	RSE (%)	HR	HR95CI	p-value
acMMAE AUC	-0.00103	0.000434	42.24	0.999	0.9981-0.9998	0.018
Log(BBCC)	-0.3567	0.1237	34.67	0.700	0.5493-0.892	0.004
Ann Arbor = 4	1.481	0.5073	34.25	4.397	1.627-11.88	0.004
ECOG0 = 0	-1.567	0.5903	37.67	0.2087	0.06562-0.6638	0.008

Source: Main_ACMMAEAUType_OS_AllModelsTable.csv (BLA_ER_AE_Main.R)

β = estimate for exposure parameter(s); SE = standard error of β estimate; RSE = relative standard error of β estimate (%); HR = hazard ratio computed as $\exp(\beta)$; HR95CI = 95% confidence intervals on hazard ratio.

(Source: Applicant's Exposure-Safety and Exposure-Efficacy Report, Table 54)

Reviewer's Comments:

There are two aspects of these analyses that are critical to note:

- In the pivotal study the planned dose amount was used for the calculation of AUC and Cmax rather than the actual dose up to the time of the AE. This means that the AUC is simply a reflection of the individual's clearance value and not actual dosing.
- In testing the multivariate covariate effects during the backward elimination, exposure was kept in the model while other covariates were removed first regardless of the relative magnitude of the p-value. Thus, exposure was assumed to be significant despite the possibility that correlations with other more significant covariates may negate the need for exposure in the model.

Additionally, the reviewer evaluated the distribution of disease factor across the exposure tertile as it may impact the evaluation of exposure-safety and exposure-efficacy relationships (**Table 32** and **Table 33**). An imbalance was identified for ECOG and LDH. In general, patients with higher acMMAE exposure are associated with ECOG status ≥ 1 , while the trend for LDH across exposure tertiles was opposite between pivotal study and supportive studies. Higher acMMAE exposure are associated with higher LDH in supportive studies, and with lower LDH in the pivotal study. Thus, the imbalance LDH and ECOG score may potentially confound the observed exposure-response relationships for efficacy and safety, as exposure remained in the model for each backward elimination step regardless of its significance. No consistent trends across exposure tertiles were noted for the unconjugated MMAE moiety.

Table 32: Patient disease characteristics at baseline for pivotal study 365

	acMMAE AUC Tertiles			Unconjugated MMAE AUC Tertiles		
	1	2	3	1	2	3
N	38	37	38	38	37	38
Mean Cycle 6 AUC	2.37	3.13	4.35	14.2	25.4	57.0
Age (yr)	66.2	64.5	66.3	64.6	65.4	65.7
ECOG 0 (%)	39	38	21	34	38	26
ECOG 1 (%)	37	46	63	47	43	57
ECOG 2 (%)	21	16	11	13	16	19
LDH (U/L)	648	540	423	618	426	569
Prior Lines Therapy	2.50	2.51	2.45	2.61	2.43	2.42
Last Duration of Response <12 mo	86%	79%	81%	85%	70%	89%
Bulky Disease	21%	41%	26%	26%	35%	26%
Stage 3-4 Disease	86%	78%	78%	79%	84%	71%
IPI High Risk (≥ 4)	32%	32%	24%	21%	30%	37%

Table 33: Patient disease characteristics at baseline for the supportive studies

	acMMAE AUC Tertiles			Unconjugated MMAE AUC Tertiles		
	1	2	3	1	2	3
N	42	41	42	42	41	42
Mean Cycle 6 AUC	1.74	3.46	4.71	15.7	31.1	67.0
Age (yr)	64.0	65.6	66.0	64.5	65.8	65.2
ECOG 0 (%)	29	27	22	24	29	24
ECOG 1 (%)	55	63	63	55	54	71
ECOG 2 (%)	17	10	15	19	17	5
LDH (U/L)	435	736	737	845	705	537
Prior Lines Therapy	4.12	3.10	3.19	3.6	3.3	3.5
Last Duration of Response <12 mo	93%	97%	92%	50%	73%	69%
Bulky Disease	71%	80%	62%	79%	68%	67%
Stage 3-4 Disease	29%	68%	60%	36%	66%	55%
IPI High Risk (≥ 4)	2%	24%	17%	17%	10%	17%

4.4 Physiologically Based Pharmacokinetic (PBPK) Analyses

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses report 1090612 entitled "Assessment of CYP3A Mediated Drug-Drug Interaction for Anti-CD79b-vc-MMAE Antibody-Drug Conjugate (Polatuzumab Vedotin or DCDS4501A) Using Simcyp PBPK Model" to support the intended uses.

Specifically, the Applicant applied the PBPK modeling approach to evaluate the effects of a strong CYP3A inhibitor (ketoconazole), and a strong CYP3A inducer (rifampin) on the PK of unconjugated monomethyl auristatin E (MMAE), and the effects of unconjugated MMAE on the PK of a CYP3A substrate (midazolam).

The Division of Pharmacometrics has reviewed the report dated 08 August 2018, the updated report dated 20 March 2019, the updated supporting modeling files, and the Applicant's responses to our information requests dated 22 March 2019 and concluded the followings.

