

Population Pharmacokinetics (PK) and Pharmacodynamics (PD) of Natalizumab in Patients with Multiple Sclerosis (MS)

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INTRODUCTION

- Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease with complex pathophysiology involving immune cell trafficking to the central nervous system (CNS).
- Reducing the trafficking of immune cells has proved to be effective in MS[2].
- Natalizumab is a first-in-class, humanized anti- $\alpha 4$ integrin antibody used to treat MS[2].

OBJECTIVES

- Develop a population PK and PD model to characterize natalizumab PK and $\alpha 4$ integrin saturation (PD) across MS subjects with intravenous or subcutaneous natalizumab administration.
- Describe demographic factors that lead to difference in exposure and alpha-4 integrin saturation.

METHODS

- Natalizumab serum PK and $\alpha 4$ integrin saturation PD data were obtained across two phase 2, three phase 3, and five post marketing clinical studies.
- In total, 12788 serum and 4917 whole blood samples were analyzed for natalizumab concentration and $\alpha 4$ integrin saturation, respectively. Samples from 1267 patients were included in the $\alpha 4$ integrin population analysis.
- PK and PD models were developed sequentially using NONMEM (version 7.3) [1].
- Simulations were conducted to understand the effects of demographic covariates on PK-PD response.

PK AND $\alpha 4$ -INTEGRIN BINDING MODEL

- Natalizumab PK was best described by a 2-compartmental model with linear and Michaelis-Menten elimination. The subcutaneous absorption was characterized using 1st-order absorption with lag time.
- Covariate analysis showed that CL, V_2 increased as body weight increased. CL was higher in subjects who were administered with phase 2B formulations, and in those who developed binding antibodies to natalizumab (Table 1).
- The relationship between natalizumab and $\alpha 4$ integrin saturation was described using a sigmoidal E_{max} direct effect model with baseline.
- The magnitude of PD response was affected by the administered natalizumab formulation and subject age (Table 1).
- The qualification of the final PK/PD model was evaluated by pcVPC, those suggested that the model accurately predicted concentrations in subjects for wide range of dose and time (Figure 1).

