CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761029Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

BLA:	**761029**
Brand Name:	ZINBRYTA™
Generic Name:	Daclizumab High Yield Product (DAC HYP)
Dosage Form & Strength:	Subcutaneous (SC) injection liquid formulation (150 mg/mL of DAC HYP per vial) via prefilled syringe (PFS)
Indication:	Treatment of patients with relapsing forms of Multiple Sclerosis (RMS)
Applicant:	AbbVie, Inc.
Submission:	351(a)
Submission Date:	02/27/2015
OND Division:	OND-1/Division of Neurology Drug Products
OCP Divisions:	Clinical Pharmacology DCP-1
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1. Executive Summary

The sponsor is seeking approval of Zinbryta (BIIB019; Daclizumab High Yield Product or DAC HYP) as a treatment for adult patients with relapsing forms of Multiple Sclerosis (RMS). DAC HYP belongs to the drug class of anti-CD25 humanized monoclonal immunoglobulin G1 (IgG1) antibody that binds the CD25, alpha subunit of interleukin-2 (IL-2) receptor, and prevents binding of CD25 to its ligand, IL-2. This modulation of IL-2 signaling underlies the direct and indirect effects of daclizumab in vivo. The available strength of Zinbryta is 150 mg/mL in clear liquid solution. The single-dose Prefilled Syringe (PFS) for self-administration was proposed for marketing. The proposed dosing regimen of Zinbryta is 150 mg injected subcutaneously (SC) (b) (4).

The sponsor conducted four Phase 1 clinical pharmacology studies in healthy subjects and one immunogenicity study in subjects with multiple sclerosis (MS) to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of DAC HYP following SC or IV administration. Additional characterization was carried out using sparse sampling from Phase 2 and 3 clinical trials in subjects with MS. The therapeutic protein-drug interaction (TP-DI) potential for DAC HYP was investigated as part of a Phase 3 study to evaluate the effect of DAC HYP on the PK of probe substrates for selected CYP isozymes in subjects with MS. A Phase 2 study, was conducted using DAC Penzberg (an investigational form of DAC used for clinical research) to support dose selection for pivotal clinical trial. Serum DAC HYP concentration was determined using validated enzyme-linked immunosorbent assay (ELISA) in all studies. The PD responses and anti-drug antibodies were assessed for DAC HYP biological activity. Population PK and PK/PD analyses were performed to evaluate the potential impact of covariates on PK and PD, as well as the potential relationship between DAC HYP exposure and efficacy endpoints from clinical trials. The Phase 3 program included 2 pivotal studies (Study 205MS201 and Study 205MS301), as well as additional long-term efficacy and safety extension studies to assess the clinical efficacy and safety in support of the approval.

From a clinical pharmacology perspective, the proposed 150 mg once a month dose is supported by the exposure/dose-efficacy relationship. Time-varying neutralizing antibodies status increased DAC HYP clearance by 19% on average and was reported to not appear to be clinically relevant since there was no discernible impact of immunogenicity status on the efficacy, safety, or PD profile of DAC HYP. No dosage adjustments are needed for medications that are substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A when given concomitantly with DAC HYP.

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 1 (OCP/DCP-1) has reviewed the submission and finds BLA 761029 acceptable from an OCP perspective provided that an agreement is reached between the Sponsor and the Agency regarding the revised labeling language.

1.2 Phase IV Commitment

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Pharmacokinetics

Single- and Multiple-dose:

- Disposition of daclizumab can be described by a two-compartment model with first-order absorption and elimination.
- Similar PK profiles between healthy volunteers and MS patients and between single-dose and multiple-dose.
- Following administration of DAC HYP 150 mg subcutaneously every 4 weeks, steady-state serum daclizumab concentrations were achieved by the fourth dose and daclizumab accumulated to a level approximately 2.5-fold compared to a single dose.
- Long elimination half-life (t1/2) of approximately 3 weeks
- The inter-subject variability (expressed as coefficient of variations) between individual patients were approximately 35-40% for exposure (Cmax and AUC) and 27-51% for clearance and volume of distribution.

Absorption:

- Slow absorption following SC administration, with the median time to reach maximum observed concentration (Tmax) of approximately 1 week.
- A cross-study population PK analysis indicated that daclizumab peak concentration (Cmax) and total exposure over time (AUC) increased more than dose-proportionally from 50 mg to 100 mg and in proportion to dose from 100 mg to 300 mg.
- The absolute bioavailability of subcutaneous DAC HYP was approximately 90% in the 100-300 mg dose range.

Distribution:

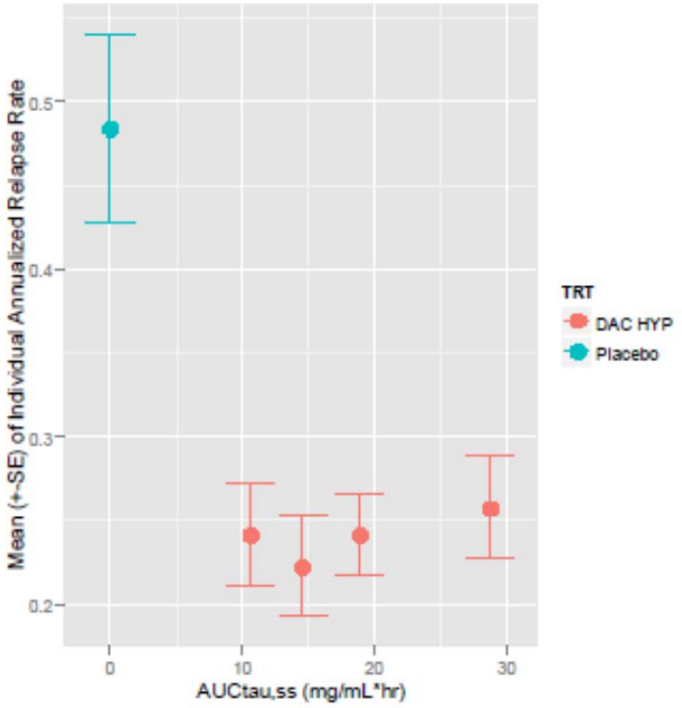
- In MS patients taking 150 mg SC doses of DAC HYP once a month, the estimated steady-state volume of distribution of daclizumab was approximately 6.34 L, suggesting that DAC HYP is largely confined to the vascular and interstitial spaces.

Metabolism and Elimination:

- Daclizumab is expected to undergo catabolism to peptides and amino acids in the same manner as endogenous IgG.
- Daclizumab is eliminated via proteolysis, target-mediated elimination, and nonspecific endocytosis, and is not expected to undergo renal elimination.
- The clearance of daclizumab is 0.212 L/day with an elimination half-life of approximately 21 days.
- Daclizumab clearance in patients who developed neutralizing antibodies was approximately 19% higher.

Exposure-Response Relationships:
A flat exposure-response relationship for efficacy was observed in the range of exposures associated with the 150 mg and 300 mg once a month doses (Figure below), which is consistent with the dose-response relationship observed in study 205MS201 (Table below). Such finding suggests that increasing the dose from 150 mg to 300 mg is unlikely to result in an increase in efficacy. Therefore, the proposed 150 mg once a month dose is supported by the exposure/dose-efficacy relationship.

Figure. Mean ARR by Placebo and DAC HYP AUCss subgroups



Source: study report CPP-14008-BIIB019 page 18

Table. Primary Efficacy Results in Study 205MS201

Study 205MS201			
	Placebo	150mg DAC HYP	300mg DAC HYP
n	196	201	203
ARR (95% CI)	0.458 (0.370, 0.566)	0.211 (0.155, 0.287)	0.230 (0.172, 0.308)
p-value		<0.0001	0.0002

Serious infection, moderate and severe cutaneous adverse events, and liver enzyme abnormalities were not found to be correlated with DAC exposure in the 150 mg and 300 mg dose range. However, the relationship between DAC exposure and the risk of other serious adverse reactions including autoimmune hepatitis could not be concluded due to limited data. It might be possible that the risk of autoimmune hepatitis is lower at a dose level below 150 mg. However, there is no data to support this hypothesis in the current submission.

Intrinsic Factors:

Age, Weight, Sex, Race and Other Potential Significant Covariates:

- None of the intrinsic factors evaluated have significant differences in DAC HYP exposure or impact on PD or clinical outcome to suggest any need for a dosage adjustment.
- No apparent PK differences were observed between Japanese and Caucasian subjects following a single-dose administration of DAC HYP at the proposed 150 mg SC dose. The effect of other races on DAC HYP PK cannot be determined due to limited subjects in the studies.
- As described in the proposed labeling, use of ZINBRYTA is not recommended in pediatric patients due to the risks of hepatic injury, autoimmune and other immune-mediated conditions, skin reactions, and malignancies.

Immunogenicity:

- Time-varying neutralizing antibodies status increased DAC HYP CL by 19% on average and was reported to not appear to be clinically relevant since there was no discernible impact of immunogenicity status on the efficacy, safety, or PD profile of DAC HYP.
- No discernible impacts of anti-drug antibodies or neutralizing antibodies (transient or persistent) were reported on MS relapse, adverse events, serious adverse events, cutaneous events, infections, and liver function test abnormalities.

Extrinsic Factors:

Effects on CYP isozymes:

Multiple doses of DAC HYP 150 mg SC every 4 weeks in MS patients had insignificant effects on the PK of probe substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A in MS patients. No dosage adjustments are needed for medications that are substrates of these CYP enzymes when given concomitantly with DAC HYP.

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2. Question Based Review

2.1 General Attributes

2.1.1 What are therapeutic indication(s) and the proposed mechanisms of action of Zinbryta?

Zinbryta (BIIB019, Daclizumab High Yield Product or DAC HYP) is proposed as a treatment for patients with relapsing forms of Multiple Sclerosis (RMS).

Daclizumab (BIIB019) belongs to the drug class of anti-CD25 humanized monoclonal immunoglobulin G1 (IgG1) antibody that binds the CD25, alpha subunit of interleukin-2 (IL-2) receptor, and prevents binding of CD25 to its ligand, IL-2. The CD25 increases the affinity of the receptor for IL-2 but does not contribute to the intracellular signal transduction of the receptor. Consequently, daclizumab-mediated blockade of CD25 limits IL-2 signaling in cells dependent on the high-affinity receptor but does not alter signaling mediated by the intermediate-affinity receptor. This modulation of IL-2 signaling underlies the direct and indirect effects of daclizumab in vivo.

2.1.2 What are the highlights of physico-chemical properties of the drug substance?

The daclizumab high-yield process (DAC HYP) drug product is formulated as a colorless to slightly yellow, clear to slightly opalescent, sterile (b) (4) solution containing (b) (4) (b) (4) 150 mg/mL of DAC HYP drug substance in (b) (4) mM succinate (b) (4), (b) (4) mM sodium chloride, (b) (4)% (w/v) polysorbate 80, pH 6.0.

The DAC HYP 100 mg/mL concentration had been studied but is no longer manufactured. The 150 mg/mL concentration is the only concentration being administered clinical studies and is the intended concentration for commercial use (in PFS). The DAC HYP drug product (DP) was used in all the clinical studies, except for supportive Study DAC-1012 in which the formulation (Penzberg DP) used in Study DAC-1012 was an investigational form of DAC for clinical research.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The recommended dosing regimen of Zinbryta is 150 mg injected subcutaneously (SC) every 4 weeks (Q4W) or monthly. The injection site include thigh, abdomen, and back of the upper arm where DAC HYP was administered in the clinical trials.

In case a dose is missed and it is within 2 weeks of the missed dose, patients should be instructed to inject their missed dose as soon as it is remembered and then remain on their original monthly dosing schedule. If a dose is missed and it is more than 2 weeks from the missed dose, patients should skip the missed dose, wait to dose again until their next scheduled dose, and then remain on their original monthly dosing schedule. Only one dose should be administered at a time.

2.1.4 What are the proposed strength(s) and dosage forms?

The proposed commercial strength of Zinbryta (DAC HYP) is 150 mg/mL liquid formulation supplied in single-dose prefilled syringe (PFS) for marketing.

DAC HYP was supplied in PFS for Studies 205MS302 and 205MS303 and in vials for the rest of the clinical studies. DAC HYP was supplied in both vials and PFS for Study 205MS203. (b) (4)

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor conducted four Phase 1 clinical pharmacology studies in healthy subjects and one immunogenicity study in subjects with multiple sclerosis (MS) to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of Daclizumab High-Yield Process (DAC HYP) following SC or IV administration. Additional characterization was carried out using sparse sampling from Phase 2 and 3 clinical trials in subjects with MS. The therapeutic protein-drug interaction (TP-DI) potential for DAC HYP was investigated as part of Phase 3 study (Study 205MS302 or Study 302) to evaluate the effect of DAC HYP on the PK of probe drugs for CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A in subjects with MS. A Phase 2 study (Study DAC-1012), was conducted using DAC Penzberg (an investigational form of DAC used for clinical research) to support dose selection for Study 205MS201 (or Study 201). Serum DAC HYP concentration was determined using validated enzyme-linked immunosorbent assay (ELISA) in all studies.

The PD response to DAC HYP was evaluated by monitoring high-affinity IL-2R alpha subunit (CD25) receptor occupancy by DAC HYP on peripheral T-cells, and by measuring serum IL-2 levels, $CD56^{bright}$ natural killer (NK) cells and $CD4^{+}CD^{127}$lowFoxP3+ T cells (Tregs) numbers. The population PK/PD relationships for CD25(2A3) binding, $CD56^{bright}$ NK cell expansion, and Treg decrease with DAC HYP treatment in RRMS subjects were characterized using data from Study 201, Study 202, Study 302, and Study 301. The potential relationship between DAC HYP exposure (area under the concentration-time curve for a dosing interval at steady state [AUCtau,ss]) and efficacy endpoints (ARR, T2 lesions and gadolinium (Gd)-enhancing lesions) was analyzed using data from Study 201 and Study 202 (150 mg and 300 mg SC every 4 weeks) and Phase 3 Study 301 (150 mg SC every 4 weeks regimen).

Immunogenicity was determined by measuring anti-drug antibodies (ADAs) using validated ADA ELISA and ADA electrochemiluminescent (ECL) assay methods. Samples that generated a positive response for ADA were further tested for the presence

of neutralizing antibodies (NAbs) in a validated cell-based assay. Observed individual ADA responses were characterized as transient or persistent, when applicable.

The key DAC HYP clinical efficacy and safety studies included 2 pivotal studies (Study 205MS201, referred to as Study 201, and Study 205MS301, referred to as Study 301) to assess the clinical efficacy and safety in support of the approval. Additional long-term efficacy and safety data were obtained in the 1 year extension Study 202 in subjects who completed treatment in Study 201, the extension Study 203 in subjects who completed treatment in Study 202, and in the extension Study 303 in subjects who completed treatment in Study 301.

A tabular summary of the clinical pharmacology and clinical studies used to support dosing or claims is presented below.

Table 1. Tabular Summary of Clinical Pharmacology and Clinical Studies

Study Identifier	Study Objectives	Study Design	Test Product; Dosage Regimen; Route of Administration	Planned Treatment Period	Number of Subjects Enrolled; Completed	Planned Age range
PK/PD Studies in Healthy Volunteers						
DAC-1015	To determine the safety, tolerability, PK, PD, and immunogenicity of SC DAC HYP	Single-dose, double-blind, placebo-controlled, dose-escalating	DAC HYP, single dose 50 mg SC (n = 7) 150 mg SC (n = 8) 300 mg SC (n = 8) Placebo SC (n = 10)[a]	Single dose	34 enrolled; 32 completed	18 to 75 years, inclusive
DAC-1014	To determine the safety, tolerability, PK, PD, and immunogenicity of multiple doses of DAC HYP administered by SC injection	Multiple-dose, randomized, double-blind, placebo-controlled	DAC HYP, multiple dose 200 mg SC every 2 weeks × 9 doses (n = 12) 200 mg SC loading dose + 100 mg SC every 2 weeks × 8 doses (n = 12) Placebo SC 9 doses (n = 8)	16 weeks	32 enrolled; 27 completed[b]	18 to 65 years, inclusive
DAC-1018	To determine the safety, tolerability, PK, PD, and immunogenicity of IV DAC HYP	Single-dose, double-blind, placebo-controlled, dose-escalating	DAC HYP, single dose 200 mg IV (n = 12) 400 mg IV (n = 12) Placebo IV (n = 7)	Single dose	31 enrolled; 30 completed	18 to 65 years
205HV102	To evaluate the PK, safety, and tolerability of DAC HYP administered as a single SC dose in Japanese and Caucasian adult HVs	Single-dose, single-blind	DAC HYP, single dose 75 mg SC (n = 28; 14 per ethnic group) 150 mg SC (n = 28; 14 per ethnic group)	Single dose	56 enrolled; 56 completed	18 to 55 years, inclusive

PK and PD Studies in MS Subjects						
205MS203 *Autoinjector PK Substudy*	To compare the systemic exposure of daclizumab following SC administration of 150 mg DAC HYP using the single-use autoinjector (PFP) to the systemic exposure following manual PFS injection	Open-label, parallel design	DAC HYP 150 mg SC from a PFS by either manual injection or by autoinjector every 4 weeks for 4 doses	16 weeks	60 enrolled; 60 completed	18 to 55 years, inclusive
205MS302 *Intensive PK Substudy*	To characterize the PK of DAC HYP following single and multiple doses of SC DAC HYP administered by the PFS in a subset of subjects with RRMS	Single-arm, open-label	DAC HYP 150 mg SC by PFS every 4 weeks for 6 doses	24 weeks	26 enrolled; 25 completed	18 to 65 years, inclusive
205MS302 *TP-DI Substudy*	To evaluate the effect of DAC HYP on the PK of probe substrates for CYP isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A) in MS subjects	Single-arm, open-label study)	DAC HYP 150 mg SC by PFS every 4 weeks for 3 doses	12 weeks	20 enrolled; 20 completed	18 to 65 years, inclusive

2.2.2 What is the basis for selecting the clinical endpoints or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

In the pivotal Study 301 and Study 201, the evaluation of the efficacy and safety of DAC HYP was based on standard measures used in registrational studies of MS therapies.

The key endpoints in Study 301 and Study 201 that support the efficacy of DAC HYP on clinical and neuro-radiological measures used to assess MS disease activity are as follows:

- Primary endpoint: Annualized relapse rate (ARR); [see Section 2.2.3.1 for results of ARR]
- Secondary endpoint: Proportion of subjects relapsing, number of new or newly enlarging T2 hyperintense lesions, and disability progression measured by EDSS, and quality of life as measured by the Multiple Sclerosis Impact Scale (MSIS)-29 physical score
- Additional endpoints: clinical measures, such as the proportion of subjects who were free of disease activity and changes in EDSS scores.

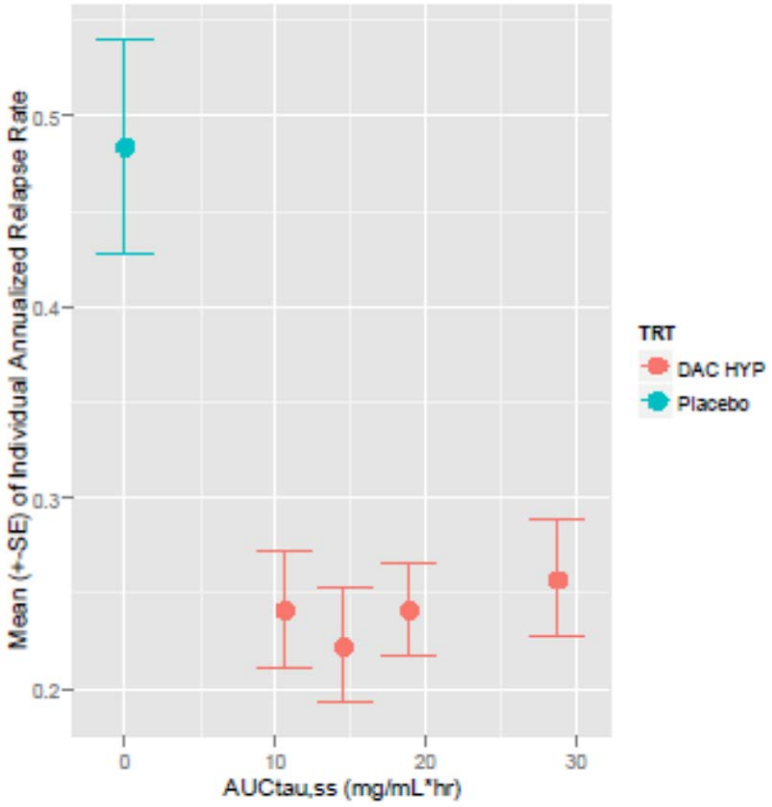
The pharmacological activity of DAC HYP was evaluated by monitoring PD parameters based on their relationship to IL-2 signaling modulation, including $CD56^{bright}$ NK cells, $CD4+CD127^{low}FoxP3+$ T cells (Tregs), $CD25^{+}$ T cells, and serum IL-2. The PD responses to DAC HYP observed in the clinical studies of MS subjects included sustained CD25 saturation on peripheral T-cells, a decrease in Tregs, and an increase in serum IL-2 and $CD56^{bright}$ NK cells during DAC HYP treatment.

