Development of a Generalized Pharmacokinetic Model to Characterize Clinical Pharmacokinetics of Monomethyl Auristatin E (MMAE)-Based Antibody-Drug Conjugates (ADCs)

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ABSTRACT

In this manuscript we have developed a generalized pharmacokinetic (PK) model for monomethyl auristatin E (MMAE)-based antibody-drug conjugates (ADCs) by analyzing clinical PK data from 18 different ADCs across various dosing regimens, targets, and indications. The dose-normalized PK profiles supported the generalizability of PK for MMAE-based ADCs, and the model was capable of simultaneously capturing the PK of four ADC analytes. Additionally, we established linear relationships between dose and PK exposure metrics using reported parameters from the literature, enabling the prediction of typical exposure values across different doses for MMAE-based ADCs. This is the first comprehensive analysis of PK data across different ADCs with a similar linker-payload platform. The generalized PK model lays the groundwork for establishing a generalized exposure-response relationship for MMAE-based ADCs, potentially supporting clinical pharmacology strategies in the development of novel ADCs with similar linker-payload.

Statements and Declarations

Conflict of Interest: Hsuan-Ping Chang, Yuen Kiu Cheung, and Dhaval K. Shah declare that they have no conflict of interest to report related to the work presented in this manuscript.

1 INTRODUCTION

Antibody-drug conjugates (ADCs) have emerged as a promising class of immunotherapy, particularly in the field of oncology, with continuous expansion of their indications to other therapeutic areas such as infectious and autoimmune diseases [1]. In the context of oncology, ADCs leverage monoclonal antibodies (mAbs) to deliver cytotoxic agents (payloads) to antigen-rich cancer cells, inducing their death. However, the complex nature of ADCs, containing both large and small molecules, necessitates the measurement of multiple ADC analytes to understand their pharmacokinetics (PK) [2]. Given the narrow therapeutic index of ADCs, it is essential to comprehend the exposure-response (E-R) relationship to optimize dosing regimens and improve therapeutic outcomes [3]. In fact, understanding the PK of ADCs and exploring which exposure metrics and which ADC analytes act as key drivers to the efficacy and/or safety of ADCs is the key step to establishing a reliable E-R relationship [4]. This study focuses on MMAE-based ADCs, which are among the most widely studied and utilized payloads with an abundance of clinical data, with five out of the 15 currently approved ADCs being MMAE-based. Despite their clinical success, however, comprehensive analyses of all clinical PK data for MMAE-based ADCs across various doses, frequencies, targets, and indications are lacking, and it remains unclear if the PK data are generalizable. As such, our study aims to evaluate the generalizability of the clinical PK data for MMAE-based ADCs and develop a generalized PK models that can capture the PK of multiple ADC analytes measured in the clinic.

A previous study has analyzed the PK of eight MMAE-based ADCs in phase 1 studies, and revealed similarities in PK across these MMAE-based ADCs developed by Genentech [5]. In our study, we have conducted a comprehensive literature review to collect up-to-date clinical PK data for additional ADCs containing vc-MMAE linker-payload, with multiple indications and targets, various ADC analytes, a wider range of doses and dosing regimens, and different average drug-antibody ratios of the ADC formulations. By pooling these collected data together, we confirmed the generalization of PK for MMAE-based ADCs across different ADCs. Furthermore, we have developed a generalized population PK model using all collected PK data. By pooling the reported PK parameters, we established a generalized relationship between dose and exposure parameters, enabling the prediction of typical exposure values for different ADC analytes for a typical MMAE-based ADC at a given dose.

Although numerous published population PK models exist for MMAE-based ADCs, most of them have been developed for individual ADCs [6-10] . To the best of our knowledge, no studies have comprehensively collected PK data across various MMAE-based ADCs and utilized this data to develop a generalized PK model. Furthermore, existing PK models only describe selected ADC analytes of an MMAE-based ADC [6-10], with none of them simultaneously capturing the four ADC analytes commonly measured in clinics, including conjugated/total mAbs and unconjugated/conjugated MMAE. In this study, after demonstrating the generalizability of PK for

MMAE-based ADCs, we have developed a generalized population PK model that is capable of simultaneously capturing all four ADC analytes in the collected PK data for MMAE-based ADCs.

More specifically, in this manuscript we have systematically collected clinical PK data from 18 different MMAE-based ADCs from multiple sources. We demonstrated the PK generalizability of these 18 MMAE-based ADCs through dose-normalization [5, 11-43]. Additionally, we established generalizable linear relationships between dose and PK exposure metrics by utilizing reported PK parameters, which enables prediction of typical values of exposure parameters across different doses for ADCs. We have also developed for the first time a generalized population PK model that can simultaneously characterize the PK all four analytes of 18 MMAE-based ADCs [5, 11-43]. The PK model is also incorporated into an R shiny web-based application to facilitate its usability during clinical development of MMAE-based ADCs.

2 METHOD

2.1 PK Data Collection

A comprehensive literature search was conducted to identify relevant publications from databases such as PubMed, Google Scholar, Google, conference proceedings, abstracts, posters, regulatory documents (i.e., submission packages in FDA and EMA), and web-based resources like ClinicalTrials.gov. Keywords such as MMAE, vc-MMAE, vendotin, MMAE-based ADC, and other related terms were used. Studies were selected based on predetermined criteria, including clinical studies involving ADCs that use vc-MMAE as a linker payload and the availability of PK profiles for at least one of the four ADC analytes (total mAb, conjugated mAb, unconjugated MMAE, conjugated MMAE), without restrictions on indication, study population, antibody target, or dosing regimens. Control groups in drug-drug interaction and organ impairment studies were also included. Studies with ADCs conjugated using different methods (e.g., site-specific conjugation) or different linker chemistry were excluded. Upon identifying eligible references, for each study, data for all ADC analytes and all doses were collected. Concentration vs. time profiles were digitized using WebPlotDigitizer [44], and the corresponding doses and units for each profile were recorded to facilitate subsequent data analysis.

2.2 PK Data Analysis

Each digitized concentration value represents the mean concentration from each study group in each study. The collected concentrations were then dose-normalized to 2.4 mg/kg. Dose-normalized PK profiles of individual ADC analytes from different ADCs were pooled together and plotted to visually evaluate the generalization across different ADCs and dosing groups.

