

Population Pharmacokinetic (PK) and Pharmacokinetic-Pharmacodynamic (PK-PD) Modeling of Serum M-Protein in an Ongoing Phase 1/2 Study of Modakafusp Alfa in Patients with Relapsed or Refractory Multiple Myeloma (RRMM)

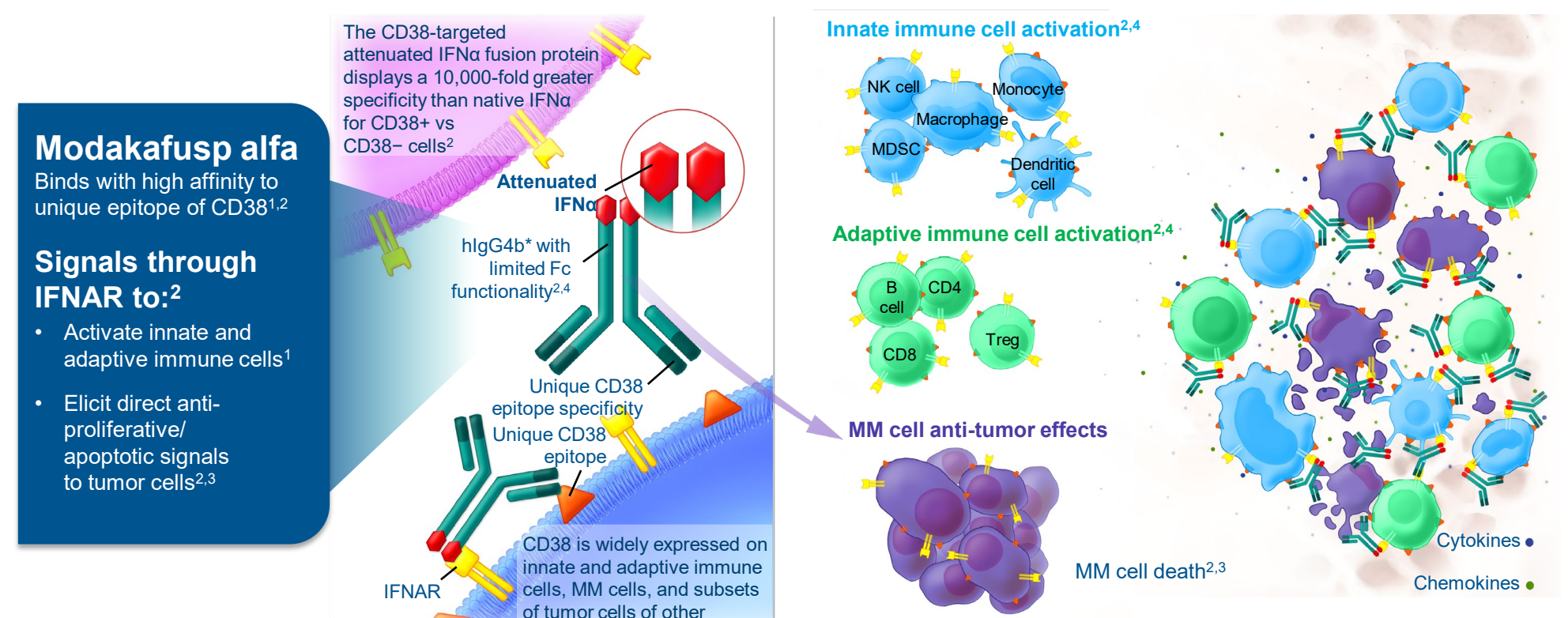
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Statement of Purpose

- Modakafusp alfa (TAK-573) is a novel, first-in-class, innate immunity enhancer that functions through targeted interferon (IFN) signaling
- Modakafusp alfa was designed to deliver attenuated IFNα2b to CD38-expressing immune and myeloma cells (**Figure 1**); targeted drug delivery and reduced affinity of attenuated IFNα2b for the IFN receptor (IFN_R) aim to minimize off-target systemic toxicity while maintaining efficacy
- We conducted a population PK analysis for modakafusp alfa and sequential PK-PD analysis of serum M-protein (i.e., myeloma protein) as a primary marker of tumor burden in RRMM