2.2.3 Exposure-Response

2.2.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

The E-R relationship for efficacy was evaluated in subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) from Phase 2 (205MS201[SELECT], 205MS202[SELECTION]) and Phase 3 (205MS301[DECIDE], 205MS302[OBSERVE]) studies. The results suggest a flat E-R relationship in the range of exposures associated with the 150 mg and 300 mg doses. Figure 1 shows that no correlation between DAC exposure and the annualized relapse rate (ARR) can be discerned, which is consistent with the dose-response relationship observed in study 205MS201 as shown in Table 2. In addition, a flat E-R relationship for the secondary efficacy endpoints including new or newly enlarging T2 lesion count and new Gd+ lesion count was observed in the range of exposures associated with the 150 mg and 300 mg doses (Figure 2, Figure 3). One possible explanation for such findings is that the exposures associated with both 150 mg and 300 mg every 4 weeks regimens are at the plateau of the E-R curve for ARR, new or newly enlarging T2 lesions and Gd-enhancing lesions.

Figure 1 Mean ARR by Placebo and DAC HYP AUCss subgroups



Source: study report CPP-14008-BIIB019 page 18

Table 2. Primary Efficacy Results in Study 205MS201

Study 205MS201			
	Placebo	150mg DAC HYP	300mg DAC HYP
n	196	201	203
ARR (95% CI)	0.458 (0.370, 0.566)	0.211 (0.155, 0.287)	0.230 (0.172, 0.308)
p-value		<0.0001	0.0002

Figure 2. Annualized New or Newly Enlarging T2 Lesion Count at Final Visit vs. DAC HYP AUCss Subgroups

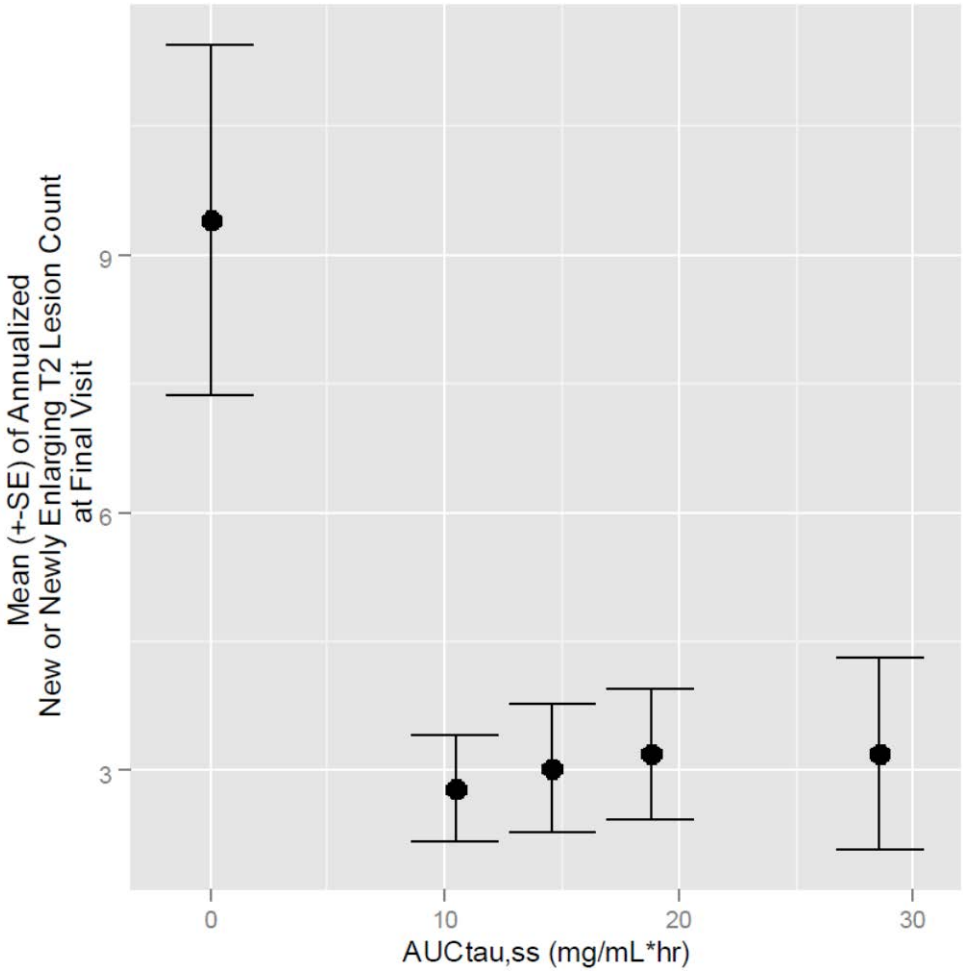


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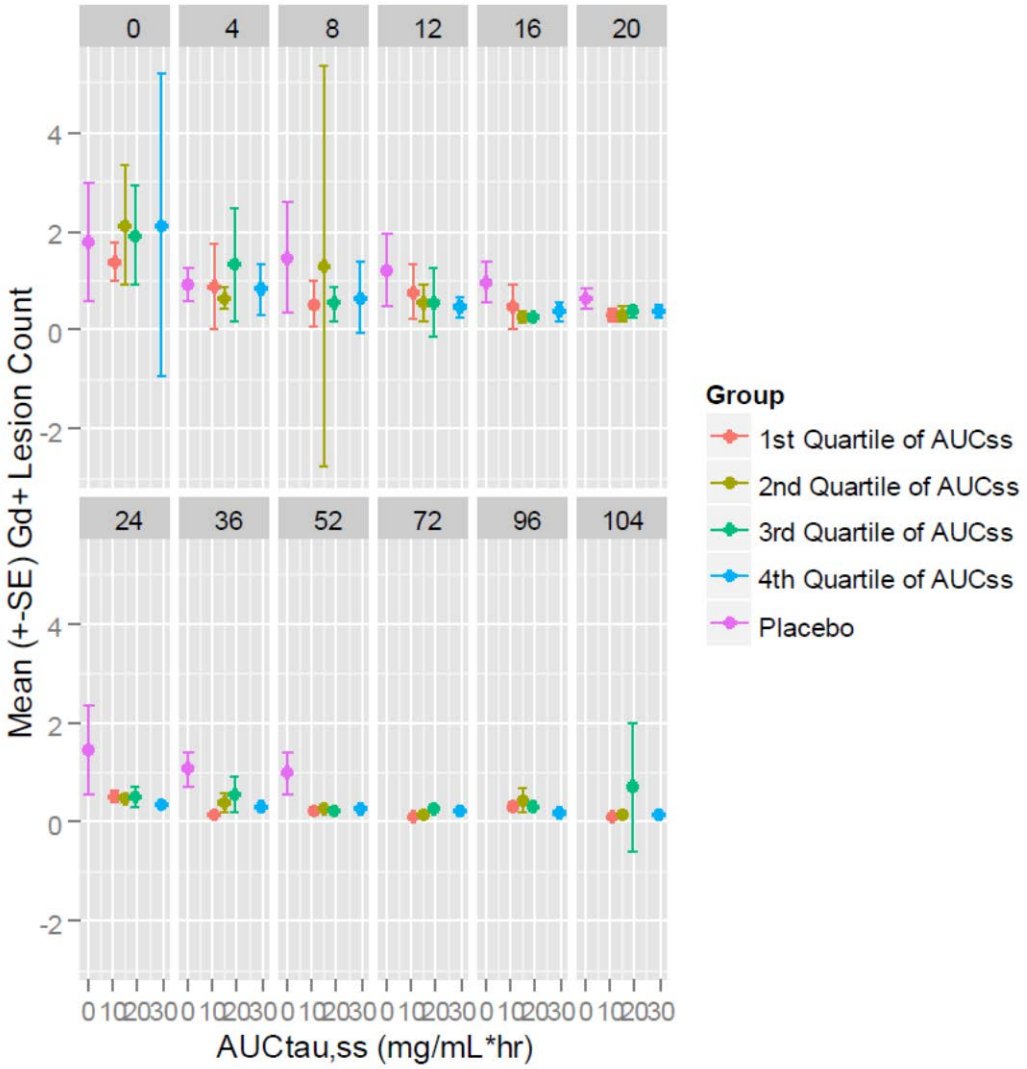
Figure 3. Mean Gd+ Lesion Count over Time by Week and DAC HYP AUCss Subgroups



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2.2.3.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

The E-R relationship for several safety endpoints, including serious infection (N=62), moderate and severe cutaneous adverse events (N=219), and liver enzyme abnormalities (N=85), was evaluated in subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) from Phase 2 (205MS201[SELECT], 205MS202[SELECTION]) and Phase 3 (205MS301[DECIDE], 205MS302[OBSERVE]) studies. The results suggest that the risk of serious infection, cutaneous AE and liver enzymes (AST/ALT) elevation are unlikely directly related to the level of exposure of DAC HYP in the 150 mg and 300 mg dose range. The serious infection status (1 and 0 representing yes and no, respectively), the

cutaneous AE status (1 and 0 representing with or without moderate or severe cutaneous adverse event), and liver enzyme abnormality status were plotted against DAC HYP AUCss in Figure 4, Figure 5, and Figure 6, respectively and no clear pattern was observed.

Autoimmune hepatitis, a life threatening AE, occurred in 3 subjects in the DAC HYP treatment groups (1 subject on 150 mg and 2 subjects on 300 mg) and 1 case resulted in death according to the sponsor's report. The relationship between DAC exposure and autoimmune hepatitis was not evaluated due to the limited number of cases in the whole clinical program. Therefore, whether the autoimmune hepatitis event is related to the DAC exposure levels cannot be concluded.

Figure 4. Serious Infection Status vs. DAC HYP AUCss

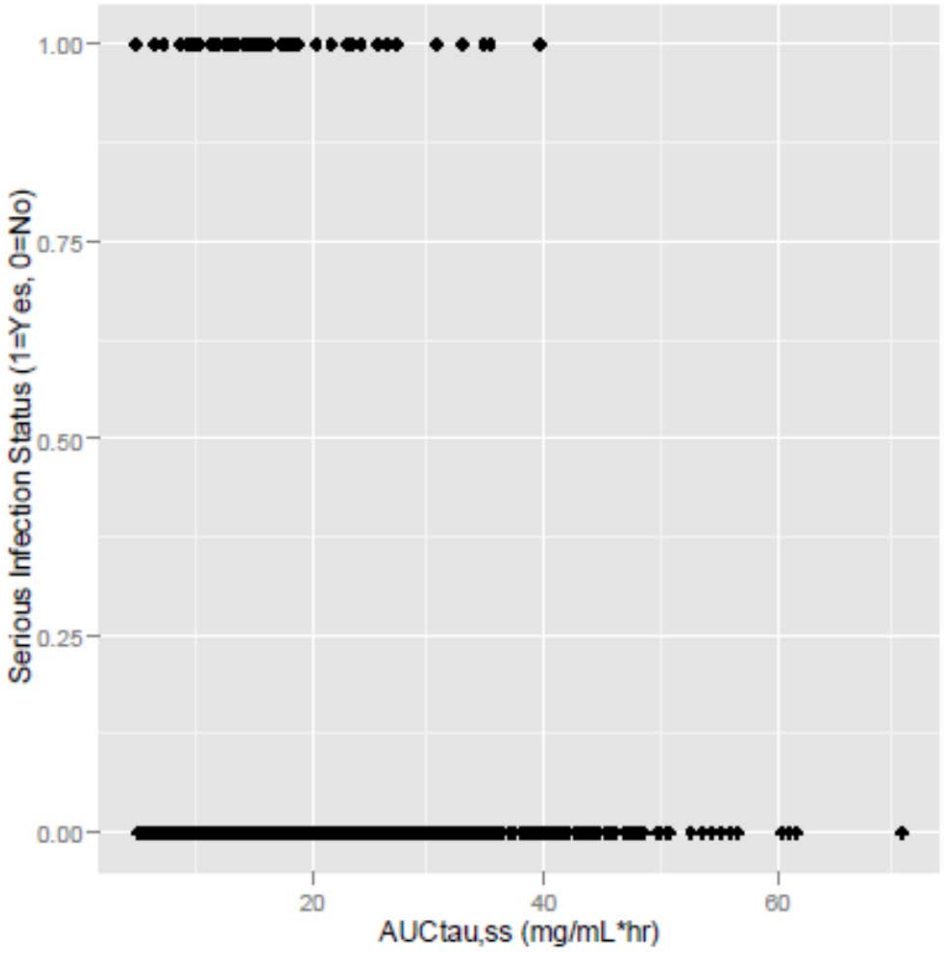

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Figure 5. Cutaneous AE Status vs. DAC HYP AUCss

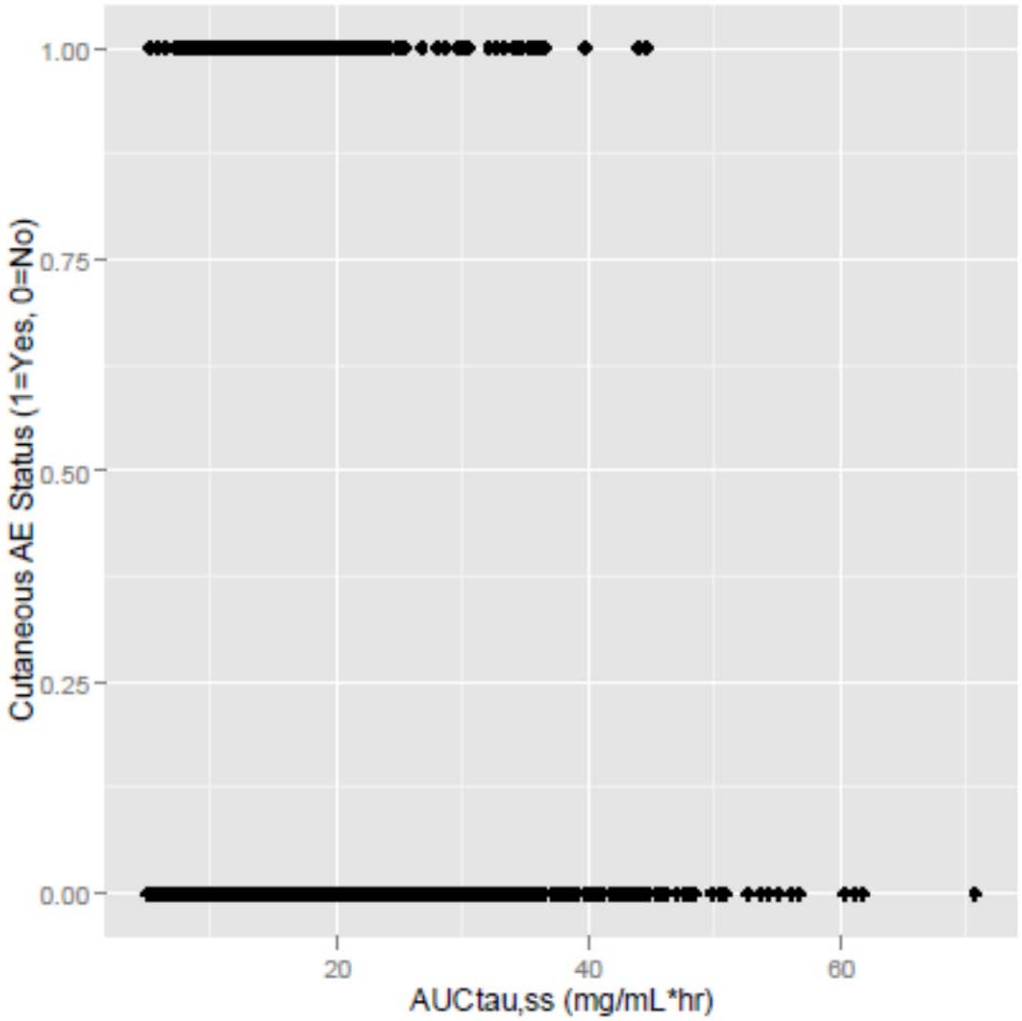

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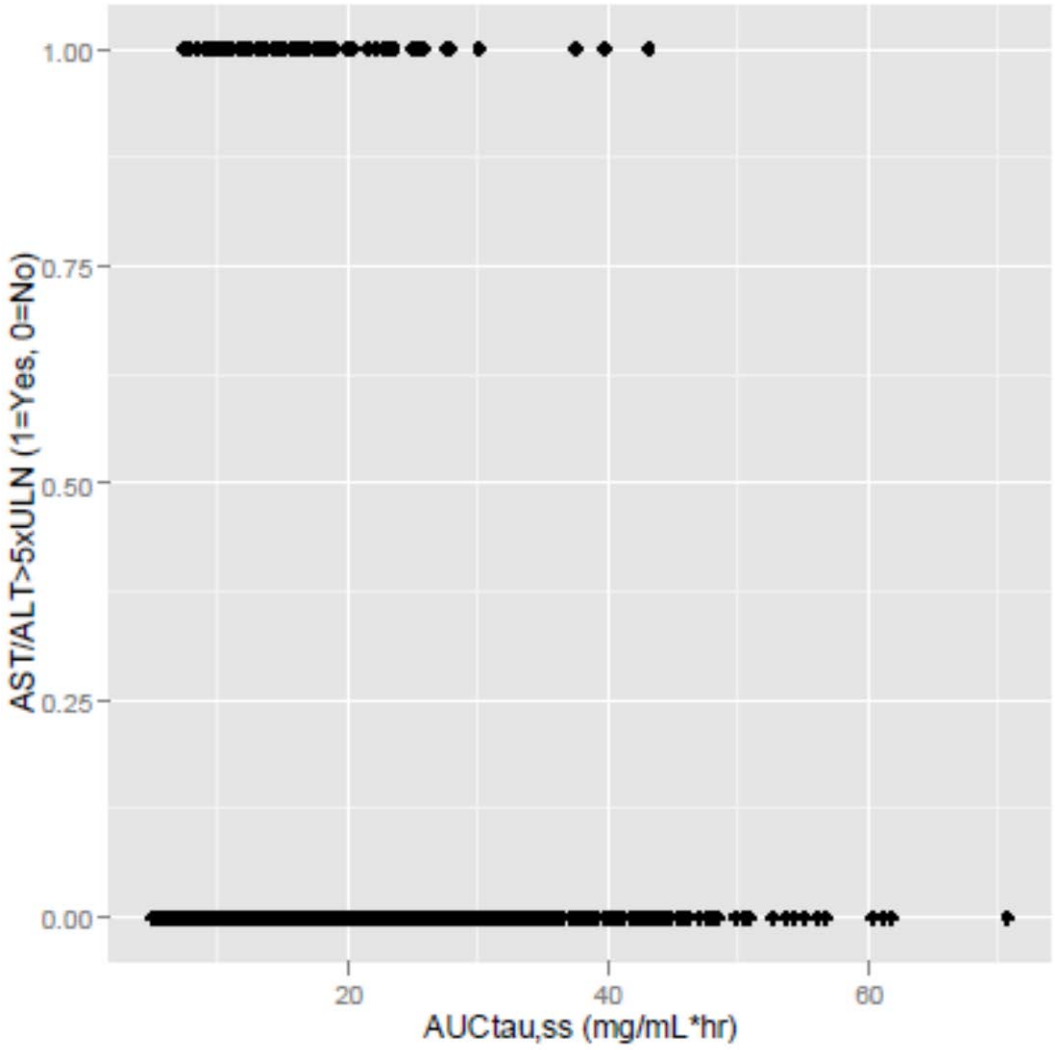
Figure 6. Liver Enzyme Abnormality Status vs. DAC HYP AUCss



Source: study report CPP-14008-BIIB019 page 32

2.2.3.3 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes. From the efficacy perspective, the proposed 150 mg once a month dose is supported by the exposure/dose-efficacy relationship. Results from study DAC-1012, which is a Phase 2, randomized, double-blind, placebo-controlled, proof-of-concept/dose-ranging study using the DAC Penzberg formulation, demonstrated that a dose of 2 mg/kg DAC Penzberg SC every 2 weeks (equivalent to 300 mg once a month DAC HYP dose) produced statistically significant reductions in new or enlarged Gd+ lesion counts, while a dose of 1 mg/kg DAC Penzberg SC every 2 weeks (equivalent to 75 mg once a month DAC HYP dose) did not result in statistically significant reductions in new or enlarged Gd+ lesion counts. Therefore, 150 mg and 300 mg monthly doses were selected for the subsequent clinical development. Results from study 205MS201 show that both 150 mg

and 300 mg once a month doses demonstrated significantly improved efficacy comparing to placebo and similar benefit was observed between 150 mg and 300 mg dose groups. This is consistent with the E-R analysis result, which shows a flat E-R relationship in the range of exposures associated with the 150 mg and 300 mg doses. The 150 mg once a month dose was further evaluated in the Phase 3 Study 205MS301 and showed superior efficacy comparing to the active control (Interferon β-1a 30 μg IM once weekly).