2.3 Development of Dose-Exposure Relationship

Literature-reported PK parameters of different ADC analytes (i.e., C_{max}, AUC_{0-t}, AUC_{inf}, half-life, CL, V_{ss}, T_{max}, etc.) were collected from various ADCs across different doses. If PK parameters for a specific ADC were not reported in the literature, digitized PK profiles were used to calculate the PK parameters for that particular ADC using Noncompartmental Analysis (NCA) conducted using WinNonlin. PK parameters of ADC analytes from different ADCs, but at the same dose levels commonly used in clinics, were then pooled together, and the mean and standard deviation (SD) were calculated. Regression analysis was performed to examine the relationships between PK parameters and dose, which provided equations describing the exposure vs. dose relationship for each ADC analyte. This analysis allows for the estimation of generalized values of PK parameters with variability for the four ADC analytes of MMAE-based ADCs at dose levels commonly used in the clinic.

2.4 PK Model Development

The structure of the generalized PK model is shown in Fig. 1, and the PK model equations are provided in Eqs. 1–8. The model describes different ADC analytes, including ADC (conjugated mAb), conjugated MMAE, unconjugated MMAE, and naked mAb. The conjugates compartment in Fig. 1 refers to ADC and conjugated MMAE both. Each ADC analyte is described using a two-compartmental PK model (parameterized in terms of CL, CLD, V1, and V2).

$$\frac{dX1_{ADC}}{dt} = -CLD_{mAb} \times \frac{X1_{ADC}}{V1_{mAb}} + CLD_{mAb} \times \frac{X2_{ADC}}{V2_{mAb}} - CL_{mAb} \times \frac{X1_{ADC}}{V1_{mAb}} - k_{dec,ADC} \times X1_{ADC} \quad (1)$$

$$\frac{dX2_{ADC}}{dt} = CLD_{mAb} \times \frac{X1_{ADC}}{V1_{mAb}} - CLD_{mAb} \times \frac{X2_{ADC}}{V2_{mAb}} - k_{dec,ADC} \times X2_{ADC} \quad (2)$$

$$\frac{dX1_{mAb}}{dt} = -CLD_{mAb} \times \frac{X1_{mAb}}{V1_{mAb}} + CLD_{mAb} \times \frac{X2_{mAb}}{V2_{mAb}} - CL_{mAb} \times \frac{X1_{mAb}}{V1_{mAb}} + k_{dec,ADC} \times X1_{mAb} \quad (3)$$

$$\frac{dX2_{mAb}}{dt} = CLD_{mAb} \times \frac{X1_{mAb}}{V1_{mAb}} - CLD_{mAb} \times \frac{X2_{mAb}}{V2_{mAb}} + k_{dec,ADC} \times X2_{mAb} \quad (4)$$

$$\frac{dX1_{acPL}}{dt} = -CLD_{mAb} \times \frac{X1_{acPL}}{V1_{mAb}} + CLD_{mAb} \times \frac{X2_{acPL}}{V2_{mAb}} - CL_{mAb} \times \frac{X1_{ADC}}{V1_{mAb}} \times DAR - k_{dec,PL} \times X1_{acPL} \quad (5)$$

$$\frac{dX2_{acPL}}{dt} = CLD_{mAb} \times \frac{X1_{acPL}}{V1_{mAb}} - CLD_{mAb} \times \frac{X2_{acPL}}{V2_{mAb}} - k_{dec,PL} \times X2_{acPL} \quad (6)$$

$$\frac{dX1_{PL}}{dt} = -CLD_{PL} \times \frac{X1_{PL}}{V1_{PL}} + CLD_{PL} \times \frac{X2_{PL}}{V2_{PL}} - CL_{PL} \times \frac{X1_{PL}}{V1_{PL}} + CL_{mAb} \times \frac{X1_{ADC}}{V1_{ADC}} \times DAR + k_{dec,PL} \times X1_{acPL} \quad (7)$$

$$\frac{dX2_{PL}}{dt} = CLD_{PL} \times \frac{X1_{PL}}{V1_{PL}} - CLD_{PL} \times \frac{X2_{PL}}{V2_{PL}} + k_{dec,PL} \times X2_{PL} \quad (8)$$

When each conjugate molecule undergoes catabolism (characterized by CL_{mAb}), it is assumed to release a certain number of payloads equivalent to the average drug-antibody ratio (DAR) value at the given time ($CL_{mAb}\times$ DAR). Additionally, the conjugated MMAE can deconjugate from the ADC ($k_{release}$) and contribute payload molecules to the free MMAE compartment. The formation of naked mAb, once conjugated mAb releases all its conjugated payloads, is characterized using k_{dec}. DAR value changes over time are calculated using the real-time concentration of conjugated MMAE and total mAb (Eq. 9). The model can simultaneously characterize the plasma PK of 4 ADC analytes commonly measured in the clinic, which are calculated using Eqs. 10–13.

$$\mathrm{DAR} = \frac{\mathrm{X1_{acPL}}}{\mathrm{X1_{ADC}} + \mathrm{X1_{mAb}}} \tag{9}$$

$$\mathrm{C_{ADC}^{plasma}} = \frac{\mathrm{X1_{ADC}}}{\mathrm{V1_{mAb}}} \tag{10}$$

$$\mathrm{C_{total\ mAb}^{plasma}} = \frac{\mathrm{X1_{ADC}} + \mathrm{X1_{mAb}}}{\mathrm{V1_{mAb}}} \tag{11}$$

$$\mathrm{C_{conjugated\ MMAE}^{plasma}} = \frac{\mathrm{X1_{acPL}}}{\mathrm{V1_{mAb}}} \tag{12}$$

$$\mathrm{C_{unconjugated\ MMAE}^{plasma}} = \frac{\mathrm{X1_{PL}}}{\mathrm{V1_{PL}}} \tag{13}$$

The population PK model estimation includes three parts. First, all collected PK data of 4 ADC analytes from all ADCs and all dosing regimens were simultaneously fitted with the generalized PK model. Population PK parameters, representing inter-ADC and inter-cohort variability, were estimated using the Stochastic Approximation Expectation Maximization (SAEM) algorithm in Monolix (2021R2) and were assumed to be lognormally distributed. Second, the random effect of the model describes variability between different study groups across various ADCs and discrete dosing groups. The distribution of random effect variability was assumed to be log-normal and was described by an exponential error model (Eq. 14). Third, the residual error models, including additive, proportional, and combined error models, were tested for total mAb, ADC, conjugated MMAE, and unconjugated MMAE.

$$\theta_i = \theta_{pop} \cdot \exp(\eta_i) \tag{14}$$

Model qualification was guided by the precision of parameter estimates, goodness-of-fit plots (observed versus model-predicted concentrations), and visual predictive check (VPC) plots. For VPC plots, one thousand datasets were simulated from the final estimated parameters, and the median and 5th and 95th percentiles of simulated data were compared with the observed data.

