

CD25 Occupancy by Daclizumab HYP in Patients with Relapsing Remitting Multiple Sclerosis

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INTRODUCTION

- Multiple sclerosis (MS) is a chronic inflammatory disease characterized by immune cell-mediated damage to central nervous system (CNS) that affects approximately 2.3 million people worldwide. This disease occurs 2-3 times more frequently in women and most people with MS are diagnosed between 20 and 50 years of age.¹
- MS primarily affects myelinated fiber tract. Focal demyelinated plaques within the CNS are the most notable pathologic characteristics of MS, and these may vary in extent of inflammation, gliosis, and neurodegeneration.²
- Daclizumab high yield process (DAC HYP) is a humanized immunoglobulin (IgG) 1 monoclonal antibody that binds to the alpha subunit of the human high-affinity IL-2 receptor (CD25) expressed on the surface of activated lymphocytes, inhibiting high-affinity but not intermediate-affinity IL-2 receptor signaling.³
- DAC HYP has been studied in patients with human autoimmune conditions characterized by abnormal T-cell responses such as MS.⁴ In pivotal trials, DAC HYP demonstrated efficacy in reducing disease activity in relapsing-relmitting multiple sclerosis (RRMS).^{5,6}
- This analysis characterized the quantitative relationships between DAC HYP exposure and CD25 occupancy on target T cells in blood of RRMS patients.

METHODS

- Three pivotal and one immunogenicity study were included in this analysis (Table 1).
 - SELECT (NCT00390221)⁵ was a Phase 2 dose finding and placebo-controlled study in RRMS. SELECTION (NCT00870740),⁷ was the extension study in which subjects were randomized to 3 cohorts: continuing exposure to DAC HYP, 24-week washout followed by re-initiation of DAC HYP, and first exposure to DAC HYP.
 - DECIDE (NCT01064401)⁶ was a Phase 3 monotherapy, active-control study to characterize the efficacy and safety of DAC HYP 150 mg subcutaneous (SC) every 4 weeks versus interferon (IFN) beta-1a (Avonex®) 30 mcg intramuscular (IM) once weekly in patients with RRMS.
 - OBSERVE (NCT01462318) was a single-arm study to assess the immunogenicity of DAC HYP in subjects with RRMS.
- CD25 occupancy by DAC HYP was measured by a validated fluorescence-activated cell sorter (FACS) assay using anti-CD25 antibodies that detected unoccupied CD25 on CD4+ T cells in the presence of DAC HYP. CD25 saturation was defined as at any time during which unoccupied CD25 was detected on ≤1% of CD4+ T cells in the presence of a measurable CD4+CD25+ T cell population (≥1% of CD4+ T cells express CD25).
- Sampling scheme for CD25 occupancy was sparse mostly once every 4 weeks except for 19 patients in the intensive PK subgroup in one study (OBSERVE) where the early sampling points included 8h and 24h (Table 1).
- Population analysis using NONMEM (Version 7.2) was applied to more than 7000 CD25 observations obtained from 1400 RRMS patients.
- A sequential approach was implemented in which the pharmacokinetic (PK) part was fixed in the modeling utilizing a developed population PK model (Table 2). Inter-individual variability (IIV) was modeled using log-normal or normal distribution as appropriate.
- Goodness-of-fit plots include observation (DV) vs population prediction (PRED), DV vs individual prediction (IPRED), conditional weighted residual (CWRES) vs TIME, CWRES vs PRED plots.
- To check the predictive performance of the model, visual predictive check (VPC) was performed.

Table 1. Dosing regimens and CD25 measurement schedule

Study	Dosing regimens	CD25 measurement schedule
SELECT	150, 300 mg every 4 weeks	Week 0, 4, 8, 16, 24, 32, 40, 48, (52, 56, 64, 72) ^a
SELECTION	150, 300 mg every 4 weeks	Week 0, 4, 12, 20, 24, 32, 40, 52, (72) ^b
DECIDE	150 mg every 4 weeks	Week 0, 4, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 164
OBSERVE	150 mg every 4 weeks	Intensive PK subgroup: predose, 8h, 24h, 72h, 120h, Day 7, 10, 14, 21 and 28, postdose at week 20 Non-intensive PK: Week 0, 2, 4, 8, 12, 16, 20, 24, (28, 32, 36, 44) ^c