From the safety perspective, although E-R analyses show that the risk of serious infection, moderate or severe cutaneous AE and liver enzymes (AST/ALT) elevation are unlikely directly related to the level of exposure of DAC HYP in the 150 mg and 300 mg dose range, safety concerns, i.e. increased risk of fetal autoimmune hepatitis, do exist. Given the limited number of autoimmune hepatitis cases, no dose/exposure response relationship can be concluded. Whether lowering the dose would reduce the risk of autoimmune hepatitis (or other serious adverse reactions) remains a question. It might be possible that the risk of autoimmune hepatitis is lower at a dose level below 150 mg. However, there is no data to support this hypothesis in the current submission.

2.2.3.4 Does this drug prolong the QT or QTc interval?

The effect of DAC HYP on QT or QTc was not studied. As justified by the Sponsor, as a monoclonal antibody, DAC HYP has a low likelihood of direct ion channel interactions. Further, no clinically relevant changes in QTc interval or any other electrocardiogram parameter were observed in DAC HYP clinical studies.

2.2.4 What are the PK characteristics of the drug and its major metabolite?

The pharmacokinetics of daclizumab were similar between healthy volunteers and patients with MS following SC administration of DAC HYP. The general PK characteristics of daclizumab are summarized as follows:

- Disposition of daclizumab can be described by a two-compartment model with first-order absorption and elimination.
- Similar PK profiles between healthy volunteers and MS patients and between single-dose and multiple-dose.
- Slow absorption following SC administration, with the median time to reach maximum observed concentration (Tmax) of approximately 1 week.
- A cross-study population PK analysis indicated that daclizumab peak concentration (Cmax) and total exposure over time (AUC) increased more than dose-proportionally from 50 mg to 100 mg and in proportion to dose from 100 mg to 300 mg.
- Following administration of DAC HYP 150 mg subcutaneously every 4 weeks, steady-state serum daclizumab concentrations were achieved by the fourth dose and daclizumab accumulated to a level approximately 2.5-fold compared to a single dose.
- The absolute bioavailability of subcutaneous DAC HYP was approximately 90% in the 100-300 mg dose range.
- Long elimination half-life (t1/2) of approximately 3 weeks
- Small volume of distribution (Vd) and low systemic clearance (CL)

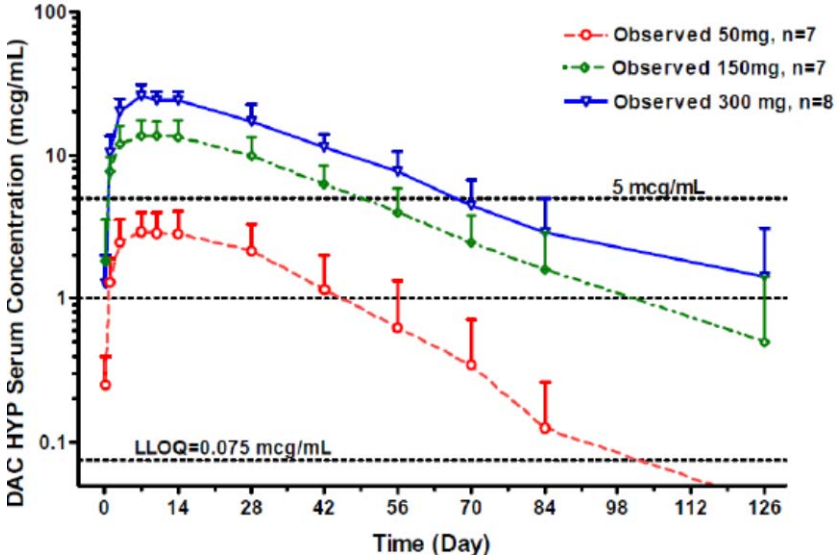
- The inter-subject variability (expressed as coefficient of variations) between individual patients were approximately 35-40% for exposure (Cmax and AUC) and 27-51% for clearance and volume of distribution.

2.2.4.1 What are the single and multiple dose PK parameters?

Single-dose:
Single-dose PK characteristics of DAC HYP were evaluated in Studies DAC-1015 and 205HV102 [see Individual Study Reviews in Appendix 4.1 for more detail].

Study DAC-1015 was a Phase 1, randomized, double-blinded, placebo-controlled, single-ascending-dose study to evaluate the safety, tolerability, PK, PD, and immunogenicity of DAC HYP following SC administration in 34 healthy subjects. Single SC doses of DAC HYP 50 mg, 150 mg and 300 mg were administered sequentially (up to 12 subjects per cohort). Representative serum DAC HYP concentration-time profiles following single SC injections are illustrated in figure below.

Figure 7. Mean (SD) serum DAC HYP concentration-time profiles following single SC injections of 50mg, 150mg, and 300mg doses (DAC-1015)



Single SC dose of DAC HYP dosed at 50, 150 or 300 mg followed one-compartment model with linear kinetics. DAC HYP showed a slow absorption (Tmax = 7~9 days), a low~moderate volume of distribution (V/F = 5.6~22.6 L) and a long elimination t1/2 (10.7~44.7 days). Inter-individual variability for V/F, CL/F, and Ka ranged 25~53%.

Study 205HV102 was a Phase 1, single-dose study to evaluate the PK, safety, and tolerability of DAC HYP 75 mg or 150 mg administered to 28 Japanese and Caucasian healthy subjects. The observed concentration-profiles and key PK parameters of DAC HYP were similar between two racial groups [see Section 2.3.1.1 for more details].

A cross-study comparison of the key PK parameters is presented in the table below. Mean Cmax values increased more than dose-proportionally for the lower 50~150 mg doses, whereas exposure (Cmax and AUC0-∞) increased dose-proportionally between 150 and 300 mg. A relatively long elimination half-life (t1/2) of 17.2~24.9 days was observed. The clearance (CL/F) of DAC HYP ranged from 19.7 mL/h at the lowest 50 mg dose to 11.0~11.2 mL/h at the higher 150~300mg doses. The volume of distribution (Vd/F) ranged from 13.4 L at the lowest 50 mg dose to 8.83~9.03 L at the higher 150~300mg doses.

Table 3. Summary of Key Pharmacokinetic Parameters of DAC HYP Following a Single SC Dose Administration (DAC-1015 and 205HV102)

SC Dose (mg)	Study	Cmax (µg/mL)	Tmax* (day)	AUC0-∞ (µg·h/mL)	t1/2 (day)
50 mg	DAC-1015	3.03 (1.18)	7 (3.42)	3362 (1529)	23.1 (7.57)
75 mg	205HV102	5.96 (2.01)	6.16 (3.71)	6234 (2055)	17.2 (2.68)
150 mg	DAC-1015	15.3 (3.54)	7 (3.86)	15553 (5497)	24.7 (9.21)
150 mg	205HV102	16.0 (2.85)	6.16 (2.89)	15568 (3902)	17.9 (3.62)
300 mg	DAC-1015	27.2 (3.29)	7 (2.56)	28310 (7763)	24.9 (9.19)

* Values were presented as Mean (SD), except for Tmax being presented as Medium

An additional single-ascending-dose characterization was carried out in a Phase 1 Study DAC-1018 to evaluate the safety, tolerability, PK, PD, and immunogenicity of DAC HYP following 30-minute IV infusion in healthy subjects at DAC HYP 200 mg (n=12), DAC HYP 400 mg (n=12), or placebo (n=7). The PK of DAC HYP followed a bi-exponential decline with an initial fast distribution phase followed by a slow elimination phase. DAC HYP exhibited a low CL (approximately 10 mL/h), a low steady state volume of distribution (5.89~6.53 L), and long elimination t1/2 (18~20 days). Dose-proportional increase in exposure was observed between 200 mg and 400 mg.

Table 4. DAC HYP PK Parameters Following a Single IV Infusion (DAC-1018)

IV Dose (mg)	Cmax (µg/mL)	AUC0-∞ (mg·h/mL)	t1/2 (day)	CL (mL/h)	Vd (L)
200 mg	51 (10)	20 (3)	20 (4)	10 (1)	4.32 (0.749)
400 mg	112 (22)	41 (8)	18 (4)	10 (2)	5.89 (1.19)

* Values were presented as Mean (SD),

Multiple-dose:

Multiple-dose PK characteristics of DAC HYP were evaluated in Study DAC-1014 in healthy subjects (once every 2 weeks doing), as well as in Study 205MS302 in MS patients for the proposed dosing regimen (150 mg SC every 4 weeks) to support the labeling [see Individual Study Reviews in Appendix 4.1 for more detail].

In Study DAC-1014, two different dosing regimens - (Arm A) 200 mg SC every 2 weeks and (Arm B) a 200 mg SC followed by 100 mg every 2 weeks for a total of 9 SC doses

over 16 weeks - in 24 subjects were planned. PK parameters were obtained from 17 out of 24 subjects who received 7-8 doses due to the suspension of the treatment. DAC HYP PK profile after multiple SC administration showed a slow absorption (Tmax ~ 7 days after the first dose) and a long elimination t1/2 (~15 days). Steady-state AUCtau values were estimated to be 8 mg·hr/mL (100 mg SC every 2 weeks) and 16 mg·hr/mL (200 mg SC every 2 weeks), with an inter-individual variability of approximately 26.4%. Cmax ~15.8 µg/mL was reported for both dosing cohorts. The CL and Vss were 12.5 mL/h and 3.323 L, respectively.

Study 205MS302 was a multicenter, single-arm, open-label study to assess the immunogenicity, PK, PD, and tolerability of DAC HYP administered SC by PFS in RRMS patients. Multiple-dose PK results were obtained from 26 subjects in the intensive PK substudy for a total of 6 injections. The mean (SD) serum DAC HYP concentration-time profiles, as well as key PK results are illustrated in figure and table below. The multiple-dose PK properties in MS patients are generally characterized by a slow absorption with median Tmax of approximately 5 days and a long elimination t1/2 of approximately 22 days, similar to single-dose PK characteristics. Steady-state was reached before Week 16. DAC HYP dosing every 4 weeks resulted in approximately 2.5-fold drug accumulation at steady-state.

Figure 8. Mean ± SD Serum DAC HYP Concentration-Time Profiles Following Administration of DAC HYP 150 mg SC Every 4 Weeks Over 20 Weeks (205MS302)

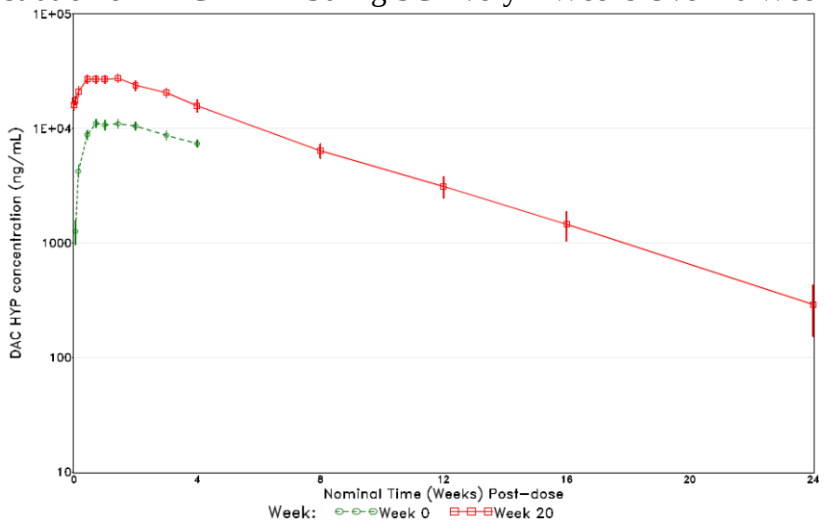


Table 5. Summary of Key Pharmacokinetic Parameters of DAC HYP Following Multiple SC Doses Every 4 Weeks (Study 205MS302)

SC Dose (mg)	Tmax* (day)	Cmax (µg/mL)	AUC0-tau (µg·h/mL)	Cmin (µg/mL)	t1/2 (day)
150 mg, Q4W x 6 doses	5.03 (3.27)	29.07 (10.8)	638 (256)	14.93 (6.33)	21.9 (5.47)

* Values were presented as Mean (SD), except for Tmax being presented as Medium

An additional study (205MS203) was designed to compare the systemic exposure of daclizumab following 150 mg DAC HYP every 4 weeks SC administration between single-use autoinjector [redacted] (b) (4) and PFS injection in 60 MS patients. Similar PK results to those from Study 205MS302 were obtained and are not presented in detail here.

2.2.4.2 What are the characteristics of drug absorption?

Following SC administration of DAC HYP to healthy or MS patients, the median time to reach peak serum concentrations (Tmax) of daclizumab occurred approximately 5~7 days. At steady state, daclizumab mean maximum serum concentration (Cmax), minimum serum concentration (Cmin) and area under the serum concentration-time curve over the dosing interval (AUCtau) values were approximately 30 µg/mL, 15 µg/mL and 640 µg·day/mL, respectively. The absolute bioavailability of 150 mg subcutaneous daclizumab was approximately 90% [see Section 4.1 Consult Review for details].

2.2.4.3 What are the characteristics of drug distribution?

Following a single IV infusion of DAC HYP 200 mg and 400 mg to healthy subjects, mean volume of distribution were approximately 5.89~6.53 L which indicates that DAC HYP is largely confined to the vascular and interstitial spaces. In MS patients taking 150 mg SC doses of DAC HYP once a month, the estimated steady-state volume of distribution of daclizumab was approximately 6.34 L.

2.2.4.4 What are the characteristics of drug metabolism and elimination?

The exact metabolic pathway for DAC HYP was not characterized. DAC HYP is not expected to undergo metabolism by hepatic enzymes such as CYP isoenzymes. Rather, as an IgG1 monoclonal antibody, DAC HYP is expected to be metabolized into peptides and amino acids via catabolic pathway.

As an IgG1 monoclonal antibody, DAC HYP is eliminated via proteolysis, target-mediated elimination, and nonspecific endocytosis, and is not expected to undergo renal elimination.

DAC HYP is characterized by a relatively low clearance (e.g., CL=10 mL/h) and a long elimination half-life (e.g., t½=18~20 days) following IV infusion or SC injection. Population PK analysis also showed a typical CL value of 0.212 L/day (or 8.83 mL/h) and an elimination t1/2 of approximately 21 days for DAC HYP. Population PK analysis showed that body weight was a significant covariate on CL of DAC HYP. Neutralizing antibodies (NAb) positive status increased the CL by approximately 19%. Body weight or immunogenicity status does not appear to have clinically significance.

2.2.4.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Mass balance study was not conducted for DAC HYP and was not deemed necessary.

2.2.4.6 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

A cross-study PK analysis for results following SC dosing of DAC HYP indicated that DAC HYP exposure (more noticeably for Cmax) is more than dose-proportional in the 50~100 mg SC dose range and is dose-proportional in the 100~300 mg SC dose range. DAC HYP PK parameters were similar following single and multiple-dose administration indicating time linearity. [see Section 2.2.4.1 for additional information].

2.2.4.7 How does the PK of the drug and its major metabolites in healthy subjects compare to that in patients?

As described in Section 2.2.4.1, no direct comparison of DAC HYP PK between healthy volunteers and MS subjects can be made since PK data from healthy volunteers are mostly from a single SC or IV doses while PK data from MS subjects are from multiple SC dosing. However, DAC HYP PK was adequately described using the same model for both healthy subjects and MS patients. A conclusion can be drawn that DAC HYP PK properties are similar between healthy subjects and MS patients, based on PK parameters from individual studies and cross-study comparison. [Refer to Section 2.2.4.1 for details]

2.2.4.8 What is the inter- and intra-subject variability of PK parameters in healthy subjects and patients?

The inter-subject variability (expressed as the percent coefficients of variation (CV%)) in healthy volunteers for key DAC HYP PK parameters after receiving single SC doses of 50, 150, or 300 mg, ranged from 12 to 39% for Cmax and from 27 to 46% for AUC0-inf. In MS subjects receiving DAC HYP 150 mg SC every 4 weeks in pivotal Phase 3 clinical trial), the CV% for Cmax and AUCtau were approximately 35-40%. Population PK analysis showed an inter-subject variability approximately 27-51% for DAC HYP Clearance and central and peripheral volumes of distribution.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, what is the impact of any differences in exposure on the pharmacodynamics, and what dosage regimen adjustments, if any, are recommended for each of these groups?

None of the intrinsic factors evaluated have significant differences in DAC HYP exposure or impact on PD or clinical outcome to suggest any need for a dosage adjustment [referred to the following Sections and the Pharmacometrics Review in Section 4.2 of Appendices for additional details].

2.3.1.1 Age, Weight, Sex, Race and Other Potential Significant Covariates

The intrinsic factors including demographic factors (age, gender, body weight) as well as race in adult patients were examined and were found not to have significant differences in DAC HYP exposure or impact on PD or clinical outcome. These data do not suggest any need for dosage adjustment based on these intrinsic factors.

Age:
No clinical studies were conducted to evaluate DAC HYP PK in pediatrics younger than 18 years old or geriatrics over 65 years old. As described in the proposed labeling, use of ZINBRYTA is not recommended in pediatric patients due to the risks of hepatic injury, autoimmune and other immune-mediated conditions, skin reactions, and malignancies.

Body weight:
Body weight was a covariate on DAC HYP CL and central volume of distribution and explained 37% and 27% of the inter-subject variability, respectively. The impact of body weight covariate effect was not deemed to be clinically relevant. In addition, no significant differences in safety or efficacy were observed among the subgroups by body weight quartile in clinical trial. [refer to the Pharmacometrics Review in Section 4.2 of Appendices for additional details].

Race:
The Sponsor conducted Study 205HV102 to evaluate the PK safety, and tolerability of DAC HYP administered as a single SC dose in Japanese and Caucasian healthy adult volunteers. Similar concentration-time profiles were observed for both racial groups following single-dose 75 mg SC (n=28; 14 per ethnic group) or 150 mg SC (n=28; 14 per ethnic group), with Tmax of approximately 6 days. For the lower 75 mg dose, the AUC values were similar, whereas mean Cmax was approximately 30% higher for Japanese subjects, compared to Caucasians without regards to subjects with positive NAb. The upper bounds of corresponding 90% CIs for Cmax did not fall within the 0.8-1.25 boundary. For the proposed 150-mg dose, mean Cmax and AUCinf were not significantly different between Japanese and Caucasian subjects, with or without regards to subjects with positive NAb.

It can be concluded that no apparent PK differences were observed between Japanese and Caucasian subjects following a single-dose administration of DAC HYP at the proposed 150 mg SC dose. The effect of other races on DAC HYP PK cannot be determined due to limited subjects in the studies (<1% of the total population PK data).

2.3.1.2 Renal Impairment and Hepatic impairment

DAC HYP is not expected to undergo hepatic metabolism by hepatic enzymes or renal elimination. No studies were conducted to assess the impact of hepatic or renal impairment on PK property of DAC HYP.

Because of the potential risk for hepatotoxicity from DAC HYP, the pertinent information and recommendations were described for the proposed labeling:

- ZINBRYTA causes life-threatening severe liver injury including liver failure, and autoimmune hepatitis, and death.
- Patients with ALT or AST more than 2X ULN were excluded from clinical trials. Patients with signs and symptoms of hepatic impairment may be at increased risk for hepatotoxicity from ZINBRYTA.
- Initiation of treatment with ZINBRYTA is contraindicated in patients with pre-existing hepatic disease or hepatic impairment.