- The PBPK model is adequate to predict the effects of a strong CYP3A inhibitor (ketoconazole) on the PK of unconjugated MMAE. The model predicted about 45% increase in the AUC of unconjugated MMAE when polatuzumab vedotin is co-administered with ketoconazole.
- The PBPK model is adequate to predict the effects of a strong CYP inducer (rifampin) on the PK of unconjugated MMAE. The model predicted about 63% decrease in the AUC of unconjugated MMAE when polatuzumab vedotin is co-administered with rifampin.
- The PBPK model is adequate to predict the effects of unconjugated MMAE on the PK of a sensitive CYP3A substrate (midazolam). The model predicted no change in the midazolam AUC when it was co-administered with polatuzumab vedotin (1.8 mg/kg).

Background

Polatuzumab vedotin is a CD79b-targeted antibody drug conjugate (ADC) that preferentially delivers a potent anti-mitotic agent (monomethyl auristatin E [MMAE]) to B cells. MMAE, upon releasing from valine-citrulline-MMAE (vc-MMAE) antibody-drug conjugates (ADCs), is expected to behave like small molecules that could be metabolized and cleared through cytochrome P450 (CYP) and transporter processes. In vitro, unconjugated MMAE is a substrate of CYP3A and P-gp, and a reversible and time-dependent CYP3A inhibitor. The proposed dose is 1.8 mg/kg administered on Day 1 of every 21-day treatment cycle for 6 cycles.

Polatuzumab vedotin contains the same linker drug as brentuximab vedotin, a previously approved ADC. Following an intravenous (i.v.) infusion of 1.8 mg/kg brentuximab vedotin for about 30 minutes, it was found that approximately 23.5% of the MMAE was recovered in both urine and feces over a 1-week period in an open label study (Han et al. The Journal of Clinical Pharmacology (2013);53(8):866-77). Of

the MMAE recovered, the median percentage of MMAE excreted in feces was 72% (range 59–77%), with the remainder excreted in urine. The Applicant's in-house bile-duct cannulated rat study with radiolabeled unconjugated MMAE dosing showed that approximately 60% of the total radioactivity recovered in bile (over 6 hours) was excreted as unchanged MMAE. These data suggested that unconjugated MMAE could be eliminated via biliary clearance pathway.

In the same open label study (Han et al. The Journal of Clinical Pharmacology (2013);53(8):866-77), the DDI potentials were evaluated for brentuximab vedotin to assess the effect of brentuximab vedotin on the PK of a sensitive CYP3A substrate (midazolam), and to assess the effect of CYP3A modulators (ketoconazole and rifampin) on the PK of brentuximab vedotin (ADC and unconjugated MMAE).

The objectives of the PBPK analyses were to evaluate the effects of CYP3A modulators (ketoconazole and rifampin) on the PK of unconjugated MMAE, and the effect of polatuzumab vedotin on a sensitive CYP3A substrate (midazolam) following administration of polatuzumab vedotin.

Methods

Software

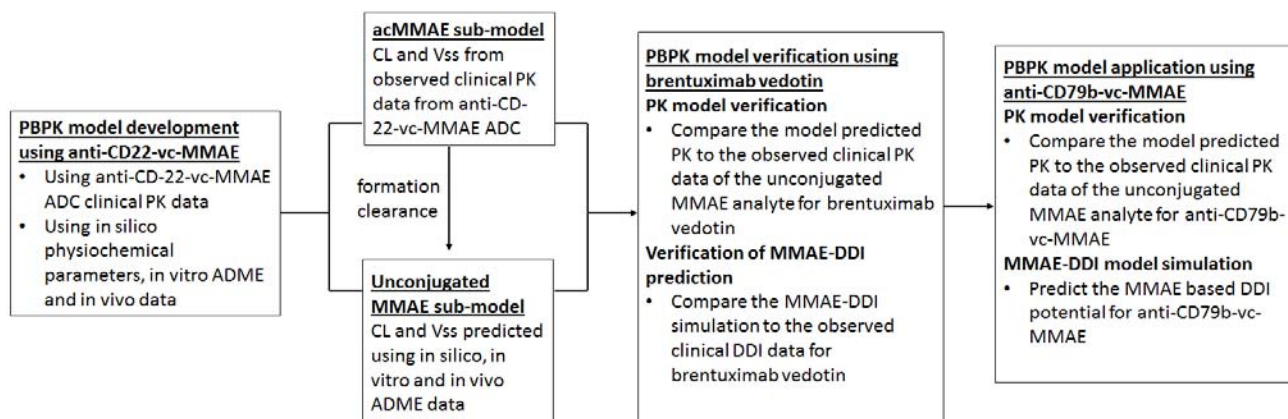
The PBPK model was originally developed in Simcyp V12. In response to the FDA's IR, the Applicant updated the simulations using Simcyp V17 for acMMAE and unconjugated MMAE PK prediction following administration of polatuzumab vedotin, and the DDI prediction between polatuzumab vedotin and CYP3A modulators and substrate. Simulations conducted by the reviewer were in Simcyp V17.