^aPatients who didn't roll-over to SELECTION, follow-up period
^bPatients who didn't roll-over to SELECTION extension, follow-up period
^cFollow-up visits

Table 2. Population PK characteristics for DAC HYP⁸

PK of DAC HYP in healthy volunteers and RRMS patients is characterized by slow clearance, linear PK at doses above 100 mg, and high subcutaneous bioavailability (88% for 100-300 mg SC dose)
Two-compartment with 1st-order absorption and elimination
Clearance (CL) = 0.212 × [body weight(kg)/68] ^{0.87} L/day Central Vd (Vc) = 3.92 × [body weight(kg)/68] ^{1.12} L Peripheral Vd (Vp) = 2.42 L Terminal half-life = 21 days
Time-varying neutralizing antibody (NAb) positive status increased the DAC HYP CL by 19%
Inter-individual variability (IIV) for CL, Vc and Ka were 27.2, 50.9 and 94.4%, respectively

- A sigmoidal Emax model was utilized to characterize the unoccupied CD25. In this equation, CD25 denotes the unoccupied CD25. Since CD25 occupancy was completely saturated by DAC HYP at sufficiently high concentration, Emax value was fixed at 1 in the model.

$$CD25 = E0 \cdot \left(1 - \frac{Cs^\gamma}{Cs^\gamma + IC50^\gamma}\right) \quad \text{Sigmoidal Emax model}$$

Cs: Serum concentration of DAC HYP
E0: Baseline % CD3+/CD4+ T cells staining positive for CD25

RESULTS

- Separate PD parameters (γ and IC50) were needed to characterize the saturation following the first dose and the desaturation after one-year treatment for CD25 occupancy (Table 3).

Table 3. Summary of the CD25 occupancy model

Parameter	Value	Bootstrap Median (2.5 th , 97.5 th) ^a
Baseline E0	55.7	55.7 (55.0, 56.4)
IIV (additive)	10.8	10.8 (10.2, 11.3)
Initial saturation stage IC50 (mg/L) γ	0.0135 (FIXED) 1 (FIXED)	
Desaturation stage IC50 (mg/L) IIV, % γ	2.07 46.9 4.44	2.02 (1.50, 2.39) 47.2 (36.1, 79.1) 4.35 (3.19, 5.18)
Residual (additive)	4.02	4.03 (3.13, 4.72)

^aSummary from 1454 successful runs out of 2000 runs

- Goodness-of-fit plots and visual predictive check were provided in Figure 1 and Figure 2. The model adequately described the relationship between DAC HYP exposure and the kinetics of CD25 occupancy.