2.3.1.3 Immunogenicity

The Sponsor's reports of the key findings related to the immunogenicity profile of DAC HYP are summarized below:

- Treatment-emergent ADAs to DAC HYP 150 mg were reported in 4% and 19% of evaluable subjects in Study 201 and Study 301, respectively. Treatment-emergent NAbs to DAC HYP 150 mg were observed in 3% and 8% of evaluable subjects in Study 201 and Study 301, respectively. The more frequent immunogenicity testing at early timepoints and a more sensitive assay used in Study 301 were attributed to the observed differences in the incidences of immunogenicity between the two studies.
- The majority of ADA and NAb reactivity to DAC HYP occurred early during treatment, and this reactivity decreased with continuing DAC HYP treatment. ADA titers observed were generally low, with only 3 persistent subjects in Study 301 reaching a titer of >1920 (highest titer observed in the transient category).
- The majority of subjects that exhibited immunogenicity showed transient responses.
- Increased detection of immunogenicity was observed during washout of DAC HYP.
- Time-varying NAb status increased DAC HYP CL by 19% on average and was reported to not appear to be clinically relevant since there was no discernible impact of immunogenicity status on the efficacy, safety, or PD profile of DAC HYP.
- No impact of ADAs and NAbs on efficacy was reported with regards to clinical endpoints (relapses) and radiological endpoints (gadolinium-enhancing lesions, T2 hyperintense lesions) by antibody status for subjects in pivotal Study 301 and Study 201.
- There was no discernible impact of ADAs or NAbs (transient or persistent) reported on MS relapse, adverse events, serious adverse events, cutaneous events, infections, and liver function test abnormalities.

2.3.1.4 Are there common underlying genetic causes that increase the risk of liver toxicity from daclizumab?

No. The sponsor conducted an exploratory GWAS to investigate possible genetic causes of daclizumab induced elevations in liver enzymes. Despite sufficient power to detect associations of markers with an allele frequency of 5% or greater with an odds ratio greater than 10, no statistically significant associations were produced. Hence, it is

unlikely that there are common genetic variants that are associated with daclizumab induced elevation in liver enzymes.

2.4 Extrinsic Factors

2.4.1 Are there clinically relevant drug-drug or drug-food interactions, and what is the appropriate management strategy including dosage regimen adjustment?

Effects on CYP isozymes:
The DAC HYP treatment resulted in an apparent increase in IL-2 levels (modulate cytokine activities) and thus has the potential to indirectly influence the expression of CYP isoenzymes. The Sponsor conducted an in vivo TP-DI substudy (as part of Study 302) with two sequential treatment periods to evaluate the effect of DAC HYP 150 mg, SC every 4 weeks on the PK of probe drugs for CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A in 20 RRMS subjects.

The probe-drug cocktail consisting of oral midazolam 5 mg (CYP3A), caffeine 200 mg (CYP1A2), S-warfarin 10 mg/vitamin K 10 mg (CYP2C9), omeprazole 40 mg (CYP2C19), and dextromethorphan 30 mg (CYP2D6) was administered 7 days before the first dose of DAC HYP in Period 2and 7 days after the third dose of DAC HYP. PK blood samples were collected at pre-Cocktail dose, 0.5, 1, 2, 2, 4, 6, 8, 10, 24, 48, 72, and 96 hours post-Cocktail dosing. Urine samples were collected for 12-hour for the measurement of dextromethorphan and dextrorphan.

Table 6. Effect of DAC HYP 150 mg SC every 4 weeks on exposure of CYP probes

		Geometric LS Mean			
Probe drug	Parameter (Unit)	Probe drug alone (n)	Probe drug with DAC HYP (n)	Ratio (a)	90% CI
Midazolam	AUCinf (ng*h/mL)	722.5 (20)	733.6 (19)	1.015	0.894, 1.153
S-Warfarin	AUCinf (ng*h/mL)	18545 (17)	18646 (18)	1.005	0.951, 1.063
Omeprazole	AUCinf (ng*h/mL)	1353.7 (18)	1348.5 (19)	0.996	0.880, 1.127
Caffeine	AUC0-12 (ng*h/mL) (b)	30799 (13)	31790 (12)	1.032	0.930, 1.145
Dextromethorphan	12-hr urine dextromethorphan to dextrorphan ratio	0.010 (20)	0.010 (20)	1.012	0.764, 1.342

(a) Test/reference = (probe drug + DAC HYP)/probe drug alone.
(b) Subjects with pre-dose caffeine concentration >5% of Cmax are excluded.

Multiple doses of DAC HYP 150 mg SC q4w in MS patients had insignificant effects on the primary PK endpoint (exposure) for concomitant probe substrates of the CYP isozymes studied, judging by the point estimates and the 90% CIs of the geometric mean ratio for probe substrate exposure being within the no-effect boundary of 0.80-1.25. For the CYP2D6 probe, the geometric mean ratio for 12-hour urine dextromethorphan:dextrorphan ratio (a phenotypic measure of CYP2D6 activity) was close to 1; however, the 90% CI (0.76~1.34) extended slightly outside the no-effect

boundary of 0.80-1.25, most likely a result of high variability associated with urine collections and CYP2D6 activity. This observation is deemed not to have a significant clinical relevance on CYP2D6 activity. No dosage adjustments are needed for medications that are substrates of these CYP enzymes when given concomitantly with DAC HYP.

Risk of hepatotoxicity (labeling recommendation by the Agency):
Because of the potential risk for hepatotoxicity from DAC HYP, the pertinent information and recommendations were described for the proposed labeling:

- Because of an increased risk of hepatotoxicity, the use of ZINBRYTA with valproic acid, carbamazepine, lamotrigine, phenytoin, isoniazid, or propylthiouracil is contraindicated. Evaluate the potential for increased risk of hepatotoxicity when considering use of other medications, over-the-counter medications, herbal products, or dietary supplements with ZINBRYTA.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation?

Not applicable

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

Not applicable

As described in the above Section 2.1.2, the 150 mg/mL concentration is the only concentration being administered clinical studies and is the intended concentration for commercial use prefilled syringe (PFS). The DAC HYP drug product, supplied as a vial or a PFS, was used in all the clinical studies, except for supportive Study DAC-1012 in which the formulation (Penzberg DP) used in Study DAC-1012 was an investigational form of DAC for clinical research. (b) (4)

2.6 Analytical Section

2.6.1 Were the active moieties identified and measured in the plasma in the clinical pharmacology study?

Yes. DAC HYP was measured in all studies [refer to the following Section 2.6.2 for details].

2.6.2 What analytical method was used to determine drug concentrations and was the analytical assay method adequately validated?

Various bioanalytical methods were used in the clinical studies to determine the serum concentration of DAC HYP, the levels of various DAC HYP-induced PD markers in serum or whole blood samples, and the presence and titers of antibodies. The concentrations of DAC HYP in human serum samples were determined using a validated quantitative sandwich enzyme linked immunosorbent assay (ELISA), with or without background subtraction, and will be presented in the tables below.

For the DAC-1012, DAC-1014, DAC-1015, and DAC-1018 studies, the assay employed background subtraction. A 4-parameter curve fit was applied to the standard curve that ranged from 400 to 12000 ng/mL, with LLOQ being 500 ng/mL and ULOQ being 7500 ng/mL. For the 205HV102, 205MS201, 205MS202, 205MS203, 205MS301, 205MS302, and 205MS303 studies, no background subtraction was used following the re-development and validation of the assay. A 4-parameter curve fit was applied to the standard curve that ranged from 25 to 2400 ng/mL, with LLOQ being 75 ng/mL and ULOQ being 2000 ng/mL.

Table 7. Validation Summary for Determination of Daclizumab in Human Serum using ELISA (Without Background Subtraction)

Parameters	**Target Criteria**	**Results**
Analytes	Daclizumab	
Matrix	Human serum (including cross-validation in Japanese human serum)	
Standard curve range	500 to 7500 ng/mL	
Intra-assay Accuracy	%AR within 80%–120% (75%–125% for LLOQ)	81.4% to 102.5% Japanese: 80.1% to 98.3% (for LLOQ, 72.2% to 95.9%)
Intra-Assay Precision	%CV ≤20% (≤25% for LLOQ)	<6% Japanese: ≤9.5%
Inter-Assay Accuracy	%AR within 80% to 120% (75% to 125% for LLOQ)	85.8% to 94.2% Japanese: 81.4% to 92.1%
Inter-Assay Precision	%CV ≤20% (≤25% for LLOQ)	≤6.7% Japanese: ≤12.8%
Dilution Linearity and Prozone Evaluation	• Diluted samples must have %AR within 80% to 120% (75% to 125% for LLOQ) and %CV within 20%. • Samples >7500 ng/mL should give OD above the ULOQ OD	• %AR was 89.7% to 99.8% • All samples >7500 ng/mL above the ULOQ OD Japanese: • %AR was 96.6% to 110.5 % • All samples ≥7500 ng/mL above the ULOQ OD
Assay Selectivity	%AR within 75% to 125% in at least 80% of samples	• %AR for all concentration levels in 10 donors with multiple sclerosis was 75.2% to 124.8% • High level of endogenous background was noted among

		Caucasian and Japanese healthy donors. This background was shown to be subtractable. Therefore, a subject's predose concentration value can be subtracted from subsequent postdose samples, if needed. • %AR for all concentration levels in 11/12 Caucasian and 10/12 Japanese donors was 77.0% to 123.5% when corrected for predose background concentration.
Assay Specificity (Cross-Reactivity)	%AR of DAC HYP in the presence of sCD25 should be within 25% nominal	Within ≤10% nominal
Stability	• Freeze/thaw (%AR 80% to 120% compared with nominal) • Bench top and refrigerator stability: ≥66% of low and high QC and ≥50% of stability samples should be within 20% of nominal values	• Demonstrated up to 6 cycles of freeze/thaw with %AR 89.5% to 100.9% • Bench top stability up to 25 hours with %AR 91.5% to 101.0% • Refrigerator stability up to 3 days with %AR 87.9% to 94.9% • Long-term stability at -20ºC %AR 84.5% to 111.3% at 6 months • Long-term stability at -70ºC %AR 81.1% to 112.1% at 36 months

Table 8. Validation Summary for Determination of Daclizumab in Human Serum using ELISA (With Background Subtraction)

Parameters	**Target Criteria**	**Results**
Analytes	Daclizumab	
Matrix	Human serum	
Standard curve range	75 to 2000 ng/mL	
Intra-assay Accuracy	%AR within 70% to 130% and %CV within 30%	98% to 118%
Intra-Assay Precision	%CV ≤30%	5.9% to 20.8%
Inter-Assay Accuracy	%AR within 70% to 130% and %CV within 30%	99.3% to 104%
Inter-Assay Precision	%CV ≤20%	10.8% to 16%
Dilution Linearity and Prozone Evaluation	Diluted samples must have %AR within 70% to 130% and %CV within 30%.	Samples may be diluted up to 1/6400; %AR = 94.4% to 120%
Assay Selectivity	%AR within 70% to 130% and %CV within 30%	8/10 normal unspiked individual serum samples are within 20% nominal concentration; high level of endogenous background noted. Recommended subject's predose OD value to be subtracted to

		subsequent postdose samples
Assay Specificity (Cross-Reactivity)	%AR within 70% to 130% and %CV within 30%	8/10 normal unspiked individual serum samples are within 20% nominal concentration; high level of endogenous background noted. Recommended subject's predose OD value to be subtracted to subsequent postdose samples
Stability	%AR within 70% to 130% and %CV within 30%	• Freeze/thaw: (b) (4) had demonstrated up to 4 cycles; TR01177 had demonstrated up to 6 cycles with %AR within 15% nominal • Bench top and refrigerator stability: up to 3 days with %AR within 30% nominal • Long-term stability at -20 ºC and -60ºC: stable up to 30 months with %AR within 125% and %CV within 30%

3. Detailed Labeling Recommendations

The Office of Clinical Pharmacology has reviewed the proposed labeling for ZINBRYTA™ (DAC HPY) and found it acceptable provided that the recommended revisions are made to the labeling language.

7 Drug interactions

7.1 (b) (4) Hepatotoxic Drugs

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and effectiveness of ZINBRYTA in (b) (4) patients (b) (4) years old have not been established. Use of ZINBRYTA is not recommended in pediatric patients due to the risks of hepatic injury, (b) (4) and (b) (4) immune-mediated (b) (4) *[see Warnings and Precautions (*5.1, 5.2, (b) (4) *)]*.

8.5 Geriatric Use

(b) (4)

8.6 Hepatic Impairment

(b) (4) -[see Dosage and Administration (2.4), Contraindications (4), and Warnings and Precautions (5.1 (b) (4))].

12.3 Pharmacokinetics

General

The pharmacokinetics of ZINBRYTA (b) (4) similar (b) (4) healthy volunteers and patients with multiple sclerosis ~~(MS)~~, (b) (4)

(b) (4)

Absorption

Following subcutaneous (b) (4) of ZINBRYTA, the maximum concentration occurred between (b) (4) -5 and (b) (4) 7 days. At steady state, daclizumab (b) (4) -mean maximum serum

concentration (Cmax), [redacted]. The absolute bioavailability of 150 mg subcutaneous [redacted] daclizumab was approximately 90% [redacted].

Distribution

[redacted] In multiple sclerosis patients taking 150 mg subcutaneous doses of ZINBRYTA [redacted] every 4 weeks, the estimated steady-state volume of distribution of [redacted] daclizumab [redacted] was approximately 6.34 [redacted] liters [redacted].

[redacted]

Metabolism and Elimination

[redacted] daclizumab is expected to undergo catabolism to peptides and amino acids in the same manner as endogenous IgG. [redacted] Daclizumab clearance in patients who developed neutralizing antibodies was [redacted] 19% higher [*see Adverse Reactions (6.1* [redacted]*)*].

[redacted]

Specific Populations

[redacted] Covariate analyses [redacted] for patients with relapsing forms of multiple sclerosis.

Drug Interaction (b) Studies

ZINBRYTA 150 mg administered subcutaneously every 4 weeks for 12 weeks in patients with multiple sclerosis did not significantly affect the systemic exposure of concomitantly administered oral midazolam (CYP3A substrate), warfarin (CYP2C9 substrate), dextromethorphan (CYP2D6 substrate), omeprazole (CYP2C19 substrate), or caffeine (CYP1A2 substrate). (b) (4)

(b) (4)

4. Appendices

4.1 Individual Study Reviews

<table>
<tr><td>Study Report #</td><td>DAC-1014</td></tr>
<tr><td>Title</td><td>A Phase 1, Randomized, Double-blinded, Placebo-controlled, Multi-dose, Parallel-group Study of Subcutaneous Daclizumab (High Yield Process Material) in Healthy Volunteers</td></tr>
<tr><td>Investigator/ Center</td><td>Sepehr Shakib, MBBS. CMAX, Adelaide, South Australia, 5000, Australia</td></tr>
<tr><td>Study Dates</td><td>July 13, 2005 – August 02, 2006</td></tr>
<tr><td>Objectives</td><td>• Primary: To determine the safety and tolerability of multiple doses of DAC HYP material administered by SC
• Secondary: To characterize PK, PD, and immunogenicity of DAC HYP material administered by SC injection</td></tr>
<tr><td>Formulation</td><td>
<table>
<tr><td>Treatment</td><td>Lot #</td></tr>
<tr><td>DAC HYP: 100 mg/mL</td><td>90670401</td></tr>
<tr><td>Placebo SC Q2W as comparator</td><td>90610401</td></tr>
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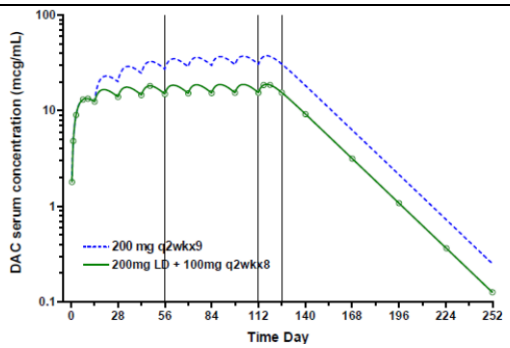
</td></tr>
<tr><td>Study Design</td><td>
• Phase 1, single-center, randomized, double-blinded placebo-controlled, multi-dose, parallel-group study of SC daclizumab (DAC HYP) in 32 healthy volunteers (18-65 years of age, inclusive) to compare 2 dosing regimens (200 mg/200 mg and 200 mg/100 mg, both Q2w) with placebo.
• N=32 randomized in a 3:3:2 ratio (N=12 received DAC HYP 200 mg/200 mg, N=12 received DAC HYP 200 mg/100 mg, and N=8 received placebo)
• Treatment Regimen:
<table>
<tr><th>Treatment Arm</th><th>DAC HYP/Placebo Loading Dose (mg)</th><th>DAC HYP/Placebo Maintenance Dose (mg)</th><th>Maximum Number of Doses</th><th>Number of Subjects</th></tr>
<tr><td>DAC HYP 200 mg/200 mg Arm A</td><td>200</td><td>200</td><td>9</td><td>12</td></tr>
<tr><td>DAC HYP 200 mg/100 mg Arm B</td><td>200</td><td>100</td><td>9</td><td>12</td></tr>
<tr><td>Placebo Arm C</td><td>0</td><td>0</td><td>9</td><td>8</td></tr>
</table>
• Duration: 48 weeks (9 SC injections over 16 weeks of treatment and 32 weeks of follow-up).
• The Sponsor’s simulated PK profiles of q2w doing regimen using a body weight of 70 kg:
</td></tr>
</table>



Assessments:

- Safety: monitoring of SAE, AE, vital signs, laboratory tests, ECG, physical examinations, and absolute CD4+ T-cell counts.
- PK: DAC HYP serum concentrations and the following PK parameters including (Cavg)ss, CL/F, (AUCτ)ss, V/F, and t1/2.
  - PK samples: Predose on Day 0 (2 hours predose and 4 hours postdose), 1 (24±4 hours after the first dose), 3, 7, 10, 14 (predose), 28 (predose), 42 (predose), 47, 56 (predose), 112 (predose and 2 hours postdose), 115, 119, 126, 140, 168, 196, and 252. [samples maybe used for ADAb assessment]
- PD: determining relative peripheral levels of CD25+ T-cells and absolute CD4+ T-cell counts by flow cytometry analysis. All samples taken for CD4+ T-cell count monitoring was also used for exploratory analyses of other lymphocyte subset absolute counts (CD8+ T-cells, B-cells, and natural killer [NK] cells).
  - Samples for CD25+ were collected on Days 0 (2 hours predose and 4 hours postdose), 3, 14, 28 (predose and 2 hours postdose), 56 (predose), 112 (predose and 2 hours postdose), 140, 168, 196, 224, and 252. Samples for CD4+ T-cell were collected on Days 28 (predose), 56 (predose), 112 (predose), 140, 168, 196, and 252
- Immunogenicity: Levels of circulating anti-Daclizumab antibodies (ADAb), with sample collection on Days 0 (2 hours predose), 224, and 252.