2.5 Web-based Application of the PK Model

The PK model dashboard was developed using R (version 4.1.3) with shiny (version 1.7.4), shinydashboard (version 0.7.2), and shinyjs (version 2.0.0) packages for design and layout. The ggplot2 (version 3.4.1) package was used for graphing, dplyr (version 1.0.9) for data manipulation, and mrgsolve (version 0.11.1) for PK model simulation using estimated typical values of PK parameters.

3 RESULTS

3.1 Data Collection

Table 1 provides a summary of the collected PK data for MMAE-based ADCs from literature and various resources. A total of 18 MMAE-based ADCs reported in phase I and phase II studies were identified, resulting in a total of 109 mean PK profiles collected [5, 11-43]. Table 1 details each ADC's name, ADC analytes with PK data reported, dosing regimen, target, indication, average DAR value, and associated references. Five of these ADCs, including brentuximab vedotin, polatuzumab vedotin, tisotumab vedotin, enfortumab vedotin, and disitamab vedotin have been approved by the FDA. In the clinic, four ADC analytes (total mAb, ADC, conjugated MMAE, unconjugated MMAE) are commonly measured, with unconjugated MMAE being measured in most of the studies. The dose levels for these ADCs range from 0.1 to 3.3 mg/kg. Most ADCs are administered every three weeks, while enfortumab vedotin and disitamab vedotin are also given weekly. Each ADC has different targets, with four developed for hematological tumors and 14 for solid tumors. The average DAR for these ADC formulations is 3.5, ranging from 2.7 to 4.

3.2 PK Profile Generalizability

To evaluate the generalizability of MMAE-based ADC PK, we pooled all digitized data and visually assessed the dose-normalized PK profiles across different ADCs and dosing groups. Dose-normalized PK profiles of ADC, total mAb, unconjugated MMAE, and conjugated MMAE were presented (Fig. 2), with each data point representing the mean concentration of each dosing group in a clinical study. For ADCs with multiple dosing data, we only presented PK data from the first dose (Fig. 2). The PK profiles of the four ADC analytes from different MMAE-based ADCs were found to be comparable, regardless of their targets, tumor indications, and average DAR.

NCA was also conducted using the digitized dose-normalized PK profiles, and the calculated PK parameters for individual MMAE-based ADCs, along with the summary statistics (mean ± SD, median, and range), are shown in Table S1. Despite variability, the exposure (i.e., C_{max}, AUC_{0-t}, AUC_{inf}), distribution (i.e., V_{ss}), and elimination (CL) properties showed no significant differences among MMAE-based ADCs, as the difference between the maximum and minimum values and the median was within a two-fold range of the median value. Moreover, for unconjugated MMAE, PK profiles and calculated PK parameters demonstrate less variability (CV% < 30%), emphasizing that the PK of released MMAE behaves like free-form MMAE.

Fig. 3 demonstrates the dose-normalized PK profiles of individual ADCs, with their different analytes plotted together. Within each ADC, the dose-normalized PK profiles of different ADC analytes across different doses are comparable, indicating that the possible contribution of lower doses to non-linear PK for individual

MMAE-based ADCs could be negligible. The generalizable properties of PK profiles support the strategy of developing a generalized PK model for MMAE-based ADCs in the clinic.

3.3 Relationship Between ADC Dose and PK Parameters

To provide a handy source for the clinical PK of MMAE-based ADCs, literature-reported PK parameters of individual MMAE-based ADCs at commonly used clinical doses for total mAb (Table 2), ADC (Table 3), unconjugated MMAE (Table 4), and conjugated MMAE (Table 5) are provided. It was observed that conjugated mAb exhibits a shorter half-life and higher CL compared to total mAb for ADCs, which may be attributed to conjugate-induced CL of ADCs. Unconjugated MMAE demonstrates a similar half-life to conjugated MMAE, but is significantly longer than that of free small molecule MMAE, suggesting formation rate-limited clearance.

More detailed literature-reported clinical PK parameters for individual ADCs across a wide dose range (0.1-4 mg/kg) are provided in Table S2 for ADC, Table S3 for total mAb, Table S4 for conjugated MMAE, and Table S5 for unconjugated MMAE. We also calculated PK parameters using digitized PK profiles (non-dose-normalized) for individual MMAE-based ADCs across different doses for total mAb (Table S6), ADC (Table S7), unconjugated MMAE (Table S8), and conjugated MMAE (Table S9). The calculated and reported PK parameters were generally comparable, validating the reliability of the digitized PK data (Table S10). However, we observed one ADC with reported C_{max} and AUC_{0-t} values significantly higher than the range of values across other ADCs, possibly due to unit reporting errors. This highlights the importance of unit transformation for different ADC analytes, and in our study, we converted all concentration units to nM for convenience in PK modeling.

Linear regression was performed to establish a quantitative relationship between ADC dose and exposure matrices (C_{max} and AUC) for conjugated MMAE (Fig 4a), unconjugated MMAE (Fig 4b), ADC (Fig 4c), and total mAb (Fig 4d). Eqs. 15–18 relate ADC dose (mg/kg) to C_{max} for conjugated MMAE, unconjugated MMAE, ADC, and total mAb, while Eqs. 19–22 relate ADC dose (mg/kg) to AUC for the four analytes. These equations enable prediction of the exposure for different ADC analytes for MMAE-based ADCs across doses ranging from 0.1 to 4 mg/kg.

$$C_{max}^{\text{conjugated MMAE}}(\text{nM}) = 513 \cdot \text{Dose (mg/kg)} - 11.3 \tag{15}$$

$$C_{max}^{\text{unconjugated MMAE}}(\text{nM}) = 3.0 \cdot \text{Dose (mg/kg)} - 0.515 \tag{16}$$

$$C_{max}^{\text{ADC}}(\text{nM}) = 133 \cdot \text{Dose (mg/kg)} + 9.32 \tag{17}$$

$$C_{max}^{\text{total mAb}}(\text{nM}) = 122 \cdot \text{Dose (mg/kg)} + 32.1 \tag{18}$$

$$\mathrm{AUC}_{\text{conjugated MMAE}}(\mathrm{nM}\cdot\mathrm{day}) = 1531\cdot \mathrm{Dose}\ (\mathrm{mg/kg}) - 82.1 \quad (19)$$

$$\mathrm{AUC}_{\text{unjugated MMAE}}(\mathrm{nM}\cdot\mathrm{day}) = 29.4\cdot \mathrm{Dose}\ (\mathrm{mg/kg}) - 2.12 \quad (20)$$

$$\mathrm{AUC}_{\mathrm{ADC}}(\mathrm{nM}\cdot\mathrm{day}) = 308\cdot \mathrm{Dose}\ (\mathrm{mg/kg}) - 29.9 \quad (21)$$

$$\mathrm{AUC}_{\text{total mAb}}(\mathrm{nM}\cdot\mathrm{day}) = 589\cdot \mathrm{Dose}\ (\mathrm{mg/kg}) - 34.6 \quad (22)$$