Figure 1. Goodness-of-fit plots for the CD25 occupancy model

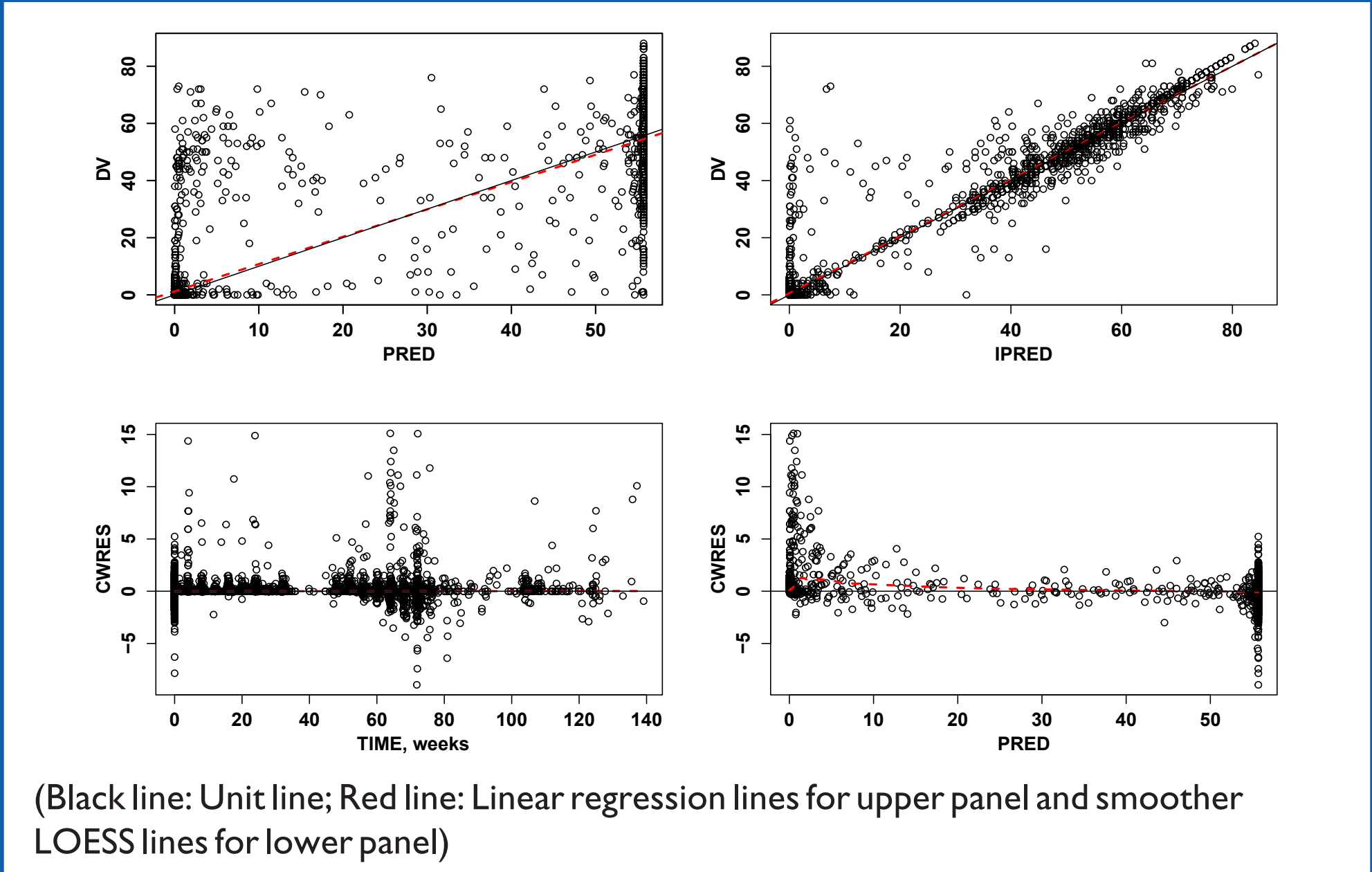