Figure 1. Modakafusp Alfa Mechanism of Action

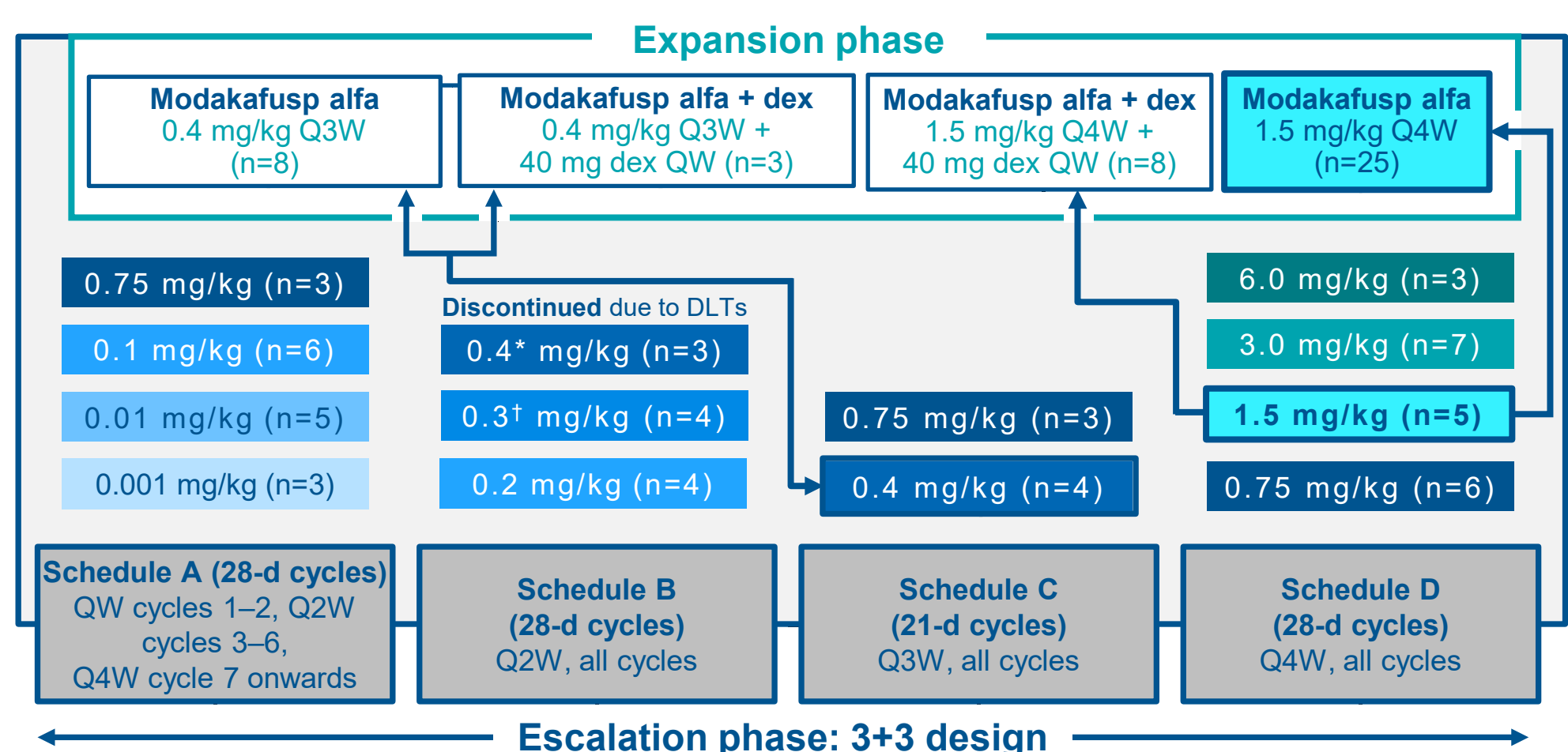


*hlgG4 is a poor inducer of Fc-mediated effector functions, such as antibody-dependent cellular cytotoxicity and phagocytosis.
hlgG4b, human immunoglobulin G4b; IFN_R, interferon α receptor; MDSC, myeloid-derived suppressor cell; MM, multiple myeloma; NK, natural killer; Treg, regulatory T cell.