Bioanalytical Methods

- DAC HYP: serum concentrations were determined using a validated sequential "sandwich" enzyme linked immunosorbent assay (ELISA) (b) (4) with a quantitative range of 0.075 - 2.00 µg/mL, with 0.075 µg/mL being the lower limit of quantification (LLOQ) [see Table below]. A validated bridging enzyme immunoassay/ELISA was utilized for measure of anti-Daclizumab antibodies (ADAb) in human serum

Table. Assay performance for DAC HYP

Analyte	Daclizumab (serum)
Method:	ELISA

	Standard Curve: Range: 75 - 2000 ng/mL Precision: 4.78-12.9% Accuracy: 96.3-102% **LLOQ:** 75 ng/mL **ULOQ:** 2000 ng/mL **LQC:** 80 ng/mL Precision: 13.5% Accuracy: 107% **MQC:** 700 ng/mL Precision: 11.05% Accuracy: 100% **HQC:** 1500 ng/mL Precision: 17.0% Accuracy: 101% • Assay performance was found acceptable.
Population/ Demographics	**Characteristics** / **Arm A DAC HYP 200 mg/200 mg (N=12)** / **Arm B DAC HYP 200 mg/100 mg (N=12)** / **Arm C Placebo (N=8)** Age (Years): Mean (SD): 34 (15.2) / 38 (15.2) / 32 (10.6) Height (cm): Mean (SD): 171.8 (8.93) / 171.9 (9.97) / 174.6 (6.97) Weight (cm): Mean (SD): 78.3 (18.99) / 82.7 (19.73) / 81.8 (22.75) **Sex [Number of subjects (%)]** Male 6 (50) / 6 (50) / 4 (50) Female 6 (50) / 6 (50) / 4 (50) **Race/Ethnic origin [number of subjects (%)]** Caucasian/Hispanic 11 (91.7) / 10 (83.3) / 8 (100) Asian 1 (8.3) / 2 (16.7) / 0 **Smoking history [number of subjects (%)]** Nonsmokers 8 (66.7) / 7 (58.3) / 4 (50) Exsmokers 3 (25) / 4 (33.3) / 2 (25) Smokers 1 (8.3) / 1 (8.3) / 2 (25) • All randomized subjects who received study drug were analyzed for PK.
PK and PD Results	PK results: Although the dose regimen was interrupted during the study, the Sponsor reported that serum concentrations of DAC HYP were >5 µg/mL during the dosing period in all Arm A subjects and in most of Arm B subjects (except for subjects who terminated early), as illustrated in Figure 1. Figure 1: Observed DAC HYP serum concentration-time profiles

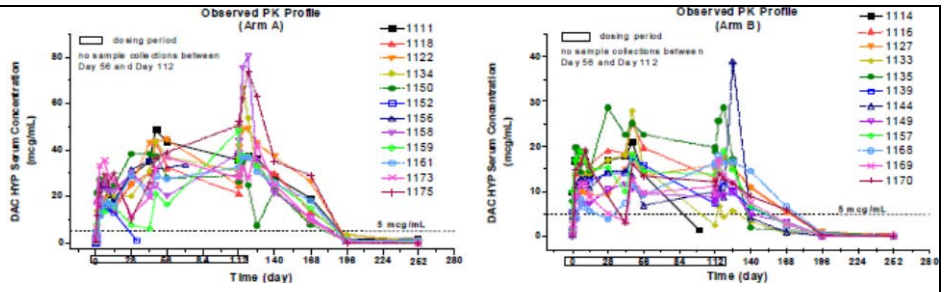


Figure 2: Observed DAC HYP serum concentration-time profiles during the first 20 days

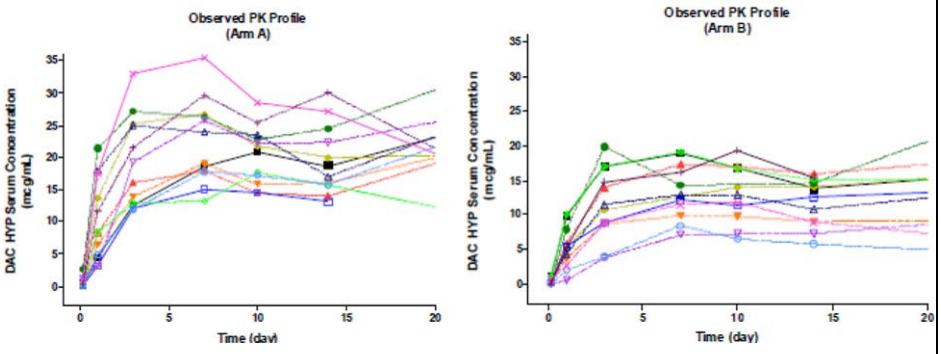
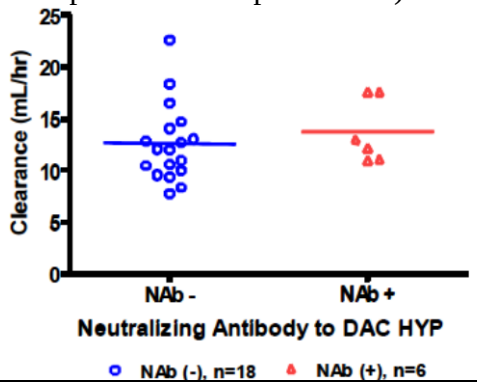


Figure 3. Influence of NAb response on clearance (lack of impact of NAb responses on PK parameters)



Safety	• Study doses were reported to be well tolerated. • The most frequently reported AEs related to DAC HYP treatment were injection site reactions by 21 (87.5%) DAC HYP-treated subjects and 8 (100%) placebo-treated subjects; upper respiratory tract infection (URTI) by 9 (37.5%) DAC HYP-treated subjects and 2 (25.0%) placebo-treated subjects; dermatitis and fatigue by 3 (12.5%) DAC HYP-treated subjects and zero placebo-treated subjects. • Most of the AEs were Grade 1 or 2 in severity and were transient in nature. • Grade 3 events were reported as SAEs. Three SAEs occurred during the study. Two SAEs were assessed as related to treatment with DAC HYP: viral pneumonia (200 mg/100 mg) and mesenteric

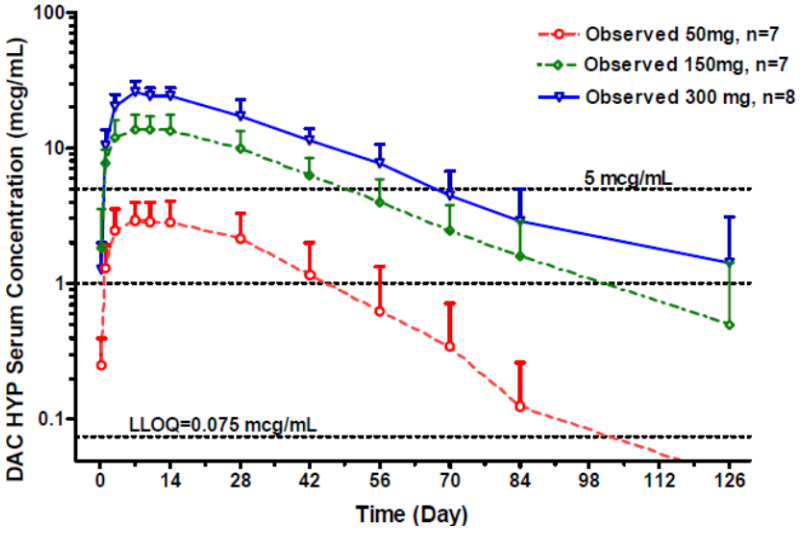
	adenitis (200 mg/200 mg). One SAE, motor vehicle accident (DAC HYP 200 mg/100 mg) was assessed as not related. • CD4+ T-cell lymphocytes decreased by approximately 20% to 25% in the DAC HYP-treated subjects compared to placebo controls. Counts either stabilized or returned to normal by the end of the study. • There were more cutaneous events and infections observed in DAC HYP-treated subjects. • No deaths or life-threatening (Grade 4) AEs were reported.
Immunogenicity	• The incidence of NAb response was higher (5 of 12) in the 200 mg/100 mg treatment group compared with the 200 mg/200 mg treatment group (1 of 12). • NAb response did not occur during the dosing period and became evident only during washout (at least 12 weeks following the final dose) despite interruptions in dosing. • NAb responses did not appear to have significant impact on drug clearance or exposure. • No reported association between the presence of NAb and reported AEs/SAEs.
Conclusion	*Pharmacokinetics:* • DAC HYP PK profile after multiple SC administrations can be described by a 2 compartment linear model and showed a slow absorption (Tmax ~7 days post-1st-dose) and a long elimination t1/2 (~15 days), similar to single dose PK (Study DAC-1015). Potential non-linear kinetics might occur when DAC HYP serum concentrations decreased to a very low level (<0.6 mcg/ml). • Steady state AUC values were estimated to be 16 mg·hr/mL and 8 mg·hr/mL for Arm A (200 mg/200 mg) and Arm B (200 mg/100 mg), respectively, with an inter-individual variability of ~26.4%. • The CL and V_{ss} were 12.5 mL/hr and 3323 mL (or 3.323 L), respectively. • C_{max} ~15.8 µg/mL was reported for both Arm A and Arm B following the first (200 mg) dose. • The steady state average concentrations were estimated to be 47.6 and 23.8 µg/mL for Arm A and Arm B, respectively. • DAC HYP concentration was maintained at >5 µg/mL for approximately 8 weeks in the 200 mg cohort and 4 weeks for most of the subjects in the 100 mg cohort after the last dose. • The covariates, such as body weight, age, gender, did not affect the PK profile. *Pharmacodynamics:* • Saturation of CD25 on peripheral $CD4_+$ T-cells was mostly observed

	within 4 hours of dosing and was maintained throughout the dosing period (16 weeks). [Duration of CD25 saturation was 199±32 days and 230±18 days for Arm B and Arm A, respectively.] • Desaturation of CD25 occurred when DAC HYP serum levels decreased to 0.62-1.26 mcg/mL in both dose groups. • There was a mild reduction (approximately 20–25%) in the frequency of CD25 on $CD4^+$ T- cells after DAC HYP treatment, similar in both Arms. No clear evidence of an association with AEs was reported.

Study Report #	**DAC-1015**
Title	A Phase 1, Randomized, Double-blinded, Placebo-controlled, Single-dose, Dose-escalation Study of Subcutaneous Daclizumab (High Yield Process Material) in Healthy Volunteers
Investigator/ Center	Minh Pham, MD. CMAX, Adelaide, South Australia, 5000, Australia
Study Dates	March 14, 2005 – October 6, 2005
Objectives	• To determine the safety and tolerability of single doses of DAC HYP • To characterize PK, PD, and immunogenicity of DAC HYP
Formulation	Treatment: DAC HYP: 100mg/mL for 50, 150, or 300 mg doses — Lot #: 90670401 Treatment: Placebo SC — Lot #: 90610401
Study Design	• Phase 1, single-center, randomized, double-blinded placebo-controlled, single-dose study of SC daclizumab (DAC HYP) in 36 healthy volunteers (male and female subjects18-75 years of age, inclusive) to compare 3 dosing regimens (A: 50mg; B: 150mg; C: 300mg) with placebo. • Up to 36 healthy volunteers in 3 dose cohorts in 2:1 ratio for each of the 3 dose cohorts (8 in the active arm and 4 in the placebo arm at each of 3 dose levels) were planned. − Cohort A: 1 injection of 0.50 mL DAC HYP or placebo from one 1 mL syringe. − Cohort B: 2 injections of 0.75 mL DAC HYP or placebo from two 1 mL syringes. − Cohort C: 3 injections of 1.0 mL DAC HYP or placebo from three 1 mL syringes. • Duration: 126 days follow-up <u>Assessments</u>: • Safety: SAE, AE, vital signs, laboratory tests, ECG, physical examinations, and absolute $CD3^+CD4^+$/$CD3^+CD8^+$ counts. • PK: − Predose on Day 0, 4 and 24 hours after dosing, and on Days 3, 7,

<table>
<tr><td></td><td>10, 14, 28, 42, 56, 70, 84, and 126.
− DAC HYP serum concentrations and PK parameters including CL/F, V/F, K_a and t1/2. Key PK parameters were estimated and reported for each dose level. PK analysis was conducted using a nonlinear mixed effects modeling population analysis approach.
• PD: including CD25 expression on peripheral T cells, and levels of circulating anti-daclizumab antibodies (ADAb)
− For CD25 analysis, whole blood samples were collected at pretreatment and on Days 0 (predose and 4 hrs postdose), 1, 3, 7, 28, 56, 70, 84, 112, and 126 or early termination.
− For absolute CD3+/CD4+ and CD3+/CD8+ T cell counts, samples were analyzed at pretreatment and on Days 0 (4 hrs postdose only), 1, 3, 7, 28, 56, 70, 84, 112, and 126 or early termination.
• Immunogenicity: Levels of circulating anti-Daclizumab antibodies (ADAb)
− Serum samples were collected from all subjects on Days 0, 70, 84, and 126 or the early termination visit. The PK samples from Days 28, 42, and 56 were tested for ADAb.</td></tr>
<tr><td>Bioanalytical Methods</td><td>• DAC HYP: serum concentrations were determined using a validated enzyme linked immunosorbent assay (ELISA) (b) (4) with a quantitative range of 0.075 - 2.00 µg/mL, with 0.075 µg/mL being the lower limit of quantification (LLOQ) [see Table below].
• The expression of CD25 on peripheral blood T cells and subset of T cells and CD3+/CD4+ and CD3+/CD8+ cells was monitored using fluorescence-activated cell sorter analysis.

Table. Assay performance for DAC HYP
<table>
<tr><td>Analyte</td><td colspan="2">Daclizumab (serum)</td></tr>
<tr><td>Method:</td><td colspan="2">ELISA</td></tr>
<tr><td>Standard Curve:</td><td>Range:</td><td>75 - 2000 ng/mL</td></tr>
<tr><td></td><td>Precision:</td><td>1.76-14.5%</td></tr>
<tr><td></td><td>Accuracy:</td><td>96.5-104%</td></tr>
<tr><td>LLOQ:</td><td colspan="2">75 ng/mL</td></tr>
<tr><td>ULOQ:</td><td colspan="2">2000 ng/mL</td></tr>
<tr><td>LQC:</td><td colspan="2">80 ng/mL</td></tr>
<tr><td></td><td>Precision:</td><td>28.6%</td></tr>
<tr><td></td><td>Accuracy:</td><td>101%</td></tr>
<tr><td>MQC:</td><td colspan="2">700 ng/mL</td></tr>
<tr><td></td><td>Precision:</td><td>13.4%</td></tr>
<tr><td></td><td>Accuracy:</td><td>93.8%</td></tr>
<tr><td>HQC:</td><td colspan="2">1500 ng/mL</td></tr>
<tr><td></td><td>Precision:</td><td>17.0%</td></tr>
<tr><td></td><td>Accuracy:</td><td>96.7%</td></tr>
</table>
• Assay performance was found acceptable.</td></tr>
</table>

Population/ Demographics	33 subjects were randomized in this study (10 to placebo, 7 to DAC HYP 50 mg, 8 to DAC HYP 150 mg, and 8 to DAC HYP 300 mg), including 17 males and 16 females, mostly Caucasian (>90%), median age ranged 31.1-44.1 years, mean height ranged 168.0-173.1 cm and mean weight ranged 72.0-75.2 kg.
PK and PD Results	PK results: The representative PK results obtained using ELISA assay were presented below (similar PK profile of DAC HYP using different assays). Figure 1: Mean DAC HYP serum concentration based on the ELISA assay by treatment group  • Mean DAC HYP serum concentrations in the 150-mg and 300-mg groups were maintained >5 µg/mL for approximately 49 and 70 days (or 7 and 10 weeks), respectively. The 50-mg group resulted in serum concentration >1 µg/mL for approximately 42 days (or 6 weeks). [Note: CD25 saturation was maintained when individual DAC HYP serum concentrations were >5 µg/mL. Saturation was defined as ≤1% of antigen-rich $CD4^+$ T cells staining positive with the DAC HYP competing Ab (clone 2A3).] Table 1. Summary of DAC HYP PK Parameters Following Single SC Doses in Healthy Volunteers

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Dose (mg)	Statistics	C_{max}[a] (µg/mL)	T_{max}[a] (days)	CL/F (mL/h)	V/F (mL)	K_A (1/h)	$AUC_{0\text{-}inf}$ (µg*h/mL)	AUC_{norm} (h/mL)	$t_{1/2}$ (days)
50	Mean	3.03	9	19.7	13393	0.0138	3362	0.0672	23.1
	Median	3.39	7	14.4	11810	0.0137	3471	0.0694	23.7
	%CV	39.0	38.0	69.0	37.7	30.6	45.5	45.5	32.8
	n	7	7	7	7	7	7	7	7
150	Mean	15.3	7	11.0	8826	0.0273	15553	0.104	24.7
	Median	16.4	7	9.92	8091	0.0185	15125	0.101	21.4
	%CV	23.1	53.0	45.5	37.4	89.0	35.3	35.3	37.2
	n	7	7	7	7	7	7	7	7
300	Mean	27.2	9	11.2	9026	0.0136	28310	0.0944	24.9
	Median	26.4	7	12.1	8859	0.0137	24855	0.0828	22.7
	%CV	12.1	29.7	23.7	16.4	39.4	27.4	27.4	36.9
	n	8	8	8	8	8	8	8	8

[a] Cmax and Tmax were obtained from observed drug serum concentrations

- It was reported that Subject 1123 may have received potentially reduced dose level; however, with and without mean PK data varied <15%, except for 26-134% higher in CL/F, V/F, and K10 values when included.

PD results:

Figure 2. Daclizumab HYP PK/PD Profile (with corresponding CD25 receptor saturation)

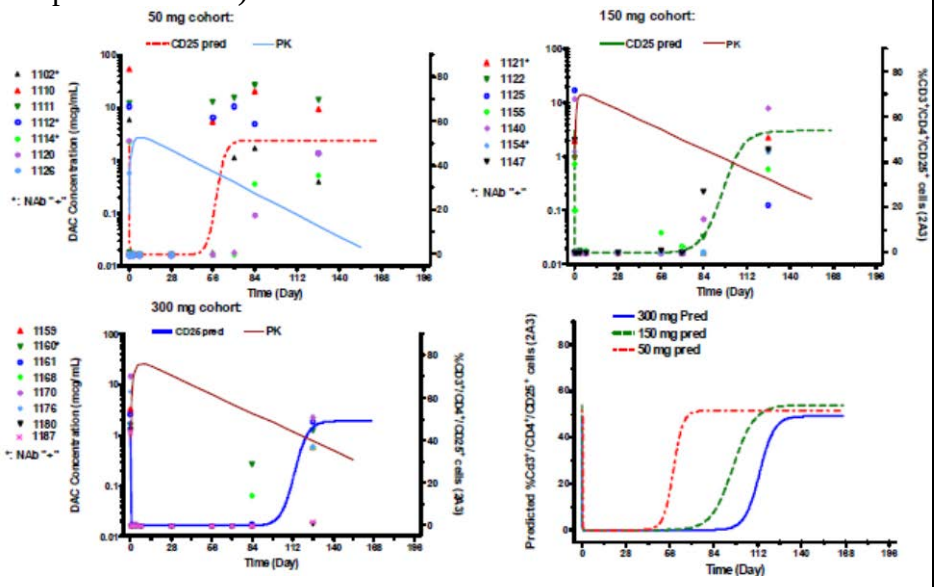
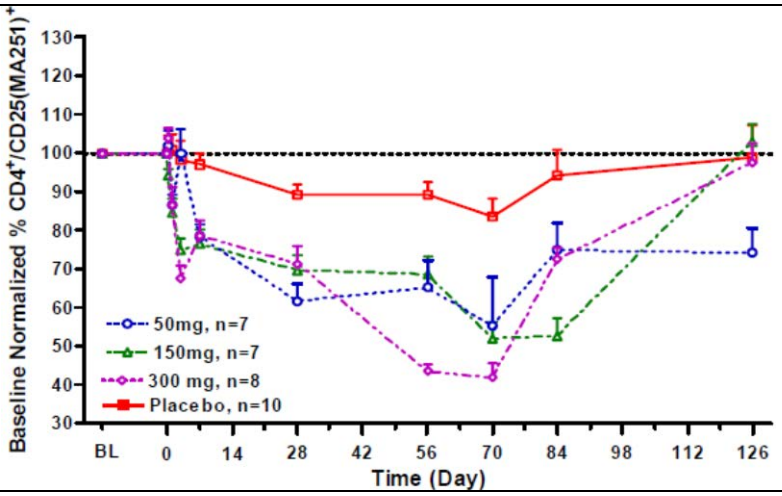
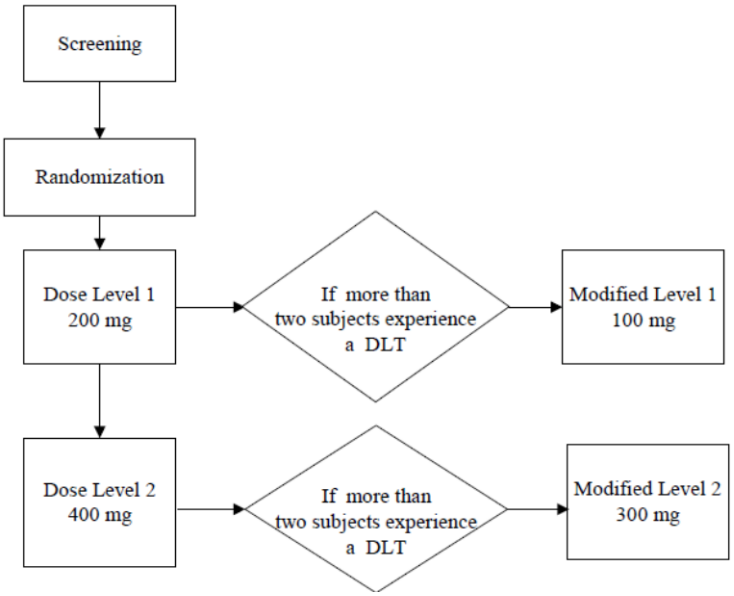


Figure 3. Changes in Percentage of CD4+/CD25 (MA251)+ Peripheral T-cells

	
Safety	• Single SC doses of DAC HYP at levels of 50, 150, and 300 mg were reported safe and well-tolerated with injection site pain (26%) and headache (17%) being the most prevalent study drug related AEs. • Majority (≥90%) of the AEs were mild (Grade1) to moderate (Grade 2) in severity, transient, and resolved. • An NCI CTCAE Grade 3 toxicity of neutropenia and hypoglycemia were observed, which were transient and resolved. • One SAE (staphylococcal bacteraemia) occurred in Subject 1110 and was considered by the investigator to be related to DAC HYP of 50 mg dose. • There was no treatment related effect on absolute CD4+ counts. • No death was reported.
Immunogenicity	• ADAb were observed in 8 (35%) subjects and NAb were detected in 6 (26%) subjects. Detection of antibodies was generally late (Day 56 or later). • The incidence of NAb was lower in the 300-mg group (1 subject compared to 2 subjects in 150-mg group and 3 subjects in 50-mg group). • Presence of NAb did not appear to have a significant effect on drug AUC or clearance.
Conclusion	*Pharmacokinetics:* • Single SC dose of DAC HYP dosed at 50, 150 or 300 mg followed one-compartment model with linear kinetics. • DAC HYP showed a slow absorption (Tmax = 7~9 days), a low~moderate volume of distribution (V/F = 5.6~22.6 L) and a long elimination t1/2 (10.7~44.7 days). • Inter-individual variability for V/F, CL/F, and Ka ranged 25~53%. *Pharmacodynamics:* • CD25 saturation on peripheral CD3+/CD4+ cells was observed within 4 hours of dosing (except for one subject in 150-mg group). • The mean (SD) duration of time that DAC HYP concentrations

	maintained the CD25 saturation was 68 (14), 102 (28), and 114 (21) days for 50 mg (n=6), 150 mg (n=7), and 300 mg (n=7) groups, respectively. • Desaturation of CD25 on peripheral T cells (n=16 out of 21 subjects) was observed when DAC HYP serum concentrations were ≤1 µg/mL. • A 40-60% reduction in the percentage of CD3+/CD4+CD25+ cells was observed across doses, being dose-and time-dependent, and generally returned to pre-treatment values after Day 84. • There was no treatment related effect on absolute CD4+ counts comparing dosing groups and placebo.