PBPK analyses strategy

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As described in **Error! Reference source not found.**, the PBPK model was first developed for anti-CD22-vc-MMAE, verified for brentuximab vedotin regarding PK and DDI, and polatuzumab vedotin (anti-CD79b-vc-MMAE) regarding PK, and applied for assessing the drug-drug interaction (DDI) potentials for polatuzumab vedotin. The three ADCs, anti-CD22-vc-MMAE, brentuximab vedotin, and polatuzumab vedotin, contained the same linker-drug. anti-CD22-vc-MMAE was an in-house ADC and consisted of a humanized anti-CD22 monoclonal IgG1 antibody conjugated to MMAE via a protease-labile linker, MC-VC-PABC, and was terminated. The PBPK model treated acMMAE (antibody conjugated MMAE) as a parent drug, and unconjugated MMAE as a metabolite.

Figure 29: Applicant's PBPK modeling approach for assessing the drug-drug interaction (DDI) potential for polatuzumab vedotin



Source: Figure 1 in the PBPK report 1090612 dated 08 August 2018.

PBPK model structures and development

acMMAE model (being treated as the parent)

The acMMAE model parameters were obtained by non-compartmental analysis (NCA) of the observed clinical PK data following i.v. infusion of anti-CD22-vc-MMAE (Table 34). The model assumed all acMMAE was eventually converted to unconjugated MMAE before being eliminated from the body. There was no human data to directly support this assumption. However, a rat ADME study dosed with anti-CD22-vc-MMAE ADCs showed that the majority of acMMAE was catabolized to MMAE prior to subsequent elimination. The same volume of distribution and slightly different parameters were obtained by non-compartmental analysis (NCA) of the observed clinical PK data (study DCS4968g) following i.v. infusion of polatuzumab vedotin at the 1.8 mg/kg and 2.4 mg/kg dose levels (Table 34). In the PBPK model, the CL_{int} values were back calculated based on the NCA clearance using the retrograde model provided by Simcyp. An arbitrary enzyme (CYP2E1) was selected.

Unconjugated MMAE model (being treated as the metabolite)

The unconjugated MMAE model was implemented as the metabolite of acMMAE and input parameters are described in Table 34. The V_{ss} was calculated using Rodgers and Rowland (2006) equations. The other distribution related parameters (V_{sac}, k_{in}, and k_{out}) were obtained by fitting the model against observed unconjugated MMAE PK data following the i.v. infusion of anti-CD22-vc-MMAE. Based on in vitro, pre-clinical, and excretion study published by Han et al., the total clearance (CL) of unconjugated MMAE was assigned to hepatic (50%, mainly via CYP3A) and biliary (50%) pathways. The in vivo metabolic CL was estimated to be 4 L/hr based on in vitro intrinsic CL (1.9 µL/min/million cells) measured in human hepatocytes using the in vitro in vivo extrapolation (IVIVE) approach built in Simcyp. Biliary clearance (CL_{biliary}) was assumed to account for about 50% of total CL of unconjugated MMAE. Therefore, the total CL of unconjugated MMAE (hepatic and biliary) was estimated to be 8 L/hr. Sensitivity analysis was performed to vary f_{m,cyp3a} between 0.3-0.5.

Table 34: Input parameters for acMMAE and unconjugated MMAE models

Parameters	Unconjugated MMAE	Reference	acMMAE	Reference
Dose (mg, 70kg) i.v. infusion for 0.5-1.5 hrs				
anti-CD22-vc-MMAE 2.4 mg/kg	NA	NA	3	Calculated ^a
brentuximab vedotin 1.2/1.8/2.7 mg/kg			1.5/2.3/3.5	
polatuzumab vedotin 1.8/2.4 mg/kg			2.3/3.1	
Drug substance properties				
MW	717.98 g/mol	Molecule formula	NA	
clogP	2.6	Calculated in MoKa		
Compound type	Monoprotic base	Molecule formula		
cpKa	8.08	Calculated in MoKa		
B/P ratio	1.45	in-house data		
f _{u,plasma}	0.178	Chen et al. 2015		
Distribution model (minimal PBPK model with a single adjusting compartment) parameters				
V _{ss} (L/kg)	8.4	Simcyp predicted	0.09	NCA of clinical data ^b
V _{sac} (L/kg)	2.0	Simcyp best fit	0.04	Simcyp best fit
k _{in} (hr ⁻¹)	8x10 ⁻⁴		0.00727	
k _{out} (hr ⁻¹)	1x10 ⁻⁸		0.00249	
Elimination parameters				
CL _{int} (μL/min/pmol)	0.04486 (CYP3A4)	IVIVE based on CL _{int} from hepatocyte, and using Simcyp retrograde model to achieve f _{m,CYP3A4} of approximately 50% of total CL (8 L/hr)	0.000288	Back calculated based on CL = 21.8 mL/day/kg ^c
	0.04 (CYP3A4) + 1.15 pmol/min/mg protein (HLM)	Calculated using Simcyp retrograde model to achieve f _{m,CYP3A4} of 40% of total CL (8 L/hr, adopted from the verified model)	0.000463	Back calculated based on CL = 38.2 mL/day/kg ^d
			0.000233	Back calculated based on CL = 19.4 mL/day/kg ^e
f _{umic}	1		1	
CL _{biliary} (μL/min/10 ⁶)	2.15	Assume approximately 50% of total CL (Han et al.), and back calculated by Simcyp	0	
CYP3A reversible inhibition parameters				
K _i (μM)	5	EMA assessment report, Chen et al.	NA	
f _{umic}	0.985	Simcyp calculated		
CYP3A time-dependent inhibition parameters				
K _{inact} (min ⁻¹)	0.10	EMA assessment report, Chen et al.	NA	
K _I (μM)	1.128			
f _{umic}	0.971	Simcyp calculated		