Methods

- The PK analysis included 96 patients with RRMM at the end of dose escalation (Part 1) and expansion (Part 2) phases of a single-agent Phase 1/2 study (iinnovate-1, NCT03215030; April 15, 2022, sample-cut) (**Figure 2**)
- Patients received modakafusp alfa intravenous infusion every week (QW, 0.001–0.75 mg/kg), every 2 (Q2W, 0.2–0.4 mg/kg), every 3 (Q3W, 0.4–0.75 mg/kg), or every 4 weeks (Q4W; 0.75–6 mg/kg)
- In an ongoing extension of iinnovate-1 (Part 3) patients are being randomized to 120 and 240 mg Q4W (fixed-dose equivalent of 1.5 and 3 mg/kg, respectively, based on the median body weight of 80 kg) to identify the optimal dose of single-agent modakafusp alfa
- Blood samples were collected to evaluate PK and anti-drug antibodies (ADA). Serum concentrations of unbound modakafusp alfa were determined with a validated enzyme-linked immunosorbent assay
 - The presence of ADA was detected using a validated bridging electrochemiluminescence assay. A data limitation was interference of high-titer ADA on the unbound PK assay. An exploratory total PK assay with greater tolerance to ADA is in development
- Population PK analysis was conducted using NONMEM[®] V7.4.4, implementing Monte Carlo importance sampling and the Beal M3 method to account for data below the lower limit of quantification (LLOQ). During structural PK model development: (1) a quasi-equilibrium (QE) bispecific target-mediated drug disposition (TMDD) model⁶ using *in vitro* binding constants for CD38 and IFN_R; (2) a single receptor pool QE TMDD model,⁷ and a reduced linear plus Michaelis-Menten (MM) model were tested to account for nonlinear PK
 - Potential ADA impact was evaluated for in each model as an additional clearance (CL_{ADA}) pathway using a Hill-type function of the observed ADA titer in each cycle. For the linear plus MM model, an alternative ADA binding model^{8,9} was also evaluated
- In the sequential PK-PD analysis, serum M-protein from patients evaluable at baseline was fit with the Claret tumor growth inhibition (TGI) model¹⁰ to explain tumor growth, drug effect using an E_{max} model, and drug resistance

Figure 2. Study Design of Parts 1 and 2 of iinnovate-1



*Per protocol version available, patients may have been enrolled under schedule A.
Dex, dexamethasone; DLT, dose-limiting toxicity.

Results – Population PK Model

- All evaluated structural PK models capably described the PK data for modakafusp alfa across cycles. The linear plus MM model (**Figure 3 and Table 1**) offered a substantial advantage over the bispecific TMDD model in terms of runtime/optimization
- The linear plus MM model performed better when utilizing the ADA binding model rather than using ADA to enhance the linear clearance (i.e., CL_{ADA}), and allowed prediction of both unbound and total drug concentrations
- Body weight was a significant predictor on central volume of distribution (V_c-Weight power of 0.509) but did not appear to impact the other model parameters including CL and V_{max}. The low impact of weight on PK is consistent with the results from a previous analysis for this study (August 2021 data-cut) and continues to support the switch from weight-based dosing to fixed dosing¹¹