3.4 Generalized PK Model Development

PK parameter estimates and the associated variability are summarized in Table 6. Including variability on CL, CLD, V1, and V2 of mAb, CL and V2 of payload, as well as deconjugation processes improved model fitting, while adding variability on CLD and V1 of payload did not enhance model performance. A proportional error model best described the residual variability for all four ADC analytes. Fig. 5 presents simulated plasma PK profiles of the four ADC analytes at a dose of 2.4 mg/kg every three weeks for four doses, shown as log (left) and linear (right) scales, superimposed with observed data dose-normalized to 2.4 mg/kg. The simulations account for PK parameter variability. Fig. 6 displays the observed versus population (upper) and individual (lower) predicted-concentration plots, and Fig. 7 shows the VPC plots for the four ADC analytes. The model was able to simultaneously characterize the PK of four clinically-measured ADC analytes for MMAE-based ADCs across different targets, indications, and dosing regimens.

3.5 Web-based Application of the PK Model

The developed PK model was incorporated into a web-based application to enhance its usability. The application can be accessed using the following link:
https://biesuniversityatbuffalo.shinyapps.io/MMAE_ADC_PK_MODELS/.
Users can select different ADC doses (mg/kg), frequencies, and average initial DAR. The model-simulated PK profiles of the four ADC analytes can be plotted together or separately. Maximum and trough concentrations of each analyte at steady state are also provided in nM or ug/mL (ng/mL for unconjugated MMAE) units.

4 DISCUSSION

MMAE is a commonly used payload in ADCs, composing one-third of FDA-approved ADCs [45]. This has resulted in abundant clinical PK data for these ADCs, which share the same payload and conjugation method, but different targets and indications. However, comprehensive analyses for MMAE-based ADCs across varying dosing regimens, targets, and indications have been limited. To address this, we aimed to develop a generalized PK model for MMAE-based ADCs, comprehensively characterizing and evaluating the PK across four clinically-measured ADC analytes. We first collected and compiled clinical PK data from 18 different MMAE-based ADCs and confirmed the generalizability of the collected data through dose-normalization. Additionally, we established continuous relationships between dose and exposure matrices of ADC analytes by pooling literature-reported PK parameters across dose ranges, which enables prediction of typical exposure values across different doses for typical MMAE-based ADC. Using all collected PK data, we developed a generalized PK model capable of simultaneously capturing the PK of four ADC analytes and applied the model to an R shiny app for user-friendly PK predictions.

Numerous investigations have been conducted on the PK of MMAE-based ADCs, yet most of them have focused on specific ADCs [19, 21-23, 25, 27-37, 39-41, 43] or those developed by the same company [5]. To our knowledge, this is the first publication to comprehensively collect and analyze PK data for ADCs with a similar linker-payload platform. These data cover various dosing regimens, targets, indications, tumor types, drug loadings, and incorporate all ADC analytes that are commonly measured in clinics, which enables generalizability of our analyses for MMAE-based ADCs. However, the data collection cut-off date was toward the end of 2021, and thus there is potential that some data may not have been included.

To establish a universal PK model for characterizing the PK of MMAE-based ADCs, the initial step involved evaluating and confirming PK generalizability across these molecules. This was achieved by comparing dose-normalized concentration-time profiles for various ADCs and doses. Our analysis demonstrated comparable dose-normalized PK profiles for four ADC analytes. Notably, unconjugated MMAE displayed similar PK profiles among different MMAE-based ADCs, with a T_{max} of 2 days (range 1–3 days) and an extended half-life (~4 days) compared to naked MMAE [46], suggesting consistent payload release properties and formation rate-limited characteristics among these vc-linker-based ADCs. For individual ADCs, dose-normalized PK profiles across dose ranges were also comparable (Fig. 3). Consequently, within the collected dose range, linear PK was assumed, and the potential contribution of non-linear PK at lower doses was negligible. The dose-normalized PK profiles of the four ADC analytes support the generalizability of PK for MMAE-based ADCs and the development of a generalized PK model.

We have proposed a novel PK model capable of simultaneously capturing all ADC analytes of MMAE-based ADCs, with PK parameters accounting for inter-ADC and inter-cohort variability (Table 6). Each ADC analyte is described by central and peripheral compartments. Deconjugation is assumed to occur in both systemic

and tissue compartments. Upon degradation, ADC can release its payload equivalent to the average DAR value at a given time. The PK parameters were estimated with good precision (%RSE ≤ 10%). Additionally, the estimated PK parameters for the compartmental PK model (Table 6) correspond to the literature-reported PK parameters calculated by NCA (Tables 2–5). For instance, the estimated elimination (including CL_{mAb} and k_{dec} pathway) and distribution (i.e., $V1_{mAb} + V2_{mAb}$) of ADC (conjugated mAb) analytes for MMAE-based ADCs were within the range of reported CL and V_{ss} values (Table 3). For conjugated MMAE, the estimated total CL (~19.4 mL/day/kg), which includes degradation (CL_{mAb}) and deconjugation ($k_{release}$) processes, corresponds to the literature-reported CL of conjugated MMAE for MMAE-based ADCs (Table 5)

Important PK characteristics of payload release can be inferred from the estimated PK parameters associated with unconjugated MMAE. For instance, a similar terminal slope and half-life were observed between unconjugated and conjugated MMAE from the PK profiles, while the estimated CL of unconjugated MMAE was faster than that of conjugated MMAE (861 vs. 12.5 mL/day/kg), demonstrating formation rate-limited kinetics of the released payload [47]. Additionally, the estimated low $V1_{PL}$ and high $V2_{PL}$ values, along with the high CLD_{PL} value, indicate extensive and rapid tissue distribution of the released MMAE, consistent with our previous publication investigating the tissue distribution of MMAE [46].