Source: Tables 1-4 in the PBPK report 1090612 dated 20 March 2019. Chen et al. Clin Pharmacokinet (2015);54:81-93. Han et al. The Journal of Clinical Pharmacology (2013);53(8):866-77. ^a acMMAE equivalent dose = (dose/MW_{ADC})x^aDARxMW_{MMAE}x70, where MW_{ADC} was the molecular weight of the ADC (146,455 dalton for anti-CD22-vc-MMAE, 153,000 dalton for brentuximab vedotin, and 145,001 dalton for polatuzumab vedotin; MW_{MMAE} was the molecular weight of the unconjugated MMAE (718 g/mol); DAR was the drug antibody ratio (3.5 for anti-CD22-vc-MMAE, 4 for brentuximab vedotin, and 3.7 for polatuzumab vedotin), and 70 (kg) was the average body weight. ^b PK parameters from NCA (non-compartmental analysis) for the acMMAE analyte in the clinical study of anti-CD22-vc-MMAE ADC or in the polatuzumab vedotin clinical study DCS4968g at the 1.8 mg/kg and 2.4 mg/kg dose levels. ^c Clearance obtained from NCA for the acMMAE analyte in the clinical study of anti-CD22-vc-MMAE

ADC. Clearance obtained from NCA for the acMMAE analyte in the polatuzumab vedotin clinical study DCS4968g^d at the 1.8 mg/kg dose level or^e at the 2.4 mg/kg doses level.

PBPK model verification

The PBPK model predictions were compared to the observed PK and DDI for the following scenarios.

- acMMAE and unconjugated MMAE PK following an i.v. infusion of 2.4 mg/ kg anti-CD22-vc-MMAE ADC
- unconjugated MMAE PK following i.v. infusion of brentuximab vedotin at dose levels of 1.2, 1.8, and 2.7 mg/kg (study SG035-0001)
- DDI between brentuximab vedotin and ketoconazole, rifampin, and midazolam
- acMMAE and unconjugated MMAE PK following i.v. infusion of polatuzumab vedotin at dose levels of 1.8 and 2.4 mg/kg (study DCS4968g)

PBPK model application

The developed PBPK models were used to predict the DDIs between a 1.8 mg/kg dose of polatuzumab vedotin and CYP3A modulators (ketoconazole, and rifampin), and a substrate (midazolam).

Reviewer's comments: The applicant's approach for model development, validation, and application appears acceptable. The PBPK model was originally developed in Simcyp V12. In response to FDA's IR, the Applicant updated the PBPK model with Simcyp V17 for polatuzumab vedotin related predictions (PK and DDI). One of the major differences between V12 and V17 was the increase in rifampin CYP3A maximal induction potential (Ind_{max}).

Results

1. Can the PBPK model predict the PK of unconjugated MMAE after administration of polatuzumab vedotin?

Yes. The predicted and observed PK parameters of acMMAE and unconjugated MMAE following administration of various ADCs are summarized in Table 35. The PBPK model was originally developed in Simcyp V12. In response to FDA's IR, the Applicant updated the polatuzumab vedotin related simulations using Simcyp V17. The reviewer conducted simulations predicting the PK of acMMAE and unconjugated MMAE following administration of anti-CD22-vc-MMAE or brentuximab vedotin using the Applicant submitted workspace files in Simcyp V17. In general, the version difference did not impact the PK predictions for acMMAE and unconjugated MMAE following i.v. infusion of the three ADCs.

Simulations were conducted in healthy volunteers while observed PK were obtained in patients. The Applicant incorporated a cancer population published by Cheeti et al. (Biopharm Drug Dispos. 2013 Apr;34(3)). Briefly, demographic data such as age, sex and body weight, and clinical laboratory measurements such as albumin, alpha-1 acid glycoprotein (AAG) and hematocrit were collected in

about 2500 patients with cancer. The simulated PK parameters for unconjugated MMAE using the cancer population were comparable to the predictions using healthy volunteers. Therefore, all simulations were conducted using healthy volunteers.

The predicted vs. observed C_{max} and AUC ratios were 0.55-1.35. The predicted AUCs were generally lower than the observed AUCs which could be due to the difference in AUC calculation. The predicted AUCs were calculated for a 21-day duration while the observed AUCs were calculated as AUC_{inf}. The predicted PK profiles for acMMAE and unconjugated MMAE agreed with observed PK profiles following i.v. infusion of polatuzumab vedotin (Figure 30).