Figure 3. Final Population PK Model Diagram

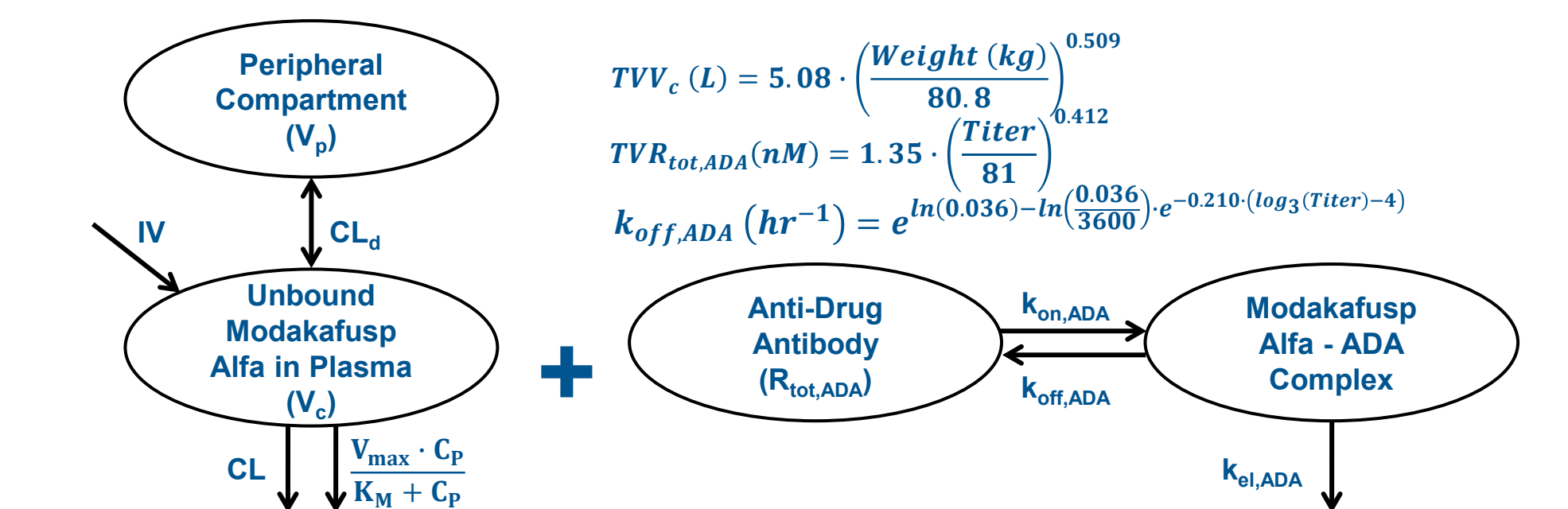


Table 1. Population PK Model Final Estimates

Parameter	Estimate	%RSE
CL (L/hr)	0.0553	8.97
V _c (L) coefficient for typical 80.8 kg patient	5.08	6.44
V _c - weight power exponent	0.509	30.4
CL _d (L/hr)	0.137	16.4
V _p (L)	4.01	16.7
V _{max} (nmol/hr)	4.77	13.6
K _m (nM)	1.26	40.0
R _{tot,ADA} (nM) coefficient for Titer of 81	1.35	118
R _{tot,ADA} - titer power coefficient	0.412	4.29
K _{off,ADA} (nM ⁻¹ ·hr ⁻¹)	3.60	Fixed ^d
K _{off,ADA,max} (hr ⁻¹) when titer = 0	3600	Fixed ^e
K _{off,ADA,min} (hr ⁻¹) when titer approaches ∞	0.0360	Fixed ^e
K _{deg} (none)	0.210	10.8
K _{deg,ADA} (hr ⁻¹)	0.0275	5.23
ω ² for CL	0.307 (60.0 %CV)	85.1
ω ² for V _c	0.391 (69.2 %CV)	28.7
ω ² for CL _d	2.84 (402 %CV)	33.0
ω ² for V _p	1.04 (135 %CV)	36.9
ω ² for V _{max}	1.14 (146 %CV)	36.0
ω ² for R _{tot,ADA}	1.63 (203 %CV)	50.4
Proportional Residual Variability (σ ²)	0.156 (39.5 %CV)	2.79

Note: Off-diagonal covariance estimates are not reported.
^aBased upon parameter reported by Chen et al.⁶; ^bBased upon parameters reported by Joyce et al.⁹