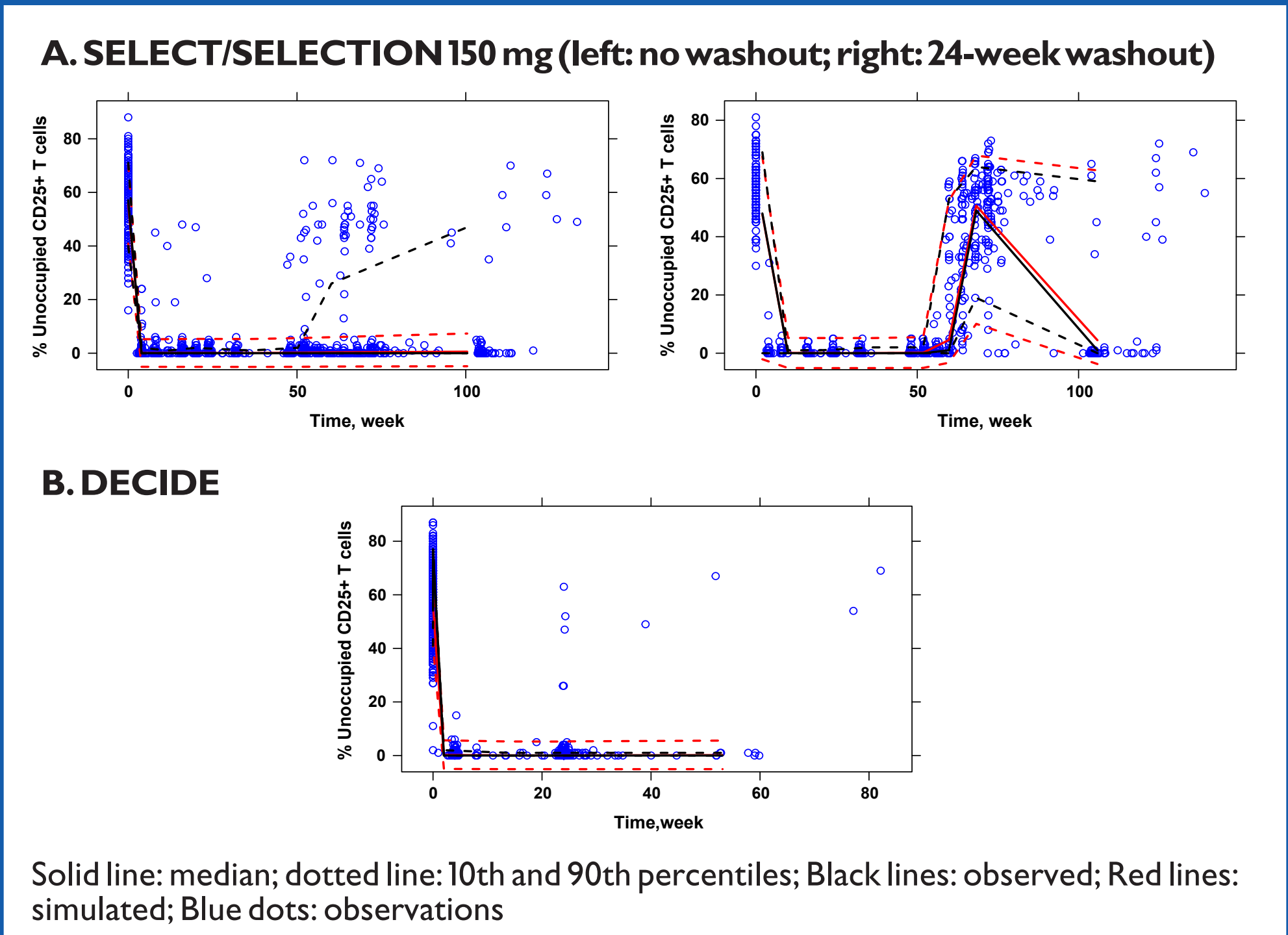
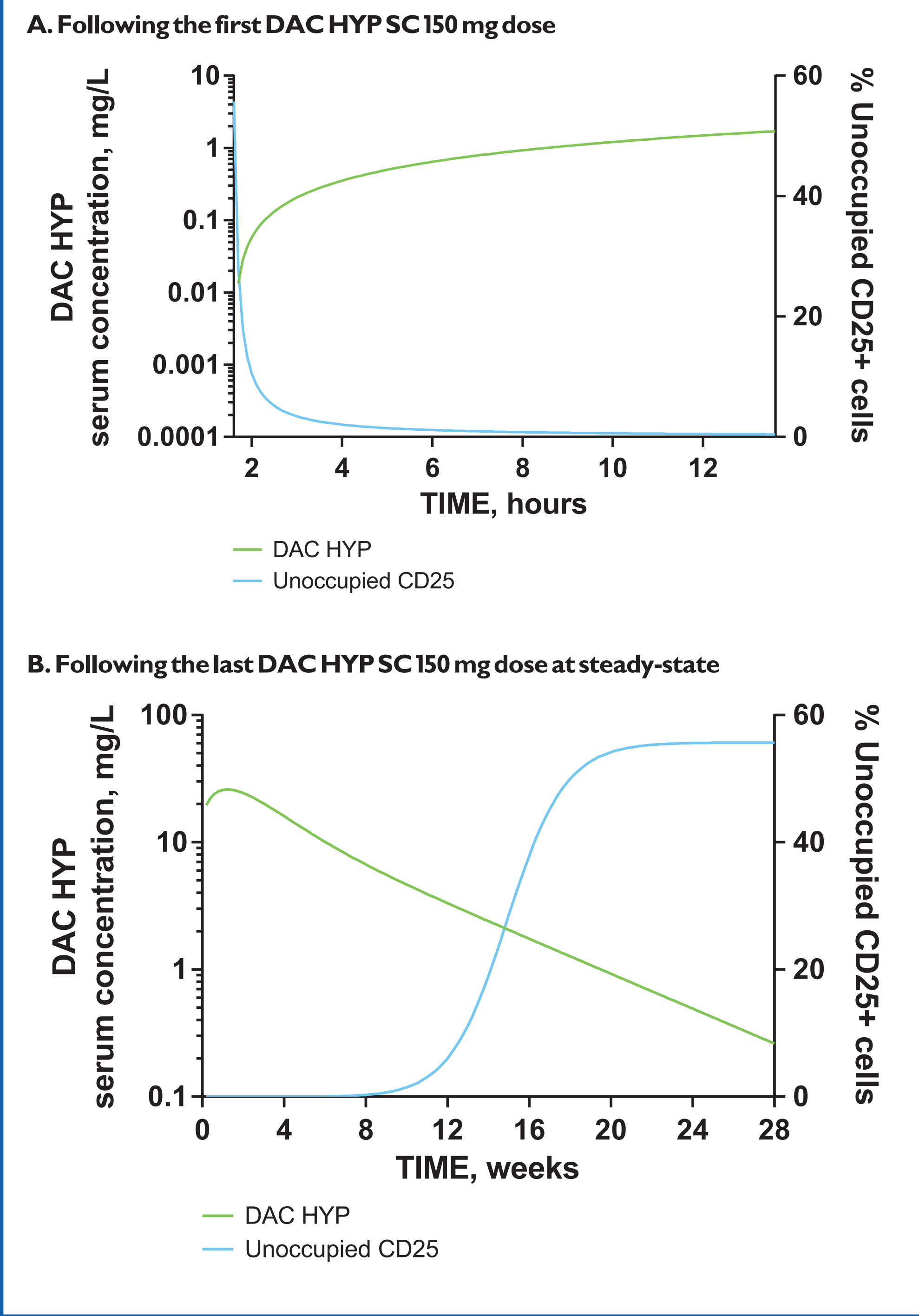