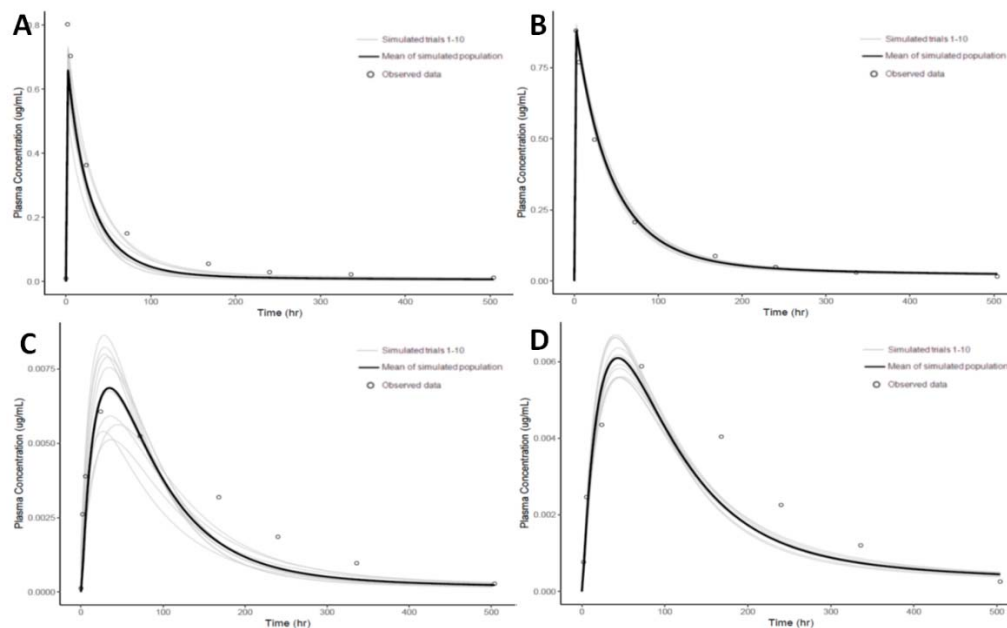
Table 35: Summary of predicted (pred.) and observed (obs.) mean PK parameters for acMMAE and unconjugated MMAE after i.v. infusion of anti-CD22-vc-MMAE, brentuximab vedotin, or polatuzumab vedotin.

ADC	Dose (mg/kg)	Cmax (µg/mL)			AUC (µg*day/mL)		
		Pred.	Obs.	Pred./Obs.	Pred. ^c	Obs. ^d	Pred./Obs.
Analyte: acMMAE							
Anti-CD22-vc-MMAE (n=11)	2.4	0.89 ^a	0.89	1.00	2.06 ^a	2.34	0.88
Polatuzumab vedotin (n=6)	1.8	0.71 ^b	0.80	0.89	1.08 ^b	1.86	0.58
Polatuzumab vedotin (n=45)	2.4	0.90 ^b	0.89	1.01	2.44 ^b	2.61	0.93
Analyte: Unconjugated MMAE							
antiCD22-vc-MMAE (n=11)	2.4	0.0073 ^a	NA	NA	0.0047 ^a	0.00544	0.86
Brentuximab vedotin (n=4)	1.2	0.00365 ^a	0.00272	1.34	0.0225 ^a	0.0203	1.11
Brentuximab vedotin (n=12)	1.8	0.0056 ^a	0.00497	1.13	0.0354 ^a	0.037	0.96
Brentuximab vedotin (n=12)	2.7	0.0085 ^a	0.007	1.21	0.0537 ^a	0.0532	1.01
Polatuzumab vedotin (n=6)	1.8	0.0073 ^b	0.0072	1.01	0.037 ^b	0.052	0.71
Polatuzumab vedotin (n=42)	2.4	0.0064 ^b	0.007	0.91	0.042 ^b	0.053	0.79

Source: PBPK report 1090612 dated 20 March 2019, and response to FDA request for information submitted on 22 March 2019. ^a predicted in Simcyp V12, ^b predicted in Simcyp V17, ^c predicted AUCs were calculated for a 21-day duration ^d observed AUCs were calculated as AUC_{inf}

Figure 30: Simulated and observed plasma concentration vs. time profiles of (A) acMMAE following administration of a 1.8 mg/kg dose of polatuzumab vedotin, (B) acMMAE following administration of a 2.4 mg/kg dose of polatuzumab vedotin, (C) unconjugated MMAE following administration of a 1.8

mg/kg dose of polatuzumab vedotin, and (D) unconjugated MMAE following administration of a 2.4 mg/kg dose of polatuzumab vedotin.



Source: Figure 4-7 of PBPK report 1090612 dated 20 March 2019

2. Can the PBPK models be used to predict the effects of CYP3A modulators (ketoconazole and rifampin) on the PK of unconjugated MMAE following administration of polatuzumab vedotin?

Yes. The PBPK model was verified by comparing the predicted to the observed effects of CYP3A modulators (ketoconazole and rifampin) on the PK of unconjugated MMAE following i.v. infusion of brentuximab vedotin (Table 36). The PBPK model was then applied to predict the effects of CYP3A modulators (ketoconazole and rifampin) on the PK of unconjugated MMAE following i.v. infusion of polatuzumab vedotin.