Results – Population PK/PD Model for Serum M-Protein

- The TGI model (**Figure 4 and Table 2**) using unbound drug as the PK-PD driver in a non-linear killing function adequately described the observed M-protein data in Parts 1 and 2 of the study (**Figure 5**)
- Alternative PK-PD models which used the binding model estimated total drug (unbound + ADA-bound drug) and time-varying neutralizing activity (NAb) did not provide a better fit
- As a disease prognostic indicator, baseline serum albumin (ALB₀) exhibited a strong inverse relationship with baseline serum M-protein (p < 0.00001)
- The PK-PD model confirmed that the dose-response relationship was not yet optimized at doses up to 0.75 mg/kg, consistent with observed lack of clinically meaningful response at these doses
- Best objective response rates (ORRs) of 43.3% and 42.9% were achieved at 1.5 mg/kg (n=30) and 3.0 mg/kg (n=7) and in agreement with model-predicted ORRs of 49% and 61%, respectively

Figure 4. Final Population PK-PD Model Diagram

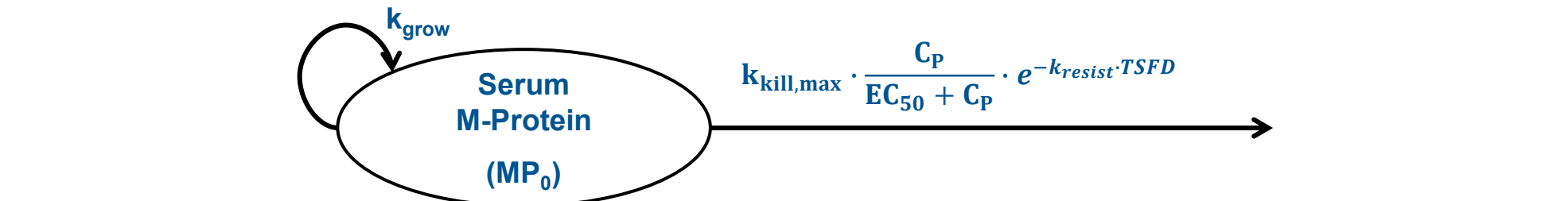


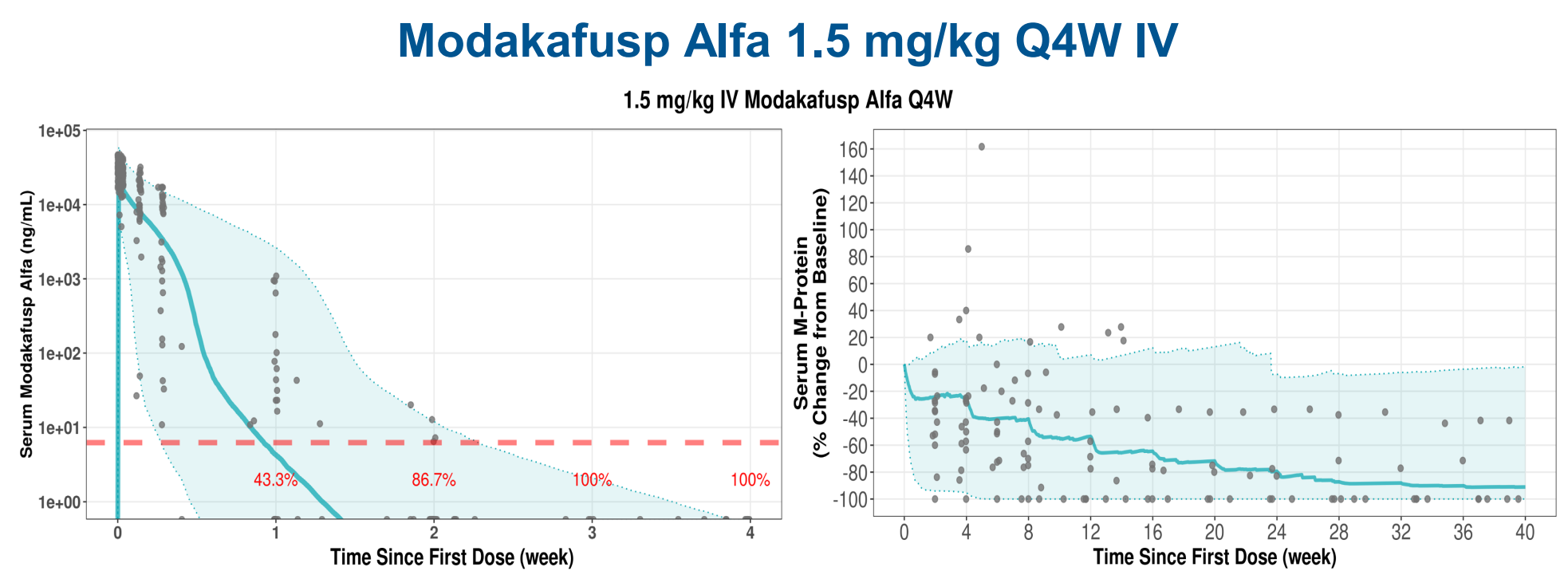
Table 2. Population PK-PD Model Final Estimates