Study Report #	**DAC-1018**
Title	A Phase 1, Randomized, Double-blinded, Placebo-controlled, Single Fixed-dose, Dose-escalation Study of Intravenous Daclizumab in Healthy Volunteers
Investigator/ Center	Minh Pham, MBBS and Sepehr Shakib, MBBS. CMAX, Adelaide, South Australia, 5000, Australia
Study Dates	October 17, 2005– October 12, 2006
Objectives	• To determine the safety and tolerability of single intravenous (IV) dose of DAC HYP (primary endpoint: maximum tolerated dose or MTD) • To characterize PK, PD, and immunogenicity of IV DAC HYP
Formulation	Treatment: DAC HYP: 100 mg/mL (200mg and 400mg dose via 30-min IV infusion) — Lot #: 90670403 and 90670404 Treatment: Placebo SC via 30-min IV infusion — Lot #: 90610203
Study Design	• Phase 1, randomized, double-blinded, placebo-controlled, single fixed-dose, dose-escalation study to evaluate the safety and tolerability of DAC HYP in healthy volunteers who were randomized to receive a single dose of DAC HYP or placebo in a 3:1 ratio within 200mg or 400 mg cohorts. • Dose escalation to 100mg or 300mg or placebo from 200mg or 400mg doses may be required because of dose-limiting toxicity (DLT). • Up to 48 healthy volunteers in up to 3 dose cohorts (12 in active arm and 4 in placebo at each of 3 dose levels) were planned. A total of 31 subjects were randomized (7 to placebo and 12 each to DAC HYP 200 and 400 mg). • Duration: 210 days (1 treatment and 30 weeks of follow-up) • Study Schema:



Assessments:

- Safety: SAE, AE, vital signs, laboratory tests, ECG, physical examinations, and absolute CD4+ T-cell counts.
- PK:
  - Samples collected at predose, at the end of infusion, 2 and 4 hours after dosing on Day 0, and on Days 1, 3, 7, 14, 28, 56, 70, 84, and 126 or early termination.
  - DAC HYP serum concentrations and PK parameters including Cmax, AUCinf, CL, Vss, and t1/2. Key PK parameters were estimated and reported for each dose level. PK analysis was conducted using a nonlinear mixed effects modeling population analysis approach.
- PD: Including CD25 expression on peripheral T cells, calculated percentage of CD25+ T cells, exploratory analyses of other lymphocyte subset absolute counts (CD8+ T cells, B cells, and natural killer [NK] cells)
  - Whole blood samples collected at screening (2 samples, drawn at least one day apart), 30 minutes before dosing and 4 hours after dosing on Day 0, and on Days 7, 14, 28, 56, 84, and 126 or early termination.
- Immunogenicity: levels of circulating anti-Daclizumab antibodies (ADAb) and neutralizing antibodies (NAb)
  - Serum samples collected on Days 0, 56, 70, 84, and 126, as well as PK samples when they are needed.

Bioanalytical Methods

- DAC HYP: serum concentrations were determined using a validated sequential "sandwich" enzyme linked immunosorbent assay (ELISA) (b) (4) with a quantitative range of 0.075 - 2.00 µg/mL, with 0.075 µg/mL being the lower limit of quantification (LLOQ) [see Table

below]. A validated bridging enzyme immunoassay/ELISA was utilized for measure of anti-Daclizumab antibodies (ADAb) in human serum

- PD of DAC HYP was assessed using fluorescence-activated cell sorter analysis after staining blood with DAC HYP competing murine IgG1 antibody (clone 2A3) and murine IgG1 non-competing antibody (clone MA251) on the CD4+ T cells.

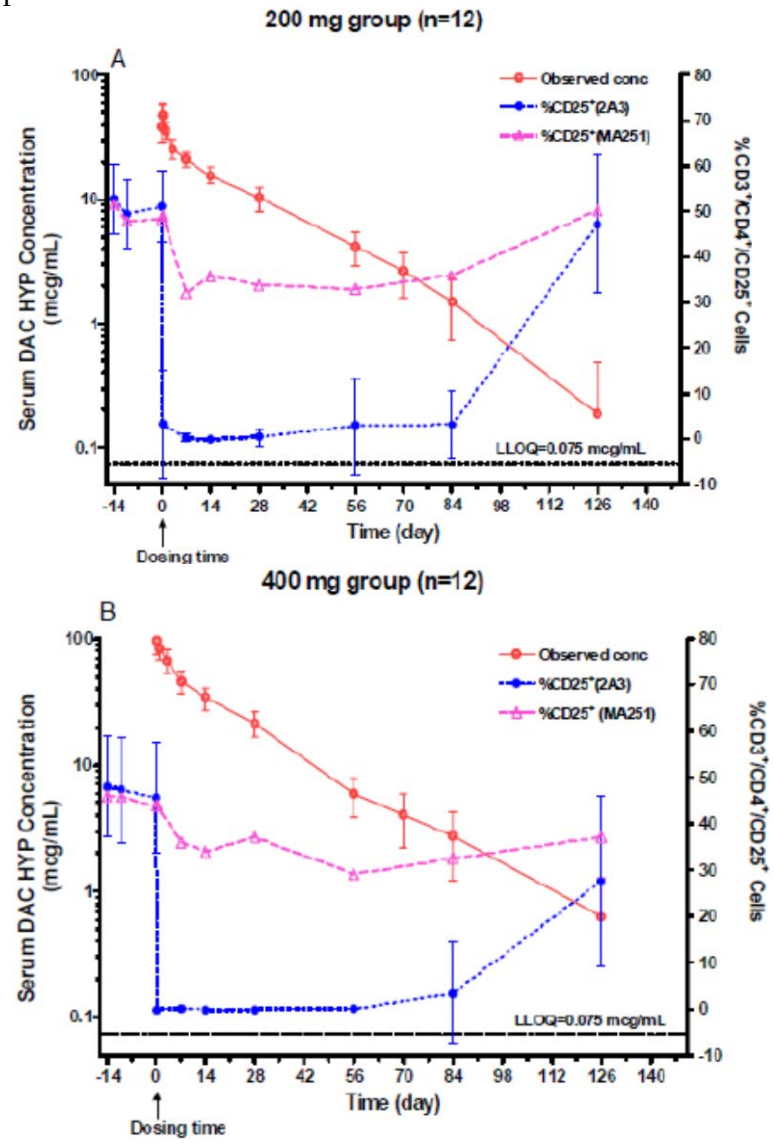
Table. Assay performance for DAC HYP

Analyte		Daclizumab (serum)
Method:		ELISA
Standard Curve:	Range:	25 - 2400 ng/mL
	Precision:	1.77-5.86%
	Accuracy:	99-102%
LLOQ:		75 ng/mL
ULOQ:		2000 ng/mL
LQC:		80 ng/mL
	Precision:	13.2%
	Accuracy:	105%
MQC:		700 ng/mL
	Precision:	6.61%
	Accuracy:	100%
HQC:		1500 ng/mL
	Precision:	10.5%
	Accuracy:	100%
UHQC:		75000 ng/mL
	Precision:	11.2%
	Accuracy:	93.5%

- Assay performance was found acceptable.

Population/ Demographics

Characteristics	**Placebo (n=7)**	**DAC HYP 200 mg (n=12)**	**DAC HYP 400 mg (n=12)**	**Total (n=31)**
Gender, n (%)				
Male	3 (42.9)	4 (33.3)	8 (66.7)	15 (48.4)
Female	4 (57.1)	8 (66.7)	4 (33.3)	16 (51.6)
Race or ethnic group, n (%)				
Caucasian/Hispanic	7 (100)	12 (100)	9 (75.0)	28 (90.3)
Asian	0	0	2 (16.7)	2 (6.5)
Other	0	0	1 (8.3)	1 (3.2)
Median age (range), years	24.0 (18.9 - 57.8)	27.2 (21.6 - 56.1)	30.0 (19.1 - 55.6)	27.8 (18.9 - 57.8)
Mean (SD) height, cm	168.9 (13.3)	172.3 (9.6)	171.2 (7.8)	171.1 (9.6)
Mean (SD) weight, kg	78.2 (12.9)	77.6 (11.6)	78.6 (17.9)	78.1 (14.1)
Number (%) of subjects with weight				
<65 kg	0	1 (8.3)	3 (25.0)	4 (12.9)
65–85 kg	5 (71.4)	9 (75.0)	5 (41.7)	19 (61.3)
>85 kg	2 (28.6)	2 (16.7)	4 (33.3)	8 (25.8)

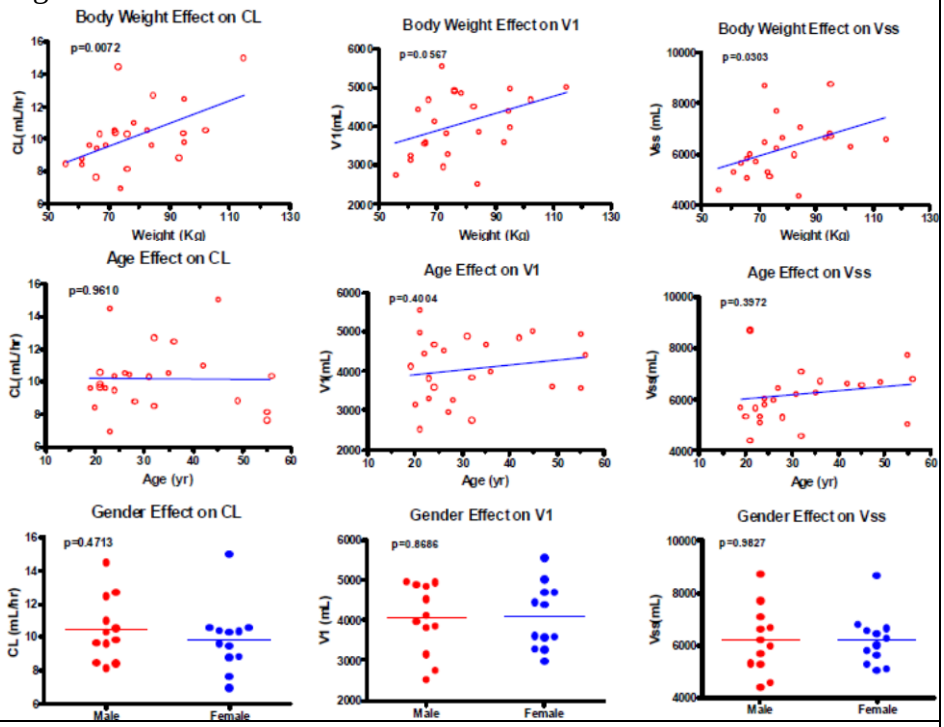
PK and PD Results	Figure 1 shows the time course of DAC HYP concentrations in relation to CD25 expression and CD25 saturation using DAC HYP competing (clone 2A3) and noncompeting (clone MA251) antibodies at dose levels of 200 and 400 mg. The PK of IV DAC HYP followed a bi-exponential decline with an initial fast distribution phase and a slow elimination phase. PK parameters are summarized in Table 1. Figure 1: Observed Mean DAC HYP Serum Concentration- and CD25 Expression-Time Profiles  Table 1. Summary of DAC HYP PK Parameters Following Single IV Infusion in Healthy Volunteers

Dose Group	Statistics	C_{max} (µg/mL)	$AUC_{0\text{-}inf}$ (h*mg/mL)	$t_{1/2}$ (day)	CL (mL/h)	V_1 (mL)	V_{ss} (mL)
200 mg	Mean	51	20	20	10	4320	6529
	SD	10	3	4	1	749	968
	%CV	20	17	18	14	17	15
	n	12	12	12	12	12	12
400 mg	Mean	112	41	18	10	3810	5888
	SD	22	8	4	2	840	1191
	%CV	20	20	25	23	22	20
	n	12	12	12	12	12	12

[a] Cmax and Tmax were obtained from observed drug serum concentrations

age, gender, or body weight analysis?
Covariate effects (including body weight, age, and gender) on DAC HYP PK was evaluated in population PK and PD analysis and were concluded to not have significant effects on the PK based on the limited data in this study. [Refer to Pharmacometric Review in Section 4.2 for more details]

Figure 2: Covariate Effects on DAC HYP PK



Safety	• No DLTs were observed; consequently, the MTD was not established. • The most frequently (>10%) reported DAC HYP-treatment related AEs vs. placebo were upper respiratory tract infection (URTI) (12.5% vs. 28.6%), headache (20.8% vs.14.3%), cough and pharyngolaryngeal pain (12.5% vs. 0%). • No study drug related CTCAE Grade 3 or Grade 4 AEs were reported. • No occurrence of subjects with two consecutive absolute CD4+ T-cell counts of <400/mm3 within 14 days postdose.

	• No statistically significant changes in trends (slopes) over time of absolute CD4+ T-, B-, and NK-cells or ratio of CD4+ to CD8+ T cells were reported. • No deaths or life-threatening (Grade 4) AEs were reported.
Immunogenicity	• 3 subjects (12.5%) showed ADAb an, 2 (8.3%) tested positive for NAb, both seen only in the 200 mg dosed subjects. • Detection of antibodies was generally late (Day 126), and NAb had no significant impact on exposure AUC or CL values.
Conclusion	*Pharmacokinetics:* • DAC HYP given IV infusion showed a low CL (10 mL/h), a small volume of distribution, a long t1/2 (18-20 days), and dose-proportionality for exposure (Cmax and AUC) within the 200-400 mg dose range. • No covariates (age, gender, or body weight) significantly affected the PK parameters based on limited data from this study. *Pharmacodynamics:* • Loss of DAC HYP competing antibody (clone 2A3) binding on T cells, indicative of CD25 saturation, was observed within 4 hours after dosing of 200 mg and 400 mg. The percentage of antibody 2A3-binding cells remained ≤1% for up to 84-126 days postdose. • It appeared that a DAC HYP serum concentration of approximately 1 µg/mL was necessary to maintain saturation of $CD25^+$ T cells.

Study Report #	**205HV102**
Title	A Single-Dose, Single-Blind, Phase 1 Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of BIIB019, Daclizumab High Yield Process (DAC HYP), in Japanese and Caucasian Adult Healthy Volunteers
Investigator/ Center	Jim Bush MBChB, PhD, MRCS(Ed), MFPM, Covance Clinical research Unit Ltd., Springfield House, Hyde Street, Leeds, LS2 9LH, UK
Study Dates	October 14, 2013 – March 24, 2014
Objectives	• To determine the PK of single SC dose of DAC HYP in Japanese and Caucasian adult healthy volunteers • To assess the safety and tolerability, PD, and immunogenicity of single SC dose of DAC HYP
Formulation	Treatment: DAC HYP: 150 mg/mL; Lot #: VVLC35
Study Design	• Phase 1, single-dose, single-blind, partially randomized study to evaluate the PK, safety, and tolerability of DAC HYP administered to 28 Japanese adult healthy volunteers and 28 Caucasian adult healthy volunteers, matched by BW and age (aged 18-55 years with a BMI of 18-30 kg/m^2, inclusive). • Both Japanese and Caucasian groups had 2 treatment arms: DAC

	HYP 75 mg SC and 150 mg SC (n=14 per dose group). • Study duration for each subject was up to 105 days - a Screening Period (within 21 days before Day -2), an In-Clinic Period in which dosing and PK sampling (Day -1 to Day 2; approximately 36~40 hours), and a Follow-up Period (follow-up visits on Days 4, 7, 14, 28, 42, 56, 70, 84, and 105). In-Clinic Period: PK Blood samples for serum concentrations of DAC HYP were collected on Days -1, 1 (4 and 8 hours postdose), and 2 (24 hours postdose). Blood samples for the determination of CD56bright natural killer (NK) cells and anti-DAC HYP antibodies were collected on Day -1. Follow-up Period: Samples for PK, PD and anti-DAC HYP antibodies were collected during follow-up visits on Days 4, 7, 14, 28, 42, 56, 70, 84, and 105. Assessments: • Safety: SAE, AE, vital signs, laboratory tests, ECG, and physical examinations • PK: DAC HYP serum concentrations and PK parameters including Cmax, AUClast, AUCinf, %AUCextrap, Tmax, CL/F, Vd/F and t1/2. Key PK parameters were estimated and reported for each dose level. PK analysis was conducted using a nonlinear mixed effects modeling population analysis approach. An ANOVA, with weight and age as covariates, was used to compare log transformed AUCinf and Cmax values between Japanese and Caucasian subjects. Ratios of geometric means along with 90% CIs using the Caucasian group as a reference were reported for AUCinf and Cmax. Statistical analyses were performed for all evaluable subjects and subjects without neutralizing antibodies. • Exploratory PD: proportion of subjects who developed immunogenicity by Day 105 (anti-DAC HYP antibodies) and changes in CD56bright NK cells. Potential relationships between PK and PD endpoints. • Immunogenicity: Levels of positive anti-Daclizumab antibodies (ADAb) and neutralizing anti-DAC HYP antibodies (NAb)
Bioanalytical Methods	• DAC HYP: serum concentrations were determined using a validated enzyme linked immunosorbent assay (ELISA) (b) (4) with a quantitative range of 500 - 7500 ng/mL, with 500 ng/mL being the lowest limit of quantification (LLOQ). [see Table below] • A validated electrochemiluminescent (ECL) method was utilized for measure of anti-Daclizumab antibodies (ADAb) in human serum. A cell-based electrochemiluminescent assay was used for the detection of NAbs in human Serum.

Table. Assay performance for DAC HYP

Analyte		Daclizumab (serum)
Method:		ELISA
Standard Curve:	Range:	500 - 7500 ng/mL
	Precision:	2.6-5.2%
	Accuracy:	98.1-103.1 %
LLOQ:		500 ng/mL
ULOQ:		7500 ng/mL
LQC:		750 ng/mL
	Precision:	5.8%
	Accuracy:	100.0%
MQC:		2000 ng/mL
	Precision:	5.4%
	Accuracy:	94.8%
HQC:		6000 ng/mL
	Precision:	6.4%
	Accuracy:	95.3%

- Assay performance was found acceptable.