In vitro, MMAE is a substrate for CYP3A and P-gp. P-gp may play a role in MMAE transport in the liver as it is partially eliminated via biliary clearance. On the other hand, ketoconazole and rifampin interact with both CYP3A and P-gp pathways. The unconjugated MMAE PBPK model did not incorporate P-gp. In response to a FDA's IR, the Applicant provided the following justification for not including P-gp in the model.

- There was no clear evidence that enterohepatic reabsorption was involved in MMAE transport based on bile duct rat study, and low in vitro Caco-2 permeability.
- Although P-gp may be involved in the transport of unconjugated MMAE, the magnitude is expected to be low as suggested by the brentuximab vedotin clinical DDI results where the unconjugated MMAE AUC was increased by about 34% when brentuximab vedotin is co-

administered with ketoconazole (a CYP3A and P-gp inhibitor) or decreased by about 46% when co-administered with rifampin (a CYP3A and P-gp inducer).

- The magnitude of P-gp inhibition on an i.v. administered substrate is expected to be low. This was based on a survey of a drug interaction database (<https://www.druginteractioninfo.org/>) for the studies that assessed the effects of P-gp inhibitors on i.v. digoxin (a P-gp substrate). The survey showed that when digoxin was co-administered with a P-gp inhibitor, digoxin AUC was increased with a median value of 46% (range: 24.2% to 180%, n=5), and the systemic clearance decreased with a median value of 34.3% (range: 18.4% to 64%, n=18).
- There are no relevant clinical data to verify the P-gp contribution even though it were incorporated into the model.

The reviewer noticed that the survey indicated the digoxin (i.v.) AUC could be increased as high as 180% (i.e., more than 2-fold) when it was co-administered with a P-gp inhibitor although the number of studies may be limited. The other justifications provided by the Applicant are acceptable. However, it should be noted that not incorporating P-gp in the model may overestimate the CYP3A contribution to the overall clearance ($f_{m,cyp3a}$) because the observed DDI effects from both CYP3A and P-gp were allocated to the CYP3A pathway.

The $f_{m,cyp3a}$ (fraction of unconjugated MMAE being metabolized by CYP3A) value is essential for predicting the effects of CYP3A modulators on the PK of unconjugated MMAE. The Applicant tested three $f_{m,cyp3a}$ values (0.3, 0.4, or 0.5) in Simcyp V12, and selected $f_{m,cyp3a} = 0.4$ as the final parameter for DDI assessment by comparing the predicted to the observed effect of ketoconazole and rifampin on the PK of unconjugated MMAE. One of the major changes between Simcyp V12 and V17 was the increase in rifampin CYP3A maximal induction potential (Ind_{max}) which was changed from 8 to 16. The reviewer conducted simulations to evaluate the impact of version difference on the DDI prediction and $f_{m,cyp3a}$ selection for brentuximab vedotin.

As shown in Table 36, the differences in versions did not impact much on the PK prediction and DDI prediction with ketoconazole (a strong CYP3A inhibitor). In both V12 and V17, using a $f_{m,cyp3a}$ of 0.3 predicted lower but closer AUCR to the observed effect of ketoconazole on the PK of unconjugated MMAE. Using a $f_{m,cyp3a}$ of 0.4 predicted a stronger DDI effect than using a $f_{m,cyp3a}$ of 0.3. Nevertheless, using either $f_{m,cyp3a}$ of 0.3 or 0.4, the predicted PK and PK ratios were within 0.78-1.12 for the DDI with ketoconazole.

The DDI effect with rifampin (a strong CYP3A inducer) was predicted to be stronger (i.e., lower C_{maxR} and AUCR) using V17 than using V12 due to the increase in rifampin CYP3A Ind_{max} . In V17, using a $f_{m,cyp3a}$ of 0.3 predicted closer AUCR to the observed effect of rifampin on the PK of unconjugated MMAE compared to using a $f_{m,cyp3a}$ of 0.4 (Table 36). The Applicant selected $f_{m,cyp3a} = 0.4$ based on the simulations of the effects of both ketoconazole and rifampin on the PK of unconjugated MMAE in V12. Overall, using $f_{m,cyp3a} = 0.4$ will provide more conservative estimation of DDI potentials compared to using $f_{m,cyp3a} = 0.3$. The impact of version and $f_{m,cyp3a}$ differences on DDI prediction for polatuzumab vedotin was further evaluated.