Parameter	Estimate	%RSE
MP ₀ (g/L)	17.4	4.40
MP ₀ - ALB ₀ power coefficient	-2.74	28.7
K _{grow} (week ⁻¹)	0.0303	18.5
K _{resist} (week ⁻¹)	0.0568	61.2
K _{kill,max} (week ⁻¹)	0.816	42.6
EC ₅₀ (ng/mL)	447	48.0
ω ² for MP ₀	0.343 (63.9 %CV)	28.7
ω ² for K _{grow}	1.01 (132 %CV)	29.9
ω ² for K _{resist}	1.25 (157 %CV)	107
ω ² for K _{kill,max}	1.11 (143 %CV)	53.5
ω ² for EC ₅₀	1.57 (195 %CV)	454
Covariance EC ₅₀ - K _{kill,max}	-0.374	174
Proportional Residual Variability (σ ²)	0.0161	5.63
Additive Residual Variability (σ ²)	6.58	13.3

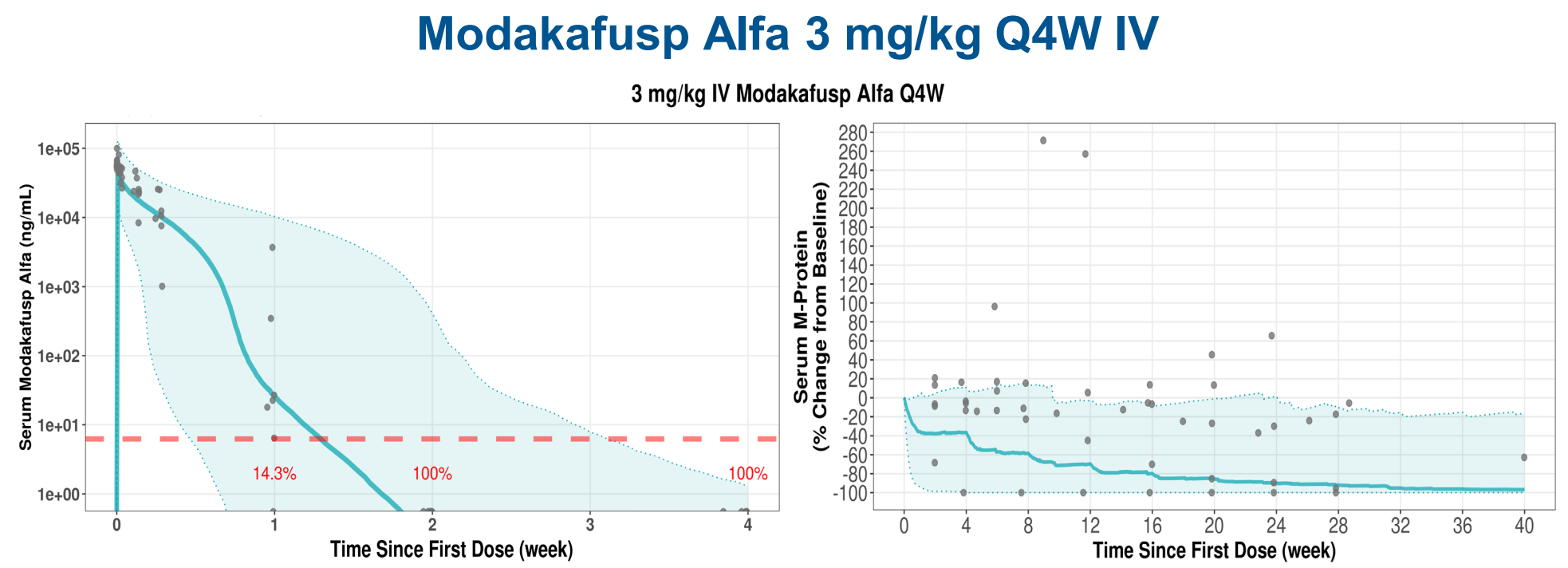
Simulation of PK, Serum M-Protein and Efficacy