Each data point in our analysis represents the mean concentration of individual treatment groups. Consequently, the random effects incorporated within the model do not indicate inter-individual variability, but rather describe the variability among treatment groups from different studies across different ADCs. Given this context, covariates cannot be included to reduce the relatively high variability observed in PK parameters. However, covariates commonly reported as significant for biotherapeutics PK have minimal impact on ADC PK parameters compared to data variability, and indeed, BW-based dosing without adjusting for intrinsic and extrinsic factors is sufficient for ADC dosing strategy [6]. This highlights the feasibility of the current generalized PK model, which utilizes BW-based parameterization.

The generalized PK model exhibits several key features. First, it is capable of simultaneously describing four commonly measured ADC analytes in clinical settings, while most published PK models for ADCs predict only specific analytes. Second, as ADCs in the body act in heterogeneous forms, we use the average DAR value to represent the overall behavior of ADC molecules. This DAR value changes over time and is determined by the real-time concentrations of conjugated MMAE and total mAb. Third, although the model is a compartmental model rather than a physiologically-based PK model, it mechanistically describes payload release pathways, including deconjugation and degradation. Lastly, the input for conjugated MMAE accounts for individual DAR values, reflecting ADC formulation differences (i.e., conjugated MMAE dose is calculated as ADC dose times initial DAR in the formulation).

Several compartmental population PK models have been developed for MMAE-based ADCs [6]. These models typically characterize two ADC analytes, including ADC or conjugated MMAE and unconjugated MMAE.

The PK model for polatuzumab vedotin employs three time-dependent elimination pathways to characterize the transformation of conjugated MMAE to unconjugated payload [8]; however, it cannot distinguish between deconjugation and degradation processes of payload release. On the other hand, the PK model for brentuximab vedotin incorporates deconjugation and degradation processes [7], while the dynamic of DAR is characterized using an empirical exponential equation instead of calculating it from real-time data predicted in the model. For enfortumab vedotin, PK models for ADC and unconjugated payload are developed separately, limiting their utility in characterizing the overall PK of ADC molecules [9]. In the case of tisotumab vedotin, a delayed compartment is incorporated to characterize the unconjugated MMAE [10]; however, this approach may not mechanistically reflect the formation rate-limited feature of the released payload. Therefore, our PK model offers several innovative aspects, such as various ADC analyte characterization, improved DAR handling, and payload release mechanisms, which may provide advantages over existing models for MMAE-based ADCs.

E-R analysis is essential in clinical dose optimization of ADCs due to their narrow therapeutic window [48]. Given the presence of multiple ADC analytes in the body, selecting the appropriate ADC analytes and exposure matrices is of significant importance during the initial decision of ER analysis. Our generalized PK model enables simultaneous quantitative understanding of different exposure matrices for all four ADC analytes of MMAE-based ADCs, allowing for a comprehensive examination of the key drivers of efficacy and safety endpoints. Indeed, our next step is to link the proposed PK model with pharmacodynamic (PD) endpoints from various MMAE-based ADCs to develop a generalized E-R relationship for MMAE-based ADCs.

5 CONCLUSION

In conclusion, we comprehensively collected and analyzed clinical PK data from 18 MMAE-based ADCs with varying targets, indications, and dosing regimens, demonstrating their PK generalizability. We have also developed a generalized population PK model capable of simultaneously characterizing all four analytes of MMAE-based ADCs for the first time. We present a linear relationships between dose and exposure metrics for MMAE-based ADCs by pooling literature-reported PK values, which enables prediction of typical exposure values for a given dose. This comprehensive PK analysis, along with the incorporation of the PK model into a user-friendly web-based application, facilitates better clinical development and optimization of MMAE-based ADCs.

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Tables

Table 1. Summary of clinical PK data for MMAE-based ADCs.

ADC	Reported PK Analytes[b]	Dose (mg/kg)	Frequency	Target	Indications	Average DAR	References
Brentuximab vedotin[a]	ADC, unMMAE	1.2, 1.8, 2.7	Q3W	CD30	Hodgkin lymphoma	4	[11, 17, 18, 24]
Polatuzumab vedotin[a]	acMMAE, Tmab, unMMAE	0.1, 0.25, 0.5, 1, 1.4, 1.8, 2.4	Q3W	CD79b	non-Hodgkin lymphoma	3.5	[12, 13, 20, 37, 38, 42]
Pinatuzumab vedotin	acMMAE, Tmab, unMMAE	2.4	Q3W	CD22	non-Hodgkin lymphoma	3.5	[25]
Lifastuzumab vedotin	acMMAE, Tmab, unMMAE	2.4	Q3W	Napi2b	Ovarian, lung	3.5	[34, 35]
Losatuxizumab vedotin	ADC, Tmab, unMMAE	0.3, 0.45, 0.67, 1, 1.5, 2.25, 3	Q3W	EGFR	EGFR-dependent solid tumors	3	[33]
Tisotumab vedotin[a]	ADC, unMMAE	0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2, 2.2	Q3W	tissue factor	Cervical	3.5	[14, 29]
Telisotuzumab vedotin	ADC, Tmab, unMMAE	0.15, 0.3, 0.6, 1.2, 1.8, 1.9, 2.4, 2.7, 3.0, 3.3	Q3W	c-Met	Non-small cell lung cancer	3	[27, 40, 41]
Glembatumumab vedotin	ADC, Tmab, unMMAE	1.88	Q3W	gpNMB	Melanoma	2.7	[19, 21, 30]
ASG-5ME	ADC, Tmab, unMMAE	0.3, 0.6, 1.2, 1.8, 2.4, 2.7, 3	Q3W	SLC44A4	Pancreatic, gastric, prostate	3.5	[22, 31]
Ladiratuzumab vedotin	ADC, unMMAE	1, 1.25, 1.5, 2.5	Q3W	LIV-1	Breast (TNBC, HR+/HER2-)	4	[16]
PSMA ADC	ADC, unMMAE	0.4, 0.7, 1.1, 1.6, 1.8, 2, 2.2, 2.5, 2.8	Q3W	PSMA	Prostate cancer	4	[32]
Vandortuzumab vedotin	acMMAE, Tmab	0.33, 0.45, 0.67, 1, 2.4	Q3W	Steap1	Prostate cancer	3.5	[5, 26, 28]
DEDN6526A	acMMAE, Tmab, unMMAE	2.4	Q3W	ETBR	Melanoma	3.5	[5]
DMOT4039A	acMMAE, Tmab, unMMAE	2.4	Q3W	MsLN	Ovarian, pancreatic	3.5	[5]
DMUC5754A	acMMAE, Tmab, unMMAE	2.4	Q3W	MUC16	Ovarian, pancreatic	3.5	[5, 23]
DFRF4539A	acMMAE, Tmab, unMMAE	2.4	Q3W	FcRH5	Multiple myeloma	3.5	[5]
Enfortumab vedotin[a]	ADC, Tmab, unMMAE	0.5. 0.75, 1, 1.25	QW	Nectin-4	Urothelial	4	[15, 36, 39]
Disitamab vedotin[a]	ADC, Tmab, unMMAE	0.1, 0.5, 1, 2, 2.5, 3.0	QW, Q3W	HER2	Gastric, urothelial	4	[43]