Population/ Demographics	• N=56 enrolled (28 Japanese subjects and 28 Caucasian subjects) to ensure that at least 48 subjects were evaluable, and completed the study. • N=28 for each group was analyzed. • The overall study population: 22 males and 34 females, with 11 male and 17 female Japanese subjects and 11 male and 17 female Caucasian subjects. Subjects were aged 19-54 years, with a mean age of 31.9 years for Japanese subjects and 32.1 years for Caucasian subjects, with similar distributions at each dose level. Mean weight was slightly higher (<10%) for Caucasian subjects (66.39 kg) relative to Japanese subjects (60.48 kg), with similar differences at each dose level.
PK and PD Results	PK results: The representative PK results obtained using ELISA assay were presented below (similar PK profiles in Caucasian and in Japanese groups) in Figures 1~2 and Tables 1~4. Figure 1. Representative serum concentrations of DAC HYP following SC administration at 75 mg dose in Caucasian and in Japanese (Top: Arithmetic mean (SD); bottom: Semi-logarithmic scale) - all PK population

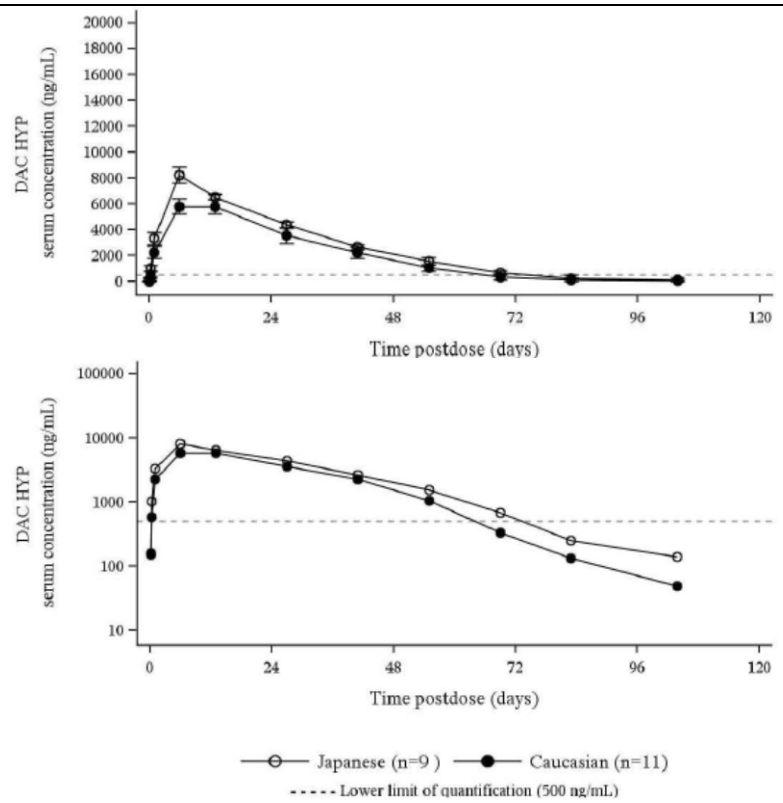
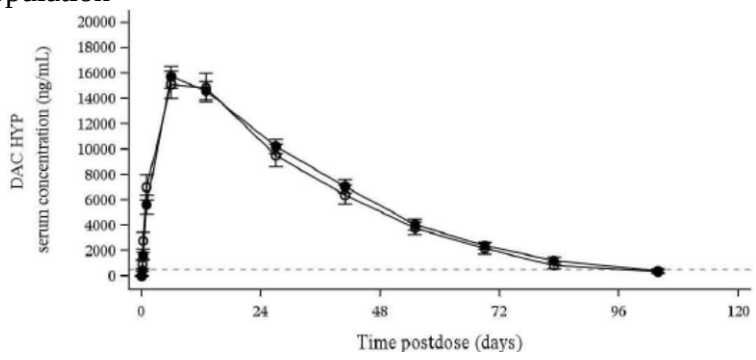


Figure 2. Representative serum concentrations of DAC HYP following SC administration at 150 mg dose in Caucasian and in Japanese (Top: Arithmetic mean (SD); bottom: Semi-logarithmic scale) - all PK population



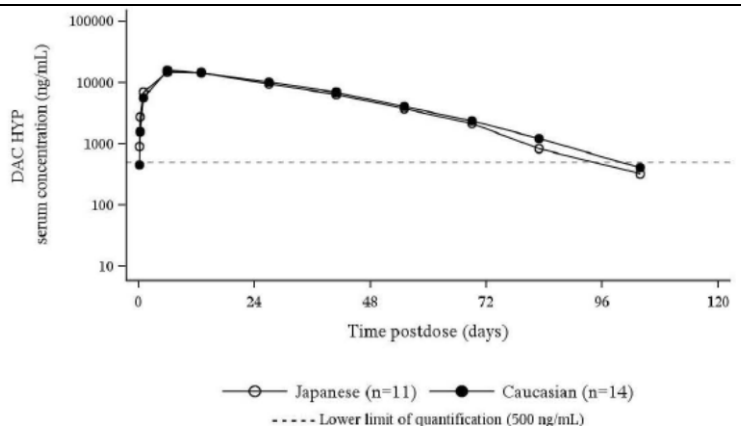


Table 1. Summary statistics of DAC HYP PK parameters for all evaluable subjects

	75 mg DAC HYP	
	Japanese	Caucasian
AUClast (ug.h/mL)	6288 (1340) [9]	4670 (2392) [11]
AUCinf (ug.h/mL)	7015 (1583) [9]	6234 (2055) [8]
Cmax (ug/mL)	8.32 (1.38) [9]	5.96 (2.01) [11]
Tmax[a] (day)	6.20 (2.05, 13.3) [9]	6.16 (2.07, 13.2) [11]
t1/2 (day)	19.8 (7.66) [9]	17.2 (2.68) [7]
CL/F (mL/min)	0.186 (0.0412) [9]	0.220 (0.0713) [8]
Vd/F (L)	7.22 (1.65) [9]	8.02 (2.95) [8]

- 5 Japanese and 3 Caucasian subjects had predose concentrations of DAC HYP >5% of Cmax and were excluded from statistical analyses.

	150 mg DAC HYP	
	Japanese	Caucasian
AUClast (ug.h/mL)	14097 (4089) [11]	14934 (3645) [14]
AUCinf (ug.h/mL)	14895 (4094) [11]	15568 (3902) [14]
Cmax (ug/mL)	16.3 (4.29) [11]	16.0 (2.85) [14]
Tmax[a] (day)	6.20 (2.09, 13.2) [11]	6.16 (2.06, 13.2) [14]
t1/2 (day)	18.0 (3.99) [11]	17.9 (3.62) [14]
CL/F (mL/min)	0.181 (0.0560) [11]	0.169 (0.0361) [14]
Vd/F (L)	6.57 (1.67) [11]	6.14 (1.16) [14]

- 3 Japanese had predose concentrations of DAC HYP >5% of Cmax and were excluded from statistical analyses.

Table 2. Summary statistics of DAC HYP PK parameters excluding subjects positive for DAC HYP NAbs

	75 mg DAC HYP	
	Japanese	Caucasian
AUClast (ug.h/mL)	6661 (1121) [4]	5954 (2588) [5]
AUCinf (ug.h/mL)	7431 (1441) [4]	6533 (2477) [5]
Cmax (ug/mL)	8.71 (1.37) [4]	6.43 (2.26) [5]
Tmax[a] (day)	6.14 (5.16, 6.20) [4]	6.14 (2.07, 13.1) [5]
t1/2 (day)	19.8 (2.70) [4]	18.1 (3.41) [4]
CL/F (mL/min)	0.172 (0.0282) [4]	0.215 (0.0827) [5]
Vd/F (L)	6.99 (0.951) [4]	8.30 (3.67) [5]

	150 mg DAC HYP	
	Japanese	Caucasian
AUClast (ug.h/mL)	15367 (3720) [8]	14958 (3793) [13]
AUCinf (ug.h/mL)	16265 (3575) [8]	15608 (4058) [13]
Cmax (ug/mL)	17.3 (4.24) [8]	16.1 (2.93) [13]
Tmax[a] (day)	6.20 (2.09, 13.2) [8]	6.16 (2.06, 13.2) [13]
t1/2 (day)	19.3 (3.74) [8]	17.9 (3.76) [13]
CL/F (mL/min)	0.161 (0.0392) [8]	0.169 (0.0376) [13]
Vd/F (L)	6.37 (1.55) [8]	6.12 (1.20) [13]

Table 3. Statistical Comparison of DAC HYP Primary PK Parameters Between Japanese and Caucasian Subjects – Including Subjects With Positive NAb Status

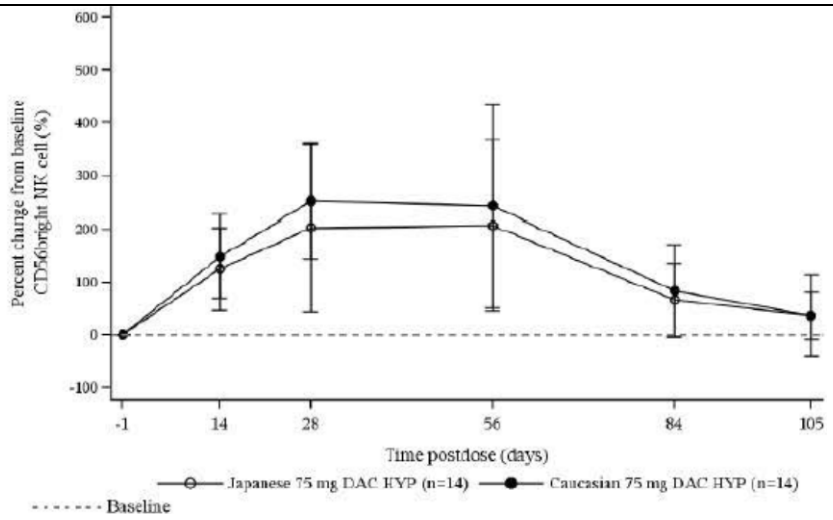
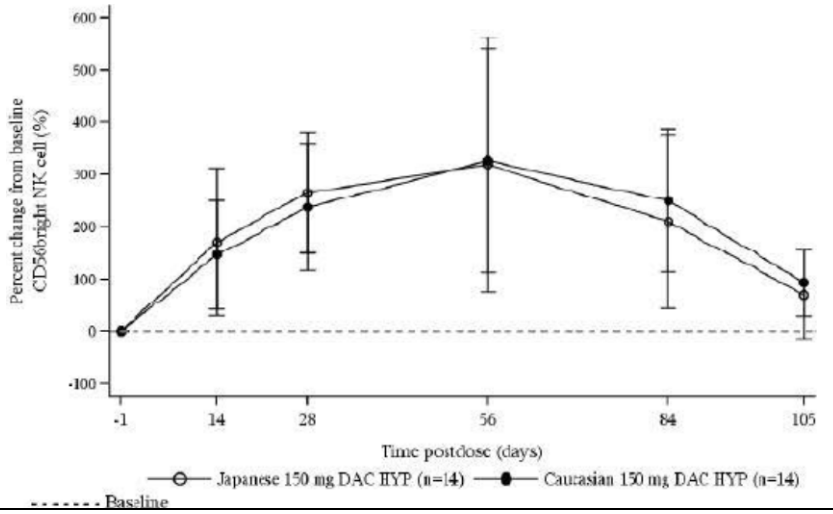
						90% CI for the ratio	
Parameter (Units)	Treatment	Group	N*	Geometric least squares means	Ratio of geometric least squares means (Japanese : Caucasian)	Lower	Upper
AUCinf (ug.h/mL)	75 mg DAC HYP	Japanese	9	6510	1.03	0.825	1.29
		Caucasian	8	6309			
	150 mg DAC HYP	Japanese	11	13902	0.894	0.766	1.04
		Caucasian	14	15552			
Cmax (ug/mL)	75 mg DAC HYP	Japanese	9	7.72	1.30	1.06	1.60
		Caucasian	11	5.93			
	150 mg DAC HYP	Japanese	11	15.4	0.959	0.836	1.10
		Caucasian	14	16.1			

Table 4. Statistical Comparison of DAC HYP Primary PK Parameters Between Japanese and Caucasian Subjects – Excluding Subjects With Positive NAb Status

						90% CI for the ratio	
Parameter (Units)	Treatment	Group	N*	Geometric least squares means	Ratio of geometric least squares means (Japanese : Caucasian)	Lower	Upper
AUCinf (ug.h/mL)	75 mg DAC HYP	Japanese	4	6969	1.09	0.818	1.44
		Caucasian	5	6420			
	150 mg DAC HYP	Japanese	8	15019	0.955	0.790	1.16
		Caucasian	13	15720			
Cmax (ug/mL)	75 mg DAC HYP	Japanese	4	8.26	1.32	0.954	1.82
		Caucasian	5	6.27			
	150 mg DAC HYP	Japanese	8	16.1	0.983	0.834	1.16
		Caucasian	13	16.3			

PD results:

Figure 3. Mean (SD) percent change from baseline (Day -1) in $CD56^{bright}$ NK cells by dose level and racial group

	 
Safety	• The incidence of TEAEs was similar between the racial groups at each dose level. Also, no TEAEs led to study withdrawal in this study. • There were no deaths or SAEs reported in this study. • The incidence of infections and cutaneous events (AEs of special interest) was similar between the racial groups. • The overall safety profile for DAC HYP in this study was reported to be comparable between the Japanese and Caucasian subjects and is consistent with previous experience with DAC HYP.
Immunogenicity	• 4 Japanese and 1 Caucasian subjects had pre-existing ADA reactivity at baseline. • Treatment-emergent ADAs were observed in 15 Japanese (9 at 75mg) and 9 (6 at 75mg) Caucasian subjects. • No positive NAb samples were detected at baseline. Treatment-emergent NAbs were observed in 10 Japanese and 7 Caucasian subjects.
Conclusion	*Pharmacokinetics:*

	• Following administration of a single 75- or 150-mg dose of DAC HYP in Japanese and Caucasian subjects, a similar PK profile was observed for both racial groups. DAC HYP concentrations increased slowly with a Tmax of approximately 6 days, followed by a gradual decline. • The least squares (LS) geometric mean Cmax was approximately 30% higher for Japanese subjects, compared to Caucasian subjects, at the 75-mg dose level, without regards to subjects with positive NAb. The corresponding 90% CIs did not fall within the 0.8-1.25 boundary. Reason is unclear, although the Sponsor noted the limited evaluable PK data per racial group for comparison. • The LS geometric mean AUCinf was similar for Japanese subjects and Caucasian subjects at the 75-mg dose level in the population excluding subjects with positive NAb, as well as for the population including all evaluable subjects. • The LS geometric mean Cmax and AUCinf were similar for Japanese and Caucasian subjects at the 150-mg dose level (i.e., the proposed dose) in the population excluding subjects with positive NAb, as well as for the population including all evaluable subjects, with no significant difference between the racial groups for either analysis. *Pharmacodynamics:* • CD^{56}bright NK cell counts increased from baseline and reached a plateau between Days 28 (~200%) and 56 (~300%) for 75mg and 150mg, respectively, and for both racial groups following administration of DAC HYP and returned to close to baseline levels by Day 105. • The percent changes from baseline for CD^{56}bright NK cell counts were similar between Japanese and Caucasian subjects. • No detectable relationship was observed between PK and PD by dose level and racial group, as explored by the Sponsor.

Study Report #	**205MS201**
Title	Multicenter, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Safety and Efficacy of Daclizumab HYP (DAC HYP) as a Monotherapy Treatment in Subjects with Relapsing-Remitting Multiple Sclerosis
Investigator/ Center	Professor Krzysztof Selmaj, Medical University of Lodz, Lodz, Poland
Study Dates	February 15, 2008 – August 30, 2011
Objectives	Primary: To determine whether DAC HYP, when compared to placebo, is effective in reducing the rate of relapses between baseline

<table>
<tr><td></td><td>and Week 52 (the primary endpoint was the annualized relapse rate between baseline and Week 52)

<u>Secondary</u>: To determine whether DAC HYP is effective in
• Reducing the number of new gadolinium (Gd)-enhancing lesions over 5 brain magnetic resonance imaging (MRI) scans at Weeks 8, 12, 16, 20, and 24 (calculated as the sum of these 5 MRIs) in a subset of subjects
• Reducing the number of new or newly-enlarging T2 hyperintense lesions at Week 52
• Reducing the proportion of relapsing subjects between baseline and Week 52
• Improving quality of life as measured by the Multiple Sclerosis Impact Scale-29 (MSIS-29) physical score at Week 52 compared to baseline</td></tr>
<tr><td>Formulation</td><td><table><tr><td>Treatment</td><td>Lot #</td></tr><tr><td>DAC HYP: 100 mg/mL</td><td>90670504, 90670505, DZA0005, E06688-001L03, E06688-001L04, E06688-002L03, E06688-003L03, E06688-003L04, E06688-007L01, E06688-009L01, E06688- 010L01, and E06688-012L01</td></tr></table></td></tr>
<tr><td>Study Design</td><td>• A multicenter, double-blind, randomized, placebo-controlled, parallel group study of DAC HYP monotherapy in subjects with relapsing-remitting multiple sclerosis (RRMS).
• Approximately male and female 600 subjects (18-55 years of age, inclusive) were to be randomized in a 1:1:1 ratio to receive one of the following treatments:
− Group 1: placebo (3 SC injections q4w for a total of 13 doses)
− Group 2: 150 mg DAC HYP (3 SC injections q4w for a total of 13 doses)
− Group 3: 300 mg DAC HYP (3 SC injections q4w for a total of 13 doses)
• MRI was performed at baseline, Week 24, Week 36, and Week 52. In addition, monthly MRI was performed for the first 6 months in the initial 307 subjects enrolled.
• An interim futility analysis was performed after 150 subjects completed the Week 24 visit.
• Duration of treatment was 52 weeks (allowing treatment effect at steady-state), at which time subjects had the option of either continuing in a 20-week follow-up period or enrolling in the DAC HYP extension study (Study 205MS202).

<u>DAC HYP concentration measurements</u>:
• Serum concentrations of DAC HYP were assessed for pre-dose trough levels at selected timepoints throughout the study and at the Follow-up Visit. Data were combined with other studies for the population PK analysis.</td></tr>
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PK modeling and parameter estimation were not performed in this study.
<u>PD response</u>:
Cell-mediated immunity using Cylex® Immunknow™ assay; CD25 expression on peripheral T cells using CD25 assay; expanded lymphocyte phenotyping addressing T and CD56+ natural killer (NK) cells; identification and/or analysis of serum biomarkers that may relate to DAC HYP efficacy or MS disease activity such as soluble CD25 level.
</td></tr>
<tr><td>Bioanalytical Methods</td><td>
DAC HYP: serum concentrations were determined using a validated sequential “sandwich” enzyme linked immunosorbent assay (ELISA) (b) (4) with a quantitative range of 500 - 7500 ng/mL, with 500 ng/mL being the lower limit of quantification (LLOQ) [see Table below]. A validated bridging enzyme immunoassay/ELISA was utilized for measure of anti-Daclizumab antibodies (ADAb) in human serum
Table A. Assay performance for DAC HYP
<table>
<tr><td>Analyte</td><td colspan="2">Daclizumab (serum)</td></tr>
<tr><td>Method:</td><td colspan="2">ELISA</td></tr>
<tr><td>Standard Curve:</td><td>Range:</td><td>500 - 7500 ng/mL</td></tr>
<tr><td></td><td>Precision:</td><td>2.3-4.2%</td></tr>
<tr><td></td><td>Accuracy:</td><td>97.7-101%</td></tr>
<tr><td>LLOQ:</td><td colspan="2">500 ng/mL</td></tr>
<tr><td>ULOQ:</td><td colspan="2">7500 ng/mL</td></tr>
<tr><td>LQC:</td><td colspan="2">750 ng/mL</td></tr>
<tr><td></td><td>Precision:</td><td>7.6%</td></tr>
<tr><td></td><td>Accuracy:</td><td>98.6%</td></tr>
<tr><td>MQC:</td><td colspan="2">2000 ng/mL</td></tr>
<tr><td></td><td>Precision:</td><td>8.1%</td></tr>
<tr><td></td><td>Accuracy:</td><td>99.5%</td></tr>
<tr><td>HQC:</td><td colspan="2">6000 ng/mL</td></tr>
<tr><td></td><td>Precision:</td><td>9.4%</td></tr>
<tr><td></td><td>Accuracy:</td><td>96.7%</td></tr>
</table>
Assay performance was found acceptable.
</td></tr>
<tr><td>Population/ Demographics</td><td>
Mean age was 36.6 years in the placebo group, 35.3 years in the DAC HYP 150 mg group, and 35.2 years in the DAC HYP 300 mg group.
Approximately two-thirds of the study population was female, with the percentages of males to females consistent across treatments.
Study population was predominantly White (96%), with Asian at 3~4% of the total population.
</td></tr>
<tr><td>Immunogenicity</td><td>
At Week 24, anti-DAC antibodies were detected in 7 (5%) placebo-
</td></tr>
</table>

	treated subjects and 6 (2%) DAC HYP-treated subjects (5 subjects in the 150 mg group and 1 subject in the 300 mg group). At Week 52, anti-DAC antibodies were present in 8 (6%) placebo-treated subjects and 4 (1%) DAC HYP-treated subjects (3 subjects in the 150 mg group and 1 subject in the 300 mg group). • At Week 24, neutralizing antibodies to DAC HYP were detected in 6 (2%) DAC HYP-treated subjects (5 subjects in the 150 mg group and 1 subject in the 300 mg group) and in none of the placebo-treated subjects. In some subjects, these antibodies were transient, and at Week 52, neutralizing antibodies to DAC HYP were present only in 1 subject in each DAC HYP dose group.
PK and PD Conclusions	*Pharmacokinetics:* • Average serum concentration levels in both DAC HYP dose groups reached a plateau by Week 16 (4th dose), consistent with the expected steady-state based on the drug half-life. • A 2-fold increase in DAC HYP dose from 150 mg to 300 mg resulted in an approximate 2-fold increase in mean serum trough concentrations (18423 ng/mL and 35043 ng/mL, respectively). *Pharmacodynamics:* • The PD response to DAC HYP as measured by both an increase in CD56bright NK cells and a decrease in CD4+CD127lowFox3 T-cells was apparent by Week 4. Both doses of DAC HYP had a similar effect on these PD markers. The changes in CD4+CD127lowFoxP3+ T-cells plateaued by Week 8; the expansion of CD56bright NK Cells increased gradually throughout the treatment period. • CD25 saturation became apparent at the first post-baseline time point in both DAC HYP groups. At Week 4, 91% of DAC HYP-treated subjects vs 1% of placebo-treated subjects demonstrated CD25 saturation. At Week 52, 87% of DAC HYP and 2% of placebo subjects demonstrated CD25 saturation.
Conclusions	• The results of Study 205MS201 demonstrated that monthly, SC injections of DAC HYP had clinically meaningful effects on RRMS, which included a reduction in annualized relapse rate (i.e., DAC HYP 150 mg and 300 mg significantly reduced the annualized relapse rate by 54% and 50%, respectively, compared to placebo), an increase in proportion of subjects who were relapse-free, a reduction in MRI lesion activity, and a reduction in confirmed disability progression. • The low rate of treatment discontinuation suggested a good tolerability profile. • The safety data indicated an increase in the risk for infections, cutaneous AEs, and increases in hepatic transaminases on laboratory testing.

	• In general, the safety profile for DAC HYP when administered at doses of 150 mg and 300 mg every 4 weeks was similar. The AEs typically improved or resolved with standard medical interventions. • Exploratory analyses showed no apparent relationship was detected between DAC exposure and the incidence of cutaneous AEs, ALT elevations, or infections.

Study Report #	**205MS302**
Title	A Multicenter, Single-Arm, Open-Label, Study to Evaluate the Immunogenicity and Pharmacokinetics of BIIB019, Daclizumab High Yield Process (DAC HYP), Prefilled Syringe Administered by Subcutaneous Injection in Subjects With Relapsing-Remitting Multiple Sclerosis
Investigator/ Center	Dr. Maciej Maciejowski, Prywatna Praktyka Lekarska, ul. W. Pola 9, 40-595 Katowice, Poland
Study Dates	November 10, 2011– February 03, 2014
Objectives	Primary: To assess the immunogenicity of DAC HYP 150 mg administered every 4 weeks by a SC injection using the prefilled syringe (PFS) in subjects with relapsing-remitting multiple sclerosis (RRMS). Secondary: • To characterize the PK of DAC HYP (using intensive PK data) following single and multiple doses of DAC HYP administered by the PFS in a subset of subjects with RRMS • To evaluate the effect of DAC HYP on the PK of probe drugs for cytochrome P450 (CYP) isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A) Additional: immunogenicity on exposure, PD response, explore the association of genetic (DNA) markers
Formulation	Treatment: DAC HYP: 150 mg/mL in PFS; Lot #: VVLC35 Midazolam: syrup formulation (2 mg/mL) Caffeine: 200-mg tablet or caplet Warfarin and vitamin K: each as 10-mg tablet Omeprazole: 40-mg capsule Dextromethorphan: syrup
Study Design	• A multicenter, single-arm, open-label study to assess the immunogenicity, PK, PD, and tolerability of DAC HYP when administered SC using a PFS in 100 DAC HYP-naïve subjects with RRMS. • In addition, 2 substudies (the Intensive PK substudy and Therapeutic Protein-Drug Interaction [TP-DI] substudy) were performed [both subject to this individual study review]. A minimum of N=25 were enrolled in PK substudy. If necessary to achieve the inclusion of ~20 subjects in the TP-DI substudy, up to 20 new subjects can be

	recruited.
	• Duration: including initial 24-week treatment period (150 mg, 6 injections, q4w) and a 20-week washout period. Eligible subjects (including subjects in TP-DI substudy) then can be enrolled in the 3-year extension phase.
	
	<u>Intensive PK substudy</u>:
	• N=26 enrolled in the Intensive PK substudy underwent serial DAC HYP PK sampling over the first and the last dosing intervals (on Day 1 [Week 0] and again on Day 141 [Week 20], the last dosing visit).
	• PK samples: pre-dose, 8, 24 (Day 2), 72 (Day 4), and 120 hours (Day 6), and 7, 10, 14, and 21 days post-injection on Weeks 0-3 and on Weeks 20-23.
	
	<u>TP-DI substudy</u>:
	N=20 enrolled in the TP-DI substudy. Serial PK sampling for DAC HYP and/or probe drugs for CYP isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A) were collected during 2 sequential treatment periods.
	• Period 1 (Week -1): the probe-drug cocktail [consisting of oral midazolam 5 mg (CYP3A), caffeine 200 mg (CYP1A2), S-warfarin 10 mg/vitamin K 10 mg (CYP2C9), omeprazole 40 mg (CYP2C19), and dextromethorphan 30 mg (CYP2D6)] was administered 7 days (fasted) before the first dose of DAC HYP in the 3-year extension phase.
	• Period 2 (Weeks 0, 4, 8, and 9): pretreatment with DAC HYP was administered at Weeks 0, 4, and 8. The probe-drug cocktail was administered 7 days after the third dose of DAC HYP.
	
	<u>PK and PD Assessments</u>:
	• PK: DAC HYP serum concentrations and PK parameters including Cmax, Tmax, AUCtau, Cmin, CL/F, Vd/F, t1/2 and Rac (Week 20/Week 0). Key PK parameters were estimated and reported for each dose level. PK analysis was conducted using a nonlinear mixed effects modeling population analysis approach.
	  • PK samples at pre-Cocktail dose, 0.5, 1, 2, 2, 4, 6, 8, 10, 24, 48, 72, and 96 hours post-Cocktail dosing.
	  • Urine PK samples: 12-hour urine samples for the measurement of dextromethorphan and dextrorphan
	  • Primary PK endpoints: AUCs for midazolam, caffeine, S-warfarin, and omeprazole, and 12-hour urine dextromethorphan to dextrorphan ratio.
	  • Log-transformed AUC and Cmax and urinary ratio were obtained using a mixed-effects model with fixed effect for treatment and random effect for subjects. Geometric least squares mean ratio

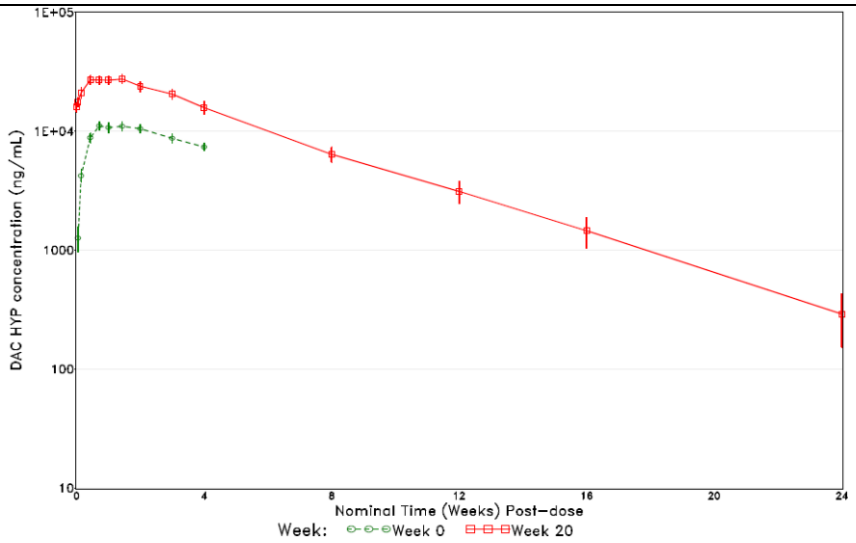
<table>
<tr><td></td><td>between treatment in Period 2 (drug cocktail + DAC HYP) and treatment in Period 1 (drug cocktail alone) was calculated along with corresponding 90% CI to evaluate the effect of DAC HYP on probe-drug PK,
• PD: lymphocyte subset analysis and phenotyping (CD56bright natural killer [NK] cells, Fox P3+ Regulatory T cells [Tregs], and CD25 expression and occupation).</td></tr>
<tr><td>Bioanalytical Methods</td><td>• DAC HYP: serum concentrations were determined using a validated enzyme linked immunosorbent assay (ELISA) (b) (4) with a quantitative range of 500 - 7500 ng/mL, with 500 ng/mL being the lower limit of quantification (LLOQ). [see Table A below]

Table A. Assay performance for DAC HYP
<table>
<tr><th>Analyte</th><td colspan="2">Daclizumab (serum)</td></tr>
<tr><th>Method:</th><td colspan="2">ELISA</td></tr>
<tr><th>Standard Curve:</th><td>Range:</td><td>500 - 7500 ng/mL</td></tr>
<tr><td></td><td>Precision:</td><td>3.9-6.6%</td></tr>
<tr><td></td><td>Accuracy:</td><td>98.7-102%</td></tr>
<tr><th>LLOQ:</th><td colspan="2">500 ng/mL</td></tr>
<tr><th>ULOQ:</th><td colspan="2">7500 ng/mL</td></tr>
<tr><th>LQC:</th><td colspan="2">750 ng/mL</td></tr>
<tr><td></td><td>Precision:</td><td>6.6%</td></tr>
<tr><td></td><td>Accuracy:</td><td>97.4%</td></tr>
<tr><th>MQC:</th><td colspan="2">2000 ng/mL</td></tr>
<tr><td></td><td>Precision:</td><td>8.7%</td></tr>
<tr><td></td><td>Accuracy:</td><td>99.4%</td></tr>
<tr><th>HQC:</th><td colspan="2">6000 ng/mL</td></tr>
<tr><td></td><td>Precision:</td><td>16.3%</td></tr>
<tr><td></td><td>Accuracy:</td><td>99.8%</td></tr>
</table>
• Assay performance was found acceptable.

• Probe-drug cocktail: Plasma samples were analyzed for midazolam, omeprazole, 5-hydroxyomeprazole, and S-warfarin using validated LC-MS/MS assays developed (b) (4) Urine samples were analyzed for dextromethorphan and dextrorphan using a validated LC-MS/MS assay developed (b) (4) [see Table B below]

Table B. Assay ranges, inter-assay precisions and accuracy/bias values
<table>
<tr><th>Analyte</th><th>Validated range</th><th>Inter-assay Precision</th><th>Accuracy/bias (%)</th></tr>
<tr><td>Midazolam</td><td>0.0500 - 50.0</td><td>4.2 ~ 11.9</td><td>-4.3 ~ 4.4</td></tr>
</table></td></tr>
</table>

	<table><tr><td>Omeprazole</td><td>0.500 – 1000</td><td>3.8 ~ 6.6</td><td>-6.5 ~ 0.6</td></tr><tr><td>5-</td><td>0.500 – 1000</td><td>3.6 ~ 24.5</td><td>-2.0 ~ 4.7</td></tr><tr><td>Caffeine</td><td>25.0 – 20000</td><td>3.4 ~ 8.6</td><td>-2.3 ~ -0.1</td></tr><tr><td>S-warfarin</td><td>5.00 – 1500</td><td>12.8 ~ 18.6</td><td>-2.7 ~ 2.6</td></tr><tr><td>Dextromethorpha</td><td>0.001 - 1.00</td><td>3.59 ~ 6.71</td><td>-12.5 ~ -6.84</td></tr><tr><td>Dextrorphan</td><td>0.0200 - 20.0</td><td>0.895 ~ 2.31</td><td>-5.88 ~ 2.89</td></tr></table> • Assay performance, including precision and accuracy of QC samples of each analyte, was found acceptable, • Serum IL-2: IL-2-Imperacer® assay was used to quantify IL-2 in human serum, with standard curve ranging 0.47~1000 pg/mL of IL-2.
Population/ Demographics	• N=133 subjects enrolled in the study, including 113 enrolled from the main study (N=26 in the Intensive PK study) and 20 newly enrolled from the TP-DI substudy. – Due to sampling and doing error, DAC HYP drug concentrations were available for NCA of Week 0 (Dose 1) from 25 subjects and Week 20 (Dose 6) from 24 subjects. • A total of 108 (96%) subjects completed the initial treatment period (Week 0 to Week 24) and 5 (4%) subjects discontinued (4 due to AEs and 1 due to consent withdrawn), with additional 3 withdrawn during the post-treatment period. • Subjects ranged 20-55 years of age (mean 36.5 years), predominantly White, with two-thirds (64%) being female. • Subjects in the Intensive PK substudy were similar to those of the safety population. Subjects ranged 24-54 years of age and the majority of the subjects were female (65%) and White (96%). • Subjects in the TP-DI substudy ranged 19-52 years of age (mean 36.0 years), predominantly female (65%) and White (80%).
PK and PD Results	Intensive PK substudy: The representative PK results from the Intensive PK substudy were presented in Figures 1~2 and Table 1 below. Figure 1. Mean ± SD Serum DAC HYP Concentration-Time Profiles Following Administration of DAC HYP 150 mg SC Every 4 Weeks Over 20 Weeks (n=25 for Week 0; n=24 for Week 20)

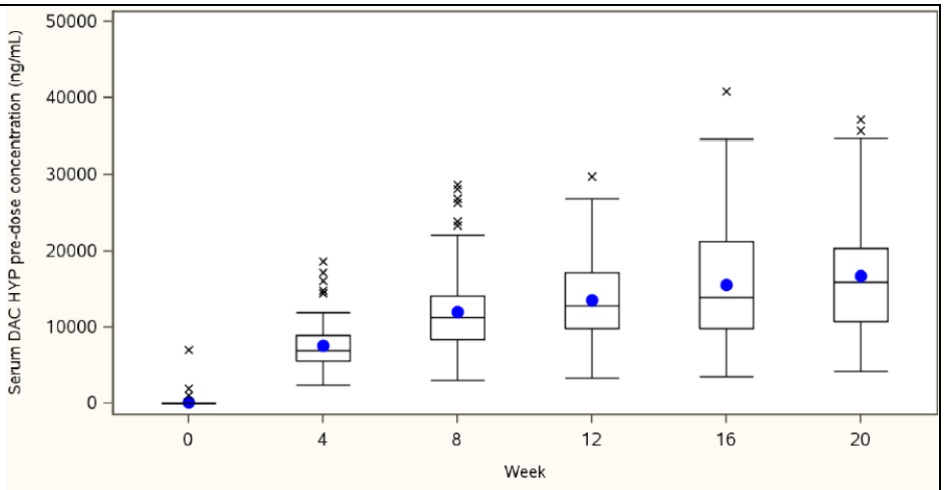


- For Dose 1 (Week 0) of DAC HYP 150 mg SC, q4w: Tmax ~7 days; Cmax ~12.63±4.64 µg/mL; AUCtau ~255.3±88.57 day·µg/mL

Table 1. Summary Statistics of Serum DAC HYP Pharmacokinetics at Steady State (Dose 6 at Week 20) Following Multiple Dosing of DAC HYP 150 mg SC Every 4 Weeks – 205MS302

	t1/2 (day)	Tmax (day)	Cmax (ug/mL)	Cmin (ug/mL)	CL/F (L/day)	V/F (L)	AUCtau (day*ug/mL)	Rac
n	24	24	24	24	24	24	24	23
Mean	21.92	6.41	29.07	14.93	0.27	8.21	638.10	2.55
SD	5.473	3.273	10.812	6.327	0.108	2.810	256.076	0.578
%CV	24.97	51.03	37.19	42.38	39.54	34.23	40.13	22.67
Geo. mean	21.29	5.71	27.14	13.75	0.25	7.79	591.05	2.48
Median	21.14	5.03	24.95	13.80	0.27	7.60	548.87	2.71
Minimum	13.5	3.0	13.2	6.8	0.1	4.6	305.4	1.3
Maximum	34.3	14.2	53.5	32.3	0.5	15.0	1286.5	3.5

Figure 2. Serum DAC HYP Predose Concentrations Following Administration of DAC HYP 150 mg SC Every 4 Weeks Over 20 Weeks (n=113, including subjects in the main study)



Note: The bottom of each box is the 25th percentile, the top is the 75th percentile, and the middle line in the box is the median. The whiskers extend to 1.5 times the interquartile range, or the maximum and minimum values if there are no outliers.

TP-DI substudy:

Table 2. Effect of DAC HYP 150 mg SC Every 4 Weeks on the CYP Probes Primary PK Parameter: - Results of the DAC HYP-Drug Interaction Study

		Geometric LS Mean			
Probe drug	Parameter (Unit)	Probe drug alone (n)	Probe drug with DAC HYP (n)	Ratio (a)	90% CI
Midazolam	AUCinf (ng*h/mL)	722.5 (20)	733.6 (19)	1.015	0.894, 1.153
S-Warfarin	AUCinf (ng*h/mL)	18545 (17)	18646 (18)	1.005	0.951, 1.063
Omeprazole	AUCinf (ng*h/mL)	1353.7 (18)	1348.5 (19)	0.996	0.880, 1.127
Caffeine	AUC0-12 (ng*h/mL) (b)	30799 (13)	31790 (12)	1.032	0.930, 1.145
Dextromethorphan	12-hr urine dextromethorphan to dextrorphan ratio	0.010 (20)	0.010 (20)	1.012	0.764, 1.342

(a) Test/reference = (probe drug + DAC HYP)/probe drug alone.
(b) Subjects with pre-dose caffeine concentration >5% of Cmax are excluded.

Safety

- No moderate, severe, related, or SAEs or discontinuations of study treatment or withdrawals from the study due to AEs were reported in either period.
- No AEs were reported for more than 1 subject, and none was considered to be DAC HYP-related.
- No ECG abnormality was reported to result in an AE in TP-DI substudy.

Conclusion

Pharmacokinetics:

PK in MS patients:

- DAC HYP 150 mg SC every 4 weeks using the PFS in subjects with RRMS showed slow absorption with median Tmax values of ~1 week, low systemic clearance, small volume of distribution, and a long elimination t1/2 of approximately 3 weeks with steady-state attained by Week 16 of dosing (4th dose).

	• Following multiple dosing of DAC HYP 150 mg SC every 4 weeks using the PFS, DAC HYP steady-state mean serum concentrations fell within 15 μg/mL and 29 μg/mL. • ADA responses appeared to have no effect on DAC HYP clearance. The impact of NAb responses on DAC HYP clearance in the Intensive PK substudy is inconclusive and will be further characterized in the planned population PK data analysis. <u>TP-DI</u>: • Multiple doses of DAC HYP 150 mg SC q4w in MS patients had no effect on the primary PK endpoint (exposure) for concomitant probe substrates midazolam (CYP3A), omeprazole (CYP2C19), S-warfarin (CYP2C9), and caffeine (CYP1A2), judging by the point estimates and the 90% CIs of the geometric mean ratio for probe substrate exposure being within the no-effect boundary of 0.80-1.25. • The geometric mean ratio for 12-hour urine dextromethorphan (CYP2D6) to dextrorphan ratio was close to 1; however, the 90% CI (0.76~1.34) extended slightly outside the no-effect boundary of 0.80-1.25, most likely a result of high intrasubject variability associated with urine collections and CYP2D6 activity. This observation is deemed not to have a significant clinical relevance on CYP2D6 activity. *Pharmacodynamics:* • PD responses were reported to be similar to those in other studies, with an increase in CD^{56}bright NK cell counts and a decrease in Tregs, and were not affected by immunogenicity. • IL-2 Concentrations remained similar over time (week43~52) in the range of 23.8~29.7 pg/mL.

4.2 Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1. SUMMARY OF FINDINGS