- During simulations, objective response was defined as ≥ 50% decrease in serum M-protein from baseline. Progressive disease was defined as a serum M-protein relative increase of ≥ 25% from the lowest value with an absolute increase of ≥ 5 g/L; or an absolute increase of ≥ 10 g/L if baseline value is ≥ 50 g/L, regardless of the relative percent increase
- A total of 200 patients with RRMM were simulated from the observed body weight distribution, while patient ADA titer versus time data were bootstrapped with replacement from the observed PK analysis population in the 1.5 or 3 mg/kg dose groups, respectively
- For the two fixed doses currently being evaluated in Part 3 of the study, the model-predicted best ORR was 43% for 120 mg Q4W and 54% for 240 mg Q4W, suggesting that 240 mg Q4W would be associated with ~10% greater ORR than 120 mg Q4W (**Figure 6**)

Figure 5. Simulated PK and Serum M-Protein Overlayed with Observed Data from Study 1501 Parts 1 (Escalation) and 2 (Expansion) (1.5 and 3 mg/kg Q4W)

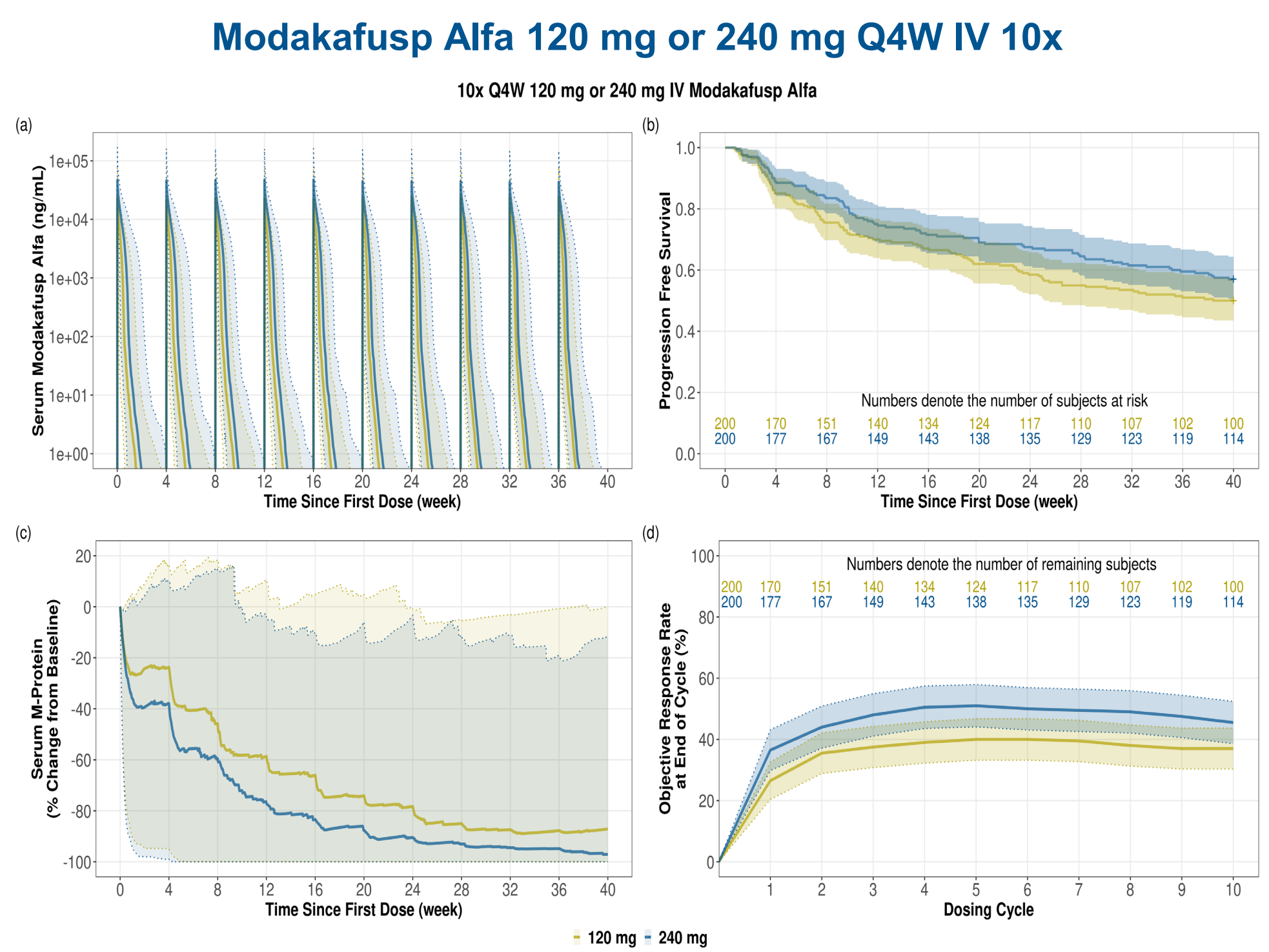


Note: The simulated median (90% PI) of the virtual cancer population (N = 2500) is shown in blue. Observed data (PK, n=34; PD, n=19) is overlaid in gray. The LLOQ is 6.25 ng/mL (red line) and the percent of data that is BLQ per 1-week bin is shown by red numbers.