Table 36: Summary of observed and predicted unconjugated MMAE PK following administration of brentuximab vedotin with or without coadministration with CYP3A modulators

PK	Obs. (CV%)	f _{m,cyp3a} = 0.3				f _{m,cyp3a} = 0.4			
		V12		V17		V12		V17	
		Pred.	Pred./Obs.	Pred.	Pred./Obs.	Pred.	Pred./Obs.	Pred.	Pred./Obs.
Ketoconazole 400 mg QD from Cycle 1, Day 19 through Cycle 2, Day 21; brentuximab vedotin 1.2 mg/kg i.v. over 30 min equivalent to 1.5 mg acMMAE, n=16									
AUC (µg/mL*h)	0.6396 (71)	0.61	0.95	0.61	0.96	0.51	0.80	0.52	0.81
T _{max} (h)	47 (23, 168)	52	1.11	52	1.10	48	1.02	48	1.02
C _{max} (ng/mL)	4.11 (71)	3.59	0.87	3.58	0.87	3.29	0.80	3.28	0.80
AUC _{inh} (µg/mL*h)	0.858 (126)	0.78	0.91	0.80	0.93	0.75	0.88	0.77	0.90
T _{maxinh} (h)	59 (5, 97)	59	1.00	59	1.00	58	0.99	58	0.98
C _{maxinh} (ng/mL)	5.13 (114)	4.04	0.79	4.05	0.79	3.98	0.78	4.00	0.78
AUCR	1.34 (0.98 – 1.84)	1.28	0.96	1.30	0.97	1.47	1.10	1.50	1.12
C _{max} R	1.25 (0.90-1.72)	1.13	0.90	1.13	0.90	1.21	0.97	1.22	0.98
Rifampin 600 mg QD from Cycle 1, Day 14 through Cycle 2, Day 21; brentuximab vedotin 1.8 mg/kg i.v. over 30 min equivalent to 2.3 mg acMMAE, n=14									
AUC (µg/mL*h)	0.961 (53)	0.93	0.97	0.92	0.96	0.78	0.81	0.77	0.80
T _{max} (h)	72 (24, 120)	51	0.71	51	0.71	48	0.67	47	0.66
C _{max} (ng/mL)	4.98 (67)	5.48	1.10	5.43	1.09	4.97	1.00	4.97	1.00
AUC _{inh} (µg/mL*h)	0.517 (38)	0.54	1.05	0.42	0.80	0.38	0.74	0.28	0.55
T _{maxinh} (h)	36 (8, 96)	40	1.10	35	0.98	35	0.96	30	0.83
C _{maxinh} (ng/mL)	2.80	4.13	1.47	3.52	1.26	3.32	1.19	2.75	0.98
AUCR	0.54 (0.43-0.68)	0.58	1.08	0.45	0.84	0.49	0.91	0.37	0.68
C _{max} R	0.56 (0.42-0.76)	0.75	1.35	0.65	1.16	0.67	1.19	0.55	0.99

Source: Applicant's updated output files, reviewer's analyses using the Applicant submitted workspace files, and Han et al. The Journal of Clinical Pharmacology (2013);53(8):866-77. Observed T_{max} values are presented as median (range). Observed AUCR and C_{max} are presented as the geometric mean ratios (90% CI) of unconjugated MMAE with / without a perpetrator. Observed AUCs were calculated AUC_{inf} while predicted AUCs were calculated for a 21-day period. PK parameters (C_{max} and AUC) are presented as geometric means. Subscript 'inh' indicates the PK parameter for unconjugated MMAE when brentuximab vedotin is co-administered with ketoconazole or rifampin.

Table 37 is a summary of predicted effects of ketoconazole or rifampin on the PK of unconjugated MMAE PK following administration of polatuzumab vedotin. With a $f_{m,cyp3a}$ of 0.4, the unconjugated MMAE AUC and C_{max} were predicted to increase by 45% and 18%, respectively, when polatuzumab vedotin (1.8 mg/kg) was co-administered with ketoconazole. With a $f_{m,cyp3a}$ of 0.4, the unconjugated MMAE C_{max} and AUC were predicted to decrease by 63% and 41% respectively when polatuzumab vedotin (1.8 mg/kg) was co-administered with rifampin. Based on the above discussion, these could be conservative estimates.

Table 37: Summary of predicted unconjugated MMAE PK following administration of polatuzumab vedotin with or without coadministration with CYP3A modulators

PK	$f_{m,cyp3a} = 0.3$		$f_{m,cyp3a} = 0.4$	
	V12	V17	V12	V17
Ketoconazole 400 mg QD from Cycle 1, Day 19 through Cycle 2, Day 21; polatuzumab vedotin 1.8 mg/kg i.v. over 30 min equivalent to 2.3 mg acMMAE				
AUC ($\mu\text{g/mL}\cdot\text{h}$)	1.03	1.01	0.86	0.86
T _{max} (h)	42	41	40	38
C _{max} (ng/mL)	7.07	0.00730	6.63	6.78
AUC _{inh} ($\mu\text{g/mL}\cdot\text{h}$)	1.34	1.28	1.26	1.25
T _{maxinh} (h)	47	45	47	45

$C_{\max\text{inh}}$ (ng/mL)	7.88	8.06	7.84	7.98
AUCR	1.30	1.27	1.48	1.45
$C_{\max R}$	1.11	1.10	1.18	1.18
Rifampin 600 mg QD from Cycle 1, Day 14 through Cycle 2, Day 21; polatuzumab vedotin 1.8 mg/kg i.v. over 30 min equivalent to 2.3 mg acMMAE				
AUC ($\mu\text{g/mL}\cdot\text{h}$)	1.02	1.01	0.85	0.86
$T_{\max}$ (h)	42	42	40	39
$C_{\max}$ (ng/mL)	7.07	7.11	6.54	6.62
AUC _{inh} ($\mu\text{g/mL}\cdot\text{h}$)	0.59	0.46	0.42	0.32
$T_{\max\text{inh}}$ (h)	33	30	29	26
$C_{\max\text{inh}}$ (ng/mL)	5.50	4.86	4.53	3.88
AUCR	0.58	0.46	0.49	0.37
$C_{\max R}$	0.78	0.68	0.69	0.59

Source: Applicant's updated output files, and reviewer's analyses using the Applicant submitted workspace files. PK parameters ($C_{\max}$ and AUC) are presented as geometric means. Subscript 'inh' indicates the PK parameter for unconjugated MMAE when brentuximab vedotin is co-administered with ketoconazole or rifampin.