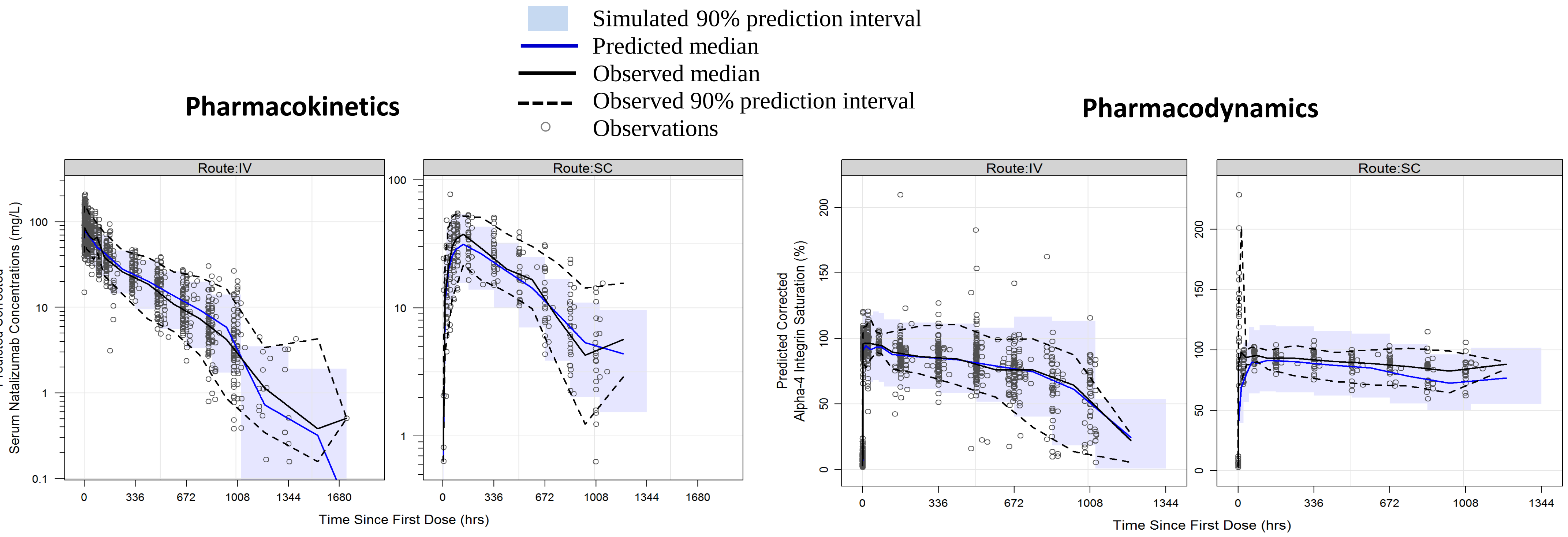


Figure 1: Left Panel: Prediction-Corrected Visual Predictive Check (pcVPC) for the Concentration-Time after dose Profiles of Natalizumab (Single-Dose). Right Panel: pcVPC for the Alpha-4 Integrin-Time after dose Profiles of Natalizumab (Single-Dose).

PHARMACOKINETIC MODEL		
PARAMETER	ESTIMATE	[†] BOOTSTRAP ESTIMATE, MEDIAN (95% CI)
CL (L/hr)	0.00625	0.00621 (0.0056-0.0067)
V_2 (L)	3.76	3.75 (3.65-3.86)
V_3 (L)	1.82	1.83 (1.62-2.06)
Q (L/hr)	0.0168	0.0169 (0.012-0.0242)
V_{MAX} (mg.hr ⁻¹ .L ⁻¹)	0.155	0.158 (0.124-0.202)
K_M (mg.L ⁻¹)	7.55	7.64 (4.71-11.7)
K_A (hr ⁻¹)	0.0111	0.0112 (0.0094-0.130)
Lag.Time (hr)	3.03	3.04 (2.73-3.46)
F (dimensionless)	0.822	0.824 (0.769-0.876)
WT on CL	0.863	0.867 (0.763-0.968)
WT on V_2	0.292	0.290 (0.174-0.398)
ADA on CL	2.54	2.55 (1.99-3.20)
FORM on CL	2.17	2.16 (1.96-2.42)
Variance on CL	0.120	0.119 (0.105-0.139)
Variance on V_2	0.0751	0.0752 (0.060-0.091)
Variance on K_A	0.121	0.112 (0.0345-0.209)
Covariance on (CL, V_2)	0.0366	0.0368 (0.027-0.045)
Proportional Error	0.260	0.260 (0.251-0.269)

PHARMACODYNAMIC MODEL		
PARAMETER	ESTIMATE	[†] BOOTSTRAP ESTIMATE, MEDIAN (95% CI)
E ₀ (%)	6.64	6.62 (6.20-7.07)
E _{MAX} (1) (%)	83.8	83.8 (81.9-86.6)
EC ₅₀ (mg.L ⁻¹)	2.51	2.51 (2.25-2.94)
Hill (1)	1.35	1.34 (1.14-1.56)
Form (2)-E _{MAX} (%)	99.6	99.8 (93.4-106.3)
Form (3)-E _{MAX} (%)	86.4	86.5 (83.6-90.2)
Age on E _{MAX}	0.249	0.249 (0.181-0.330)
Form (2)-Hill	0.679	0.675 (0.561-0.834)
Form(3)-Hill	1.030	1.02 (0.876-1.20)
Age on Hill	-1.090	-1.09 (-1.50 - -0.702)
Variance on E _{MAX}	0.0119	0.0116 (0.008-0.015)
Variance on Hill	0.238	0.231 (0.151-0.331)
Additive error (%)	9.72	9.73 (9.26-10.2)

Table 1: Parameter estimates of the final natalizumab population PK-PD model. Abbreviations: CL – Clearance, V_2 : Central volume of distribution, V_3 : Peripheral volume of distribution, Q: Inter compartmental clearance, V_{MAX} : Maximum binding rate, K_M : Concentration at half maximum binding rate, K_A : Rate of absorption, F: Relative bioavailability of S.C. route of administration to I.V. route of administration. [†]Calculated from 1000 bootstrap data sets, 988 runs were successful. 12 runs with minimization terminated were skipped when calculating the bootstrap results. E0: Baseline % $\alpha 4$ saturation value (Assay background noise), EMAX: Magnitude of saturation, EC50: Natalizumab serum concentration at half maximum saturation, Hill: Shape factor, Add. Err: Additive error. ^{††} Calculated from 1000 bootstrap data sets, 980 runs were successful. 20 runs with minimization terminated were skipped when calculating the bootstrap results. Form (1): Effect for commercial formulations . Form (2): Effect for experimental formulations. Form (3): Effect for formulations Phase 2/3 formulations grouped together.