ADC conjugated antibody, unMMAE unconjugated MMAE, acMMAE conjugated MMAE, Tmab total antibody
[a] Received FDA approval

Table 2. Literature reported PK parameters for total antibody analyte for MMAE-based ADCs.

Dose (mg/kg)	C_{max} (nM)	AUC_{0-t} (day·nM)	AUC_{inf} (day·nM)	$T_{1/2}$ (day)	CL (mL/day/kg)	V_{ss} (mL/kg)	Reference[b]
Polatuzumab vedotin							
1.8	268 ± 68.6	776[a]	1590 ± 919	8.70 ± 2.98	17.1 ± 16.5	87.8 ± 24.4	[13, 20, 38, 42]
2.4	254 ± 20.9	1212 ± 444[a]	1415 ± 176	6.90 ± 0.797	15.4 ± 3.37	97.8 ± 17.5	[5, 12, 13, 20]
Pinatuzumab vedotin							
2.4	275 ± 18.5	1687 ± 860[a]	1592 ± 413	9.03 ± 3.41	14.5 ± 4.90	115 ± 24.1	[5, 25]
Lifastuzumab vedotin							
2.4	336 ± 36.2	1505 ± 337[a]	1516 ± 307	6.84 ± 0.709	11.5 ± 2.36	89.2 ± 26.8	[5, 34, 35]
Losatuxizumab vedotin							
1.5	167[a]	528[a]	563[a]	4.60	17.8[a]	108[a]	[33]
Glembatumumab vedotin							
1.88	347 ± 52.8	801 ± 222	864 ± 195	1.53 ± 0.0666	19.5 ± 2.09	34.5 ± 5.71	[19, 30, 49]
ASG-5ME							
2.4	385 667 ± 22 156[c]	2224 667[c]	2404[a]	8.65 ± 0.170	6.65[a]	27.8	[31]
2.7	334 000 ± 10 370[c]	1802 000[c]	2005[a]	9.87 ± 1.03	8.98[a]	55.3	[31]
PSMA ADC							
2.4	320	-	736	1.84	28.1	68.9	[32]
Vandortuzumab vedotin							
2.4	374	1822 ± 61.4[a]	2100	7.52	8.24	63.2	[26, 28]
DEDN6526A							
2.4	303	827[a]	853	3.92	20.9	70.6	[5]
DMOT4039A							
2.4	249	902[a]	800	4.26	23.6	118	[5]
DMUC5754A							
2.4	275	930[a]	1167	6.33	15.6	93.1	[5]
DFRF4539A							
2.4	373	1744[a]	2007	6.00	9.02	61.5	[5, 23]
Enfortumab vedotin							
1.25	247 ± 42.6	532 ± 60.1	725 ± 125[a]	2.94 ± 0.257[a]	11.8 ± 2.2[a]	44.5 ± 4.9[a]	[15, 36, 39]
Disitamab vedotin							
2.5	373	1267	1267	1.53	33.6	72.4	[43]

C_{max}, AUC_{0-t}, AUC_{inf} were converted to nanomolar concentration units, CL and V_{ss} were presented as per body weight units, and in case the unit was not reported as per body weight units, the reported values were divided by 70 kg, - not available

[a] Values not available from the literature and were calculated based on digitalized concentration-time profiles

[b] Data are shown as mean ± standard deviation (SD) of reported values from multiple references. When the value was reported in one literature, only the mean value was provided

[c] The reported units of C_{max} (mg/mL) and AUC_{0-t} (day·mg/mL) provide ~1000 higher values than the average reported values of C_{max} and AUC_{0-t} for ADC analytes of MMAE-based ADCs, and thus the units of C_{max} and AUC_{0-t} should be corrected to μg/mL and day*μg/mL, respectively

Table 3. Literature reported PK parameters for ADC (i.e., conjugated antibody) analyte for MMAE-based ADCs.

Dose (mg/kg)	C_{max} (nM)	AUC_{0-t} (day·nM)	AUC_{inf} (day·nM)	$T_{1/2}$ (day)	CL (mL/day/kg)	V_{ss} (mL/kg)	Reference[b]
Brentuximab vedotin							
1.2	144 ± 15.9	286 ± 47.4	334 ± 23.3	4.75 ± 1.35	26.7 ± 1.84	109 ± 35.4	[11, 18, 24]
1.8	224 ± 18.5	511	564 ± 49.5	4.91 ± 0.831	24.4 ± 1.15	126 ± 15.0	[11, 17, 18]
Losatuxizumab vedotin							
1.5	167 ± 18.9[a]	430 ± 154[a]	445 ± 170[a]	3.5	24.2 ± 9.26[a]	98.8 ± 1.68[a]	[33]
Tisotumab vedotin							
2.0	215	349	370[a]	1.86[a]	36[a]	58.5[a]	[29]
2.2	370	566	717[a]	2.18[a]	20.5[a]	40.9[a]	[14]
Telisotuzumab vedotin							
2.4	403 ± 46.0	1382	1314 ± 115	4.18	12.9 ± 1.58[a]	58.3 ± 9.25[a]	[27, 41]
2.7	386 ± 48.8	1099	1281 ± 232	2.91	14.9 ± 0.985[a]	69.0 ± 9.18[a]	[27, 41]
Glembatumumab vedotin							
1.88	297 ± 73.1	644 ± 21.9	497 ± 171	1.23 ± 0.133	31.1 ± 8.49	43.9 ± 4.53	[19, 30, 49]
ASG-5ME							
2.4	440 334 ± 129 636[c]	1593 333[c]	1427[a]	6.87± 0.233	11.2[a]	40.8	[31]
2.7	373 000 ± 66 468[c]	1422 000[c]	1363[a]	7.40	13.2[a]	121[a]	[31]
Ladiratuzumab vedotin							
2.5	549[a]	1083[a]	1611[a]	5.56[a]	10.3[a]	65.9[a]	[16]
PSMA ADC							
2.5	267	408[a]	364	1.69	55.9	104	[32]
Enfortumab vedotin							
1.25	187 ± 29.6	220 ± 19.4	285 ± 37.2[a]	3.35	29.6 ± 4.18[a]	70.1 ± 13.5[a]	[15, 36, 39]
Disitamab vedotin							
2.5	353	306	306	1.90	55.2	159	[43]