Note: The simulated median (90% PI) of the virtual cancer population (N = 2500) is shown in blue. Observed data (PK, n=7; PD, n=8) is overlaid in gray. The LLOQ is 6.25 ng/mL (red line) and the percent of data that is BLQ per 1-week bin is shown by red numbers.

Figure 6. Simulated PK and Efficacy for Part 3 (Extension) of Study 1501 (120 and 240 mg Q4W)



Note: Two hundred virtual patients were included for each simulated dose prior to patient dropout; plots show median (90% Prediction Interval) in (a) and (c), and probability (95% confidence interval) in (b) and (d).

Conclusions

- The final PK model, based on data from Parts 1 and 2 of iinnovate-1 (April 15, 2022 sample cut-off), accounted for a low impact of body weight on V_c and characterized apparent changes in unbound drug concentrations due to time-varying ADA titers
- The PK model in conjunction with the TGI PK-PD model provided a simulation framework of efficacy and projected that 240 mg Q4W would provide a greater ORR than 120 mg Q4W in the ongoing Part 3 of the study
- The potential impact of immunogenicity on the PK, efficacy, and safety of modakafusp alfa remains to be further characterized in larger cohort trials during modakafusp alfa development

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Note

The results in this abstract have been previously presented at the American Conference on Pharmacometrics, National Harbor, MD, USA on November 5–8, 2023 and published in the conference proceedings as abstract PMX686.