Figure 2. Representative VPC of the CD25 occupancy model



- DAC HYP PK and CD25 occupancy for a typical subject following DAC HYP 150 mg every 4 weeks was simulated (Figure 3).
 - CD25 occupancy is rapid with complete saturation predicted ~7 h.
 - Saturation maintained when DAC HYP ≥ 5 mg/L.
 - Unoccupied CD25 levels returned to baseline between 20-24 weeks after last dose when DAC HYP concentration ≤ 1 mg/L.

Figure 3. Simulations of DAC HYP PK and CD25 occupancy



CONCLUSIONS

- The model described the relationship between DAC HYP exposure and the kinetics of CD25 occupancy.
- At DAC HYP exposures determined to be efficacious in clinical trials, CD25 occupancy on target T cells was rapid, complete and reversible in parallel with DAC HYP clearance from the body.

References

- National Multiple Sclerosis Society. Multiple Sclerosis: Just the Facts general information. 2013. Available at: <http://www.nationalmssociety.org/What-is-MS/Who-Gets-MS>. Accessed on April 15, 2015.
- Popescu BF, et al. Continuum (Minneapolis) 2013;19:901-921.
- Wiendl H, et al. Nat Rev Neurol. 2013 Jul;9(7):394-404.
- D'Amico E. Expert Opin Drug Saf. 2015 Mar 31;1:1-12.
- Gold R, et al. Lancet. 2013;381(9884):2167-2175.
- Kappos L, et al. Daclizumab HYP versus interferon beta-1a in relapsing-remitting multiple sclerosis: Primary results of the DECIDE study. Presented at: 67th Annual Meeting of the American Academy of Neurology; April 18-25, 2015; Washington, DC.
- Giovannoni G, et al., Lancet Neurol. 2014 May;13:472-81.
- Diao L, et al. Population Pharmacokinetics of Daclizumab High-yield Process (HYP) in Subjects with Multiple Sclerosis EAN European Academy of Neurology - 1st Congress #P4140

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