C_{max}, AUC_{0-t}, AUC_{inf} were converted to nanomolar concentration units, CL and V_{ss} were presented as per body weight units, and in case the unit was not reported as per body weight units, the reported values were divided by 70 kg, - not available

[a] Values not available from the literature and were calculated based on digitalized concentration-time profiles

[b] Data are shown as mean ± standard deviation (SD) of reported values from multiple references. When the value was reported in one literature, only the mean value was provided

[c] The reported units of C_{max} (mg/mL) and AUC_{0-t} (day·mg/mL) provide ~1000 higher values than the average reported values of C_{max} and AUC_{0-t} for ADC analytes of MMAE-based ADCs, and thus the units of C_{max} and AUC_{0-t} should be corrected to μg/mL and day*μg/mL, respectively

Table 4. Literature reported PK parameters of unconjugated MMAE analyte for MMAE-based ADCs.

Dose (mg/kg)	T_{max}[b] (day)	C_{max} (nM)	AUC_{0-t} (day·nM)	AUC_{inf} (day·nM)	$T_{1/2}$ (day)	Reference[b]
Brentuximab vedotin						
1.2	1.07 (1.07, 3.00)	5.46 ± 1.58	47.6 ± 3.44[a]	40.7 ± 14.0	3.42 ± 0.410	[11, 17, 18]
1.8	2.09 (1.97, 2.09)	6.53 ± 0.705	50.1	44.4 ± 10.3	3.42 ± 0.312	[11, 18, 24]
Polatuzumab vedotin						
1.8	5.60 (2.49, 5.98)	4.29 ± 2.62	29.8 ± 2.31	51.1 ± 37.3	4.30 ± 0.495	[13, 20, 37, 38, 42]
2.4	3.58 (2.95, 3.94)	9.75 ± 1.68	74.2 ± 17.7[a]	80.1 ± 9.01	3.84 ± 0.401	[5, 12, 13, 20, 37]
Pinatuzumab vedotin						
2.4	3.32 (2.87, 4.10)	8.70 ± 1.20	59.3 ± 23.9[a]	70.8 ± 11.4	3.47 ± 0.483	[5, 25]
Lifastuzumab vedotin						
2.4	2.06	5.86 ± 1.59	59.4 ± 14.7[a]	52.3 ± 14.8	3.94 ± 0.294	[5, 34, 35]
Losatuxizumab vedotin						
1.5	2.00[a]	3.27[a]	30.7[a]	31.4[a]	3.20	[33]
Tisotumab vedotin						
2.2	7.00[a]	6.80	36.9	89.1[a]	6.88[a]	[14]
Telisotuzumab vedotin						
2.4	7.02	2.35	31.0	35.2[a]	5.80	[41]
2.7	7.02	3.90	44.3	68.9 ± 1.13[a]	4.01	[41]
Glembatumumab vedotin						
1.88	2.53 (1.06, 5.05)	7.87 ± 0.420	77.9 ± 5.09	78.5 ± 26.4	3.02 ± 0.311	[19, 30, 49]
ASG-5ME						
2.4	3.60	6685 237 ± 984 829[c]	4.82E+10[c]	107[a]	4.06	[31]
2.7	4.30	5919 220 ± 1083 312[c]	7.20E+10[c]	88.7[a]	4.39	[31]
Ladiratuzumab vedotin						
2.5	3.00[a]	8.24[a]	46.6[a]	159[a]	11.9[a]	[16]
PSMA ADC						
2.5	2.49	12.8	90.5[a]	99.2	2.68	[32]
2.4	2.99	7.95	61.0[a]	60.3	3.91	[32]
Vandortuzumab vedotin						
2.4	2.00	7.88	61.0	62.5	3.62	[26, 28]
DEDN6526A						
2.4	2.07	9.36	77.9[a]	70.1	2.99	[5]
DMOT4039A						
2.4	2.03	6.17	52.2[a]	46.9	3.35	[5]
DMUC5754A						
2.4	2.96	9.76	77.5[a]	80.2	3.76	[5]
DFRF4539A						
2.4	3.10	4.39	49.3[a]	49.2	5.00	[5, 23]
Enfortumab vedotin						
1.25	2.01 (1.94, 2.07)	5.20 ± 1.15	37.2 ± 34.8	44.2 ± 3.28[a]	5.27 ± 1.15[a]	[15, 36, 39]
Disitamab vedotin						
2.5	2.99	8.36	52.9	57.5	2.55	[43]

C_{max}, AUC_{0-t}, AUC_{inf} were converted to nanomolar concentration units, CL and V_{ss} were presented as per body weight units, and in case the unit was not reported as per body weight units, the reported values were divided by 70 kg

[a] Values not available from the literature and were calculated based on digitalized concentration-time profiles

[b] Data are shown as mean ± standard deviation (SD) or mean (range) of reported values from multiple references. When the value was reported in one literature, only the mean value was provided

[c] The reported units of C_{max} (mg/mL) and AUC_{0-t} (day·mg/mL) provide ~1000,000 higher values than the average reported values of C_{max} and AUC_{0-t} for free MMAE of MMAE-based ADCs, and thus the units of C_{max} and AUC_{0-t} should be corrected to ng/mL and day·ng/mL, respectively

Table 5. Literature reported PK parameters for conjugated MMAE analyte for MMAE-based ADCs.