PK-PD SIMULATIONS

- Classification used in the simulation represents the 10th and 90th percentile, respectively, for weight, age in the overall study population.
- Although a significant covariate, body weight explains only 6% of the overall variability of 40% in exposure to natalizumab in MS subjects (Figure 2).
- Simulations indicate that at steady state, independent of age, subjects receiving 300 mg Q4W natalizumab were able to maintain a sustained complete PD (% alpha-4 integrin saturation >70%) (Figure 2).

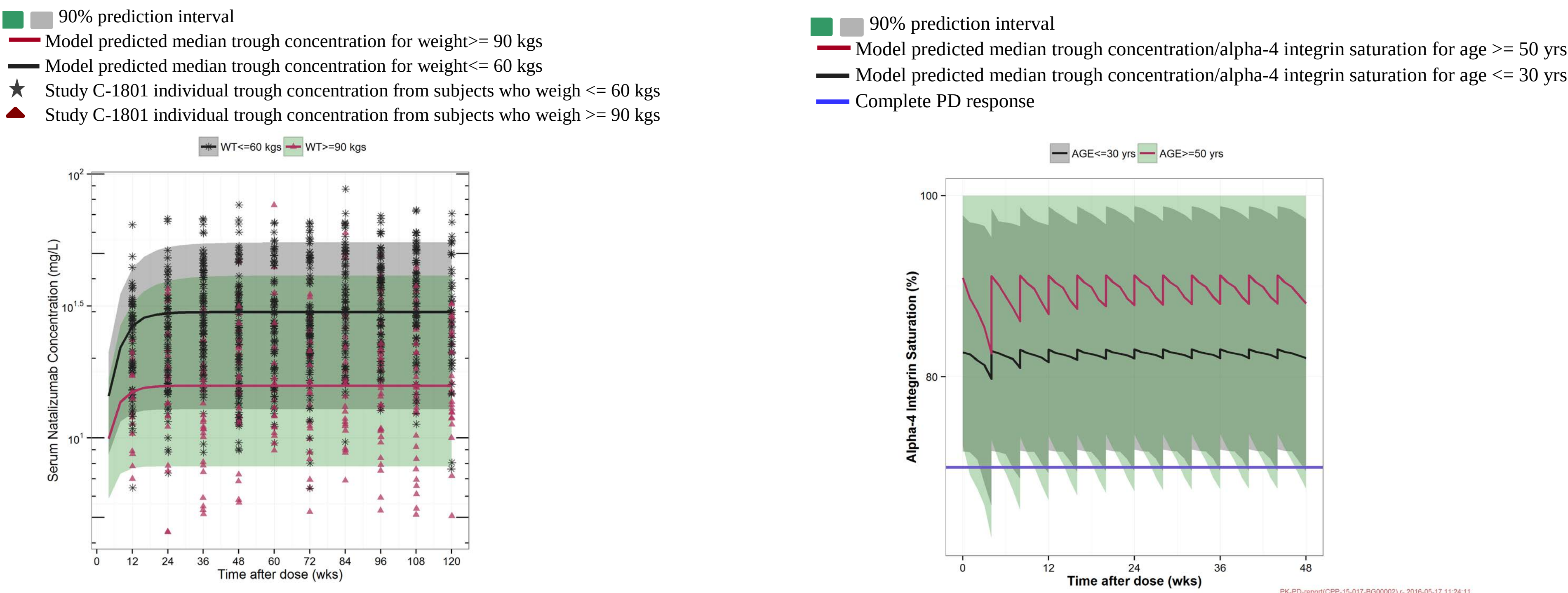


Figure 2: Left Panel. Simulations of the time course of median trough concentrations (90% prediction interval) in lighter (<60 kgs) or heavier (>90 kgs) MS subjects dosed with 300 mgs IV natalizumab Q4W for a duration of 120 weeks. Right Panel. Predicted effect of age on alpha-4 integrin saturation following Q4W dosing of 300 mgs Natalizumab

CONCLUSIONS

- The developed population PK/PD model adequately quantifies natalizumab PK and $\alpha 4$ integrin saturation.
- The EC₅₀ for $\alpha 4$ integrin saturation is estimated to be 2.51 mg/L. This value was comparable to published literature and in-vitro data[2].
- Although Phase 2 formulations have 2.17 fold lower clearance, minor impact on $\alpha 4$ integrin saturation is observed relative to Phase 3 and commercial formulation.
- Based on the simulation analysis, the current approved clinical dosing regimen (300 mg IV Q4W) is expected to ensure a rapid and sustained PD response, regardless of the demographics of the patient population.

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