3. Can the PBPK model be used to predict the effect of unconjugated MMAE on the PK of a sensitive CYP3A substrate (midazolam)?

Yes. The ability of the Applicant's model to evaluate the effect of unconjugated MMAE on a CYP3A substrate (midazolam) was verified by comparing the predicted to the observed changes in midazolam PK when it was administered with brentuximab vedotin. The model was able to predict the observed lack of effect of brentuximab vedotin on midazolam (i.v.) PK, although it underpredicted midazolam PK published by Han et al. The model was then used to predict the effect of polatuzumab vedotin on midazolam PK.

The Simcyp midazolam model was developed using historically published data which did not include the data set published by Han et al. The midazolam PK outcomes in the paper by Han et al. seem to be higher than those used in building the midazolam PK model by Simcyp. Nevertheless, the PBPK analysis was able to capture the lack of effect of brentuximab vedotin on midazolam (i.v.) PK, as the predicted AUCR and $C_{\max R}$ were close to the observed values (within 15% predictive error).

The reviewer conducted additional simulations to evaluate the effect of unconjugated MMAE on the PK of oral midazolam, and sensitivity analysis on the unconjugated MMAE CYP3A inhibition parameters. Simulations suggested that there was no effect of unconjugated MMAE on the PK of oral midazolam. Increasing the unconjugated MMAE CYP3A inhibition potential by 10-fold did not impact the effect of unconjugated MMAE on the PK of midazolam.

Overall, the Applicant's analysis is adequate to support that MMAE does not affect the PK of a CYP3A substrate at clinically relevant concentrations.

Table 38: Summary of observed and predicted midazolam PK when it is coadministered with 1.8 mg/kg brentuximab vedotin and predicted midazolam PK when it is coadministered with 1.8 mg/kg polatuzumab vedotin. Brentuximab vedotin or polatuzumab vedotin 1.8 mg/kg (equivalent to 2.3 mg acMMAE) i.v. over 30 min on day 1, midazolam (1 mg) i.v. was administered on day 3

	Brentuximab vedotin	Polatuzumab vedotin
--	---------------------	---------------------

		V12		V17		V12	V17
	Obs. (CV%) (n = 15)	Pred.	Pred./Obs.	Pred.	Pred./Obs.	Pred.	Pred.
AUC (µg/mL*h)	0.079 (92)	0.042	0.53	0.039	0.49	0.042	0.042
C _{max} (µg/mL)	0.073 (116)	0.014	0.19	0.022	0.30	0.014	0.024
AUC _{inh} (µg/mL*h)	0.074 (74)	0.042	0.57	0.040	0.54	0.042	0.043
C _{maxinh} (µg/mL)	0.084 (176)	0.014	0.17	0.023	0.27	0.014	0.024
AUCR	0.94 (0.81-1.10)	1.00	1.06	1.00	1.06	1.00	1.00
C _{maxR}	1.15 (0.76-1.74)	1.00	0.87	1.00	0.87	1.00	1.00

Source: Applicant's updated output files, reviewer's analyses using the Applicant submitted workspace files, and Han et al. The Journal of Clinical Pharmacology (2013);53(8):866-77. Observed T_{max} values are presented as median (range). Observed AUCR and C_{max} are presented as the geometric mean ratios (90% CI) of midazolam with / without a perpetrator. Observed AUCs were calculated AUC_{inf} while predicted AUCs were calculated for 24-hour interval. PK parameters (C_{max} and AUC) are presented as geometric means. Subscript 'inh' indicates the PK parameter for midazolam when it is co-administered with brentuximab vedotin or polatuzumab vedotin.

Conclusions

The Applicant's PBPK model is adequate to evaluate the effects of a strong CYP3A inhibitor (ketoconazole), or a strong CYP3A inducer (rifampin) on the PK of unconjugated MMAE, and the effects of unconjugated MMAE on the PK of a CYP3A substrate (midazolam) following administration of polatuzumab vedotin.

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/s/

SALAHELDIN HAMED
05/23/2019 08:41:47 AM

JUSTIN C EARP
05/23/2019 09:10:56 AM

XINYUAN ZHANG
05/23/2019 09:12:45 AM

YUCHING N YANG
05/23/2019 10:07:03 AM

LIAN MA
05/23/2019 10:11:09 AM

GUOXIANG SHEN
05/23/2019 10:16:52 AM

NAM ATIQR RAHMAN
05/23/2019 10:18:24 AM
I concur.