Dose (mg/kg)	C_{max} (nM)	AUC_{0-t} (day·nM)	AUC_{inf} (day·nM)	$T_{1/2}$ (day)	CL (mL/day/kg)	V_{ss} (mL/kg)	Reference[b]
Polatuzumab vedotin							
1.8	872 ± 185	3539 ± 812[a]	2860 ± 429	5.52 ± 1.23	18.8 ± 6.72	81.6 ± 15.5	[13, 20, 37, 38, 42]
2.4	1241 ± 29.3	3860 ± 1435[a]	3961 ± 431	5.39 ± 0.801	18.0 ± 2.82	74.4 ± 18.4	[5, 12, 13, 20]
Pinatuzumab vedotin							
2.4	1205 ± 42.2	4215 ± 2216[a]	3187 ± 634	5.53 ± 1.88	23.2 ± 3.70	94.4 ± 15.5	[5, 25]
Lifastuzumab vedotin							
2.4	1236 ± 143	4231 ± 1599[a]	3820 ± 836	5.38 ± 0.516	16.8 ± 3.73	79.3 ± 22.5	[5, 34, 35]
Vandortuzumab vedotin							
2.4	1231	3122 ± 53.0[a]	3384	5.84	17.4	75.4	[26, 28]
DEDN6526A							
2.4	1259	2673[a]	2897	4.62	22.6	60.1	[5]
DMOT4039A							
2.4	1010	2308[a]	2006	3.8	30.2	96.0	[5]
DMUC5754A							
2.4	1153	1825[a]	2618	5.12	25.6	85.3	[5]
DFRF4539A							
2.4	1233	3253[a]	3774	4.88	16.6	77.4	[5, 23]

C_{max}, AUC_{0-t}, AUC_{inf} were converted to nanomolar concentration units, CL and V_{ss} were presented as per body weight units, and in case the unit was not reported as per body weight units, the reported values were divided by 70 kg

[a] Values not available from the literature and were calculated based on digitalized concentration-time profiles

[b] Data are shown as mean ± standard deviation (SD) of reported values from multiple references. When the value was reported in one literature, only the mean value was provided

Table 6. Estimated parameter values for the generalized PK model for MMAE-based ADCs.

PK parameter (unit)	**Estimate (%RSE)**	
CL_{mAb} (L/day/kg)	0.0125 (6.39)	
CLD_{mAb} (L/day/kg)	0.0247 (7.98)	
$V1_{mAb}$ (L/kg)	0.0509 (2.57)	
$V2_{mAb}$ (L/kg)	0.0612 (8.47)	
CL_{PL} (L/day/kg)	0.861 (3.39)	
CLD_{PL} (L/day/kg)	13.7 (2.51)	
$V1_{PL}$ (L/kg)	0.430 (1.08)	
$V2_{PL}$ (L/kg)	1.24 (10.0)	
k_{dec} (1/day)	0.104 (9.30)	
$k_{release}$ (1/day)	0.135 (5.33)	
Random effect[a]	**CV% (%RSE)**	
CL_{mAb} (L/day/kg)	60.2 (8.47)	
CLD_{mAb} (L/day/kg)	60.0 (12.4)	
$V1_{mAb}$ (L/kg)	24.8 (7.81)	
$V2_{mAb}$ (L/kg)	82.9 (10.0)	
CL_{PL} (L/day/kg)	27.4 (9.33)	
$V2_{PL}$ (L/kg)	82.2 (12.0)	
k_{dec} (1/day)	86.7 (9.15)	
$k_{release}$ (1/day)	34.3 (13.8)	
Residual error[b]	**Additive (nM)**	**Proportional (%)**
ADC	0.384 (19.8)	14.0 (4.82)
Total antibody	1.34 (15.3)	18.1 (5.95)
Unconjugated MMAE	0.198 (12.4)	21.4 (7.59)
Conjugated MMAE	0.466 (26.4)	11.7 (7.60)

%RSE relative standard error

[a] Random effect expressed as %CV indicating variability among individual study groups with different MMAE-based ADC and doses

[b] Combined proportional and additive residual error models selected for all analytes in the PK model

Figure legends

Fig. 1. Structures of generalized PK models for MMAE-based ADCs. The PK model describes conjugates (including conjugated antibody and conjugated MMAE), unconjugated MMAE, and naked antibody, where each analyte is captured using two-compartment models. The degradation of conjugated MMAE is assumed to release all its conjugated payloads equivalent to the average DAR value at the given time, as described via CL_{mAb}·DAR. The deconjugation of conjugated MMAE is assumed to release one conjugated payload, denoted via $k_{release}$.

Fig. 2. Clinical PK profiles of four ADC analytes across various MMAE-based ADCs. The collected PK profiles of ADC (conjugated antibody), total antibody, unconjugated MMAE, and conjugated MMAE for various ADCs are dose-normalized to 2.4 mg/kg and plotted together. For ADCs with multiple-dose PK data, only the PK profiles after the first dose are shown.

Fig. 3. Clinical PK profiles of different ADC analytes for individual MMAE-based ADCs. The collected PK profiles of ADC (conjugated antibody), total antibody, unconjugated MMAE, and conjugated MMAE for individual ADCs are dose-normalized to 2.4 mg/kg and plotted together.

Fig. 4. Dose-exposure relationships for ADC analytes using linear regression analysis based on literature-reported values. The relationships between exposure matrices (C_{max} or AUC) and dose are shown for **(a)** conjugated MMAE, **(b)** unconjugated MMAE, **(c)** ADC, and **(d)** total mAb. Correlation coefficients (R) are provided for each relationship. Equations describing the relationships between dose (mg/kg) and C_{max} or AUC for the four analytes are provided. Literature-reported C_{max} or AUC values across the dose range are shown as dots, and the shaded area indicates the 90% CI.

Fig. 5. Model simulation of PK profiles for four ADC analytes (ADC, total antibody, unconjugated MMAE, and conjugated MMAE) in MMAE-based ADCs administered at 2.4 mg/kg every 3 weeks for 4 doses. The simulated PK profiles are superimposed with observed data dose-normalized to 2.4 mg/kg (red

dots). The simulations account for the random effect of PK parameters. The black line represents the median, and the shaded area represents the 90% CI.

Fig. 6. Diagnostic plots for four ADC analytes (ADC, total antibody, unconjugated MMAE, and conjugated MMAE) for MMAE-based ADCs. The plots display population and individual predictions versus observed concentrations, with the identity line (*solid line*) and 2-fold boundary lines (*dashed lines*).

Fig. 7. Visual predictive check (VPC) for four ADC analytes (ADC, total antibody, unconjugated MMAE, and conjugated MMAE) in MMAE-based ADCs. The solid lines represent the 50^{th} percentile of the observed data, while the dashed lines depict the 5^{th} and 95^{th} percentiles. The red shaded areas represent the 95% CI for the 50^{th} percentile, and the blue shaded areas represent the 95% CI for the 5^{th} and 95^{th} percentiles, derived from 1000 stochastic profiles simulated using the generalized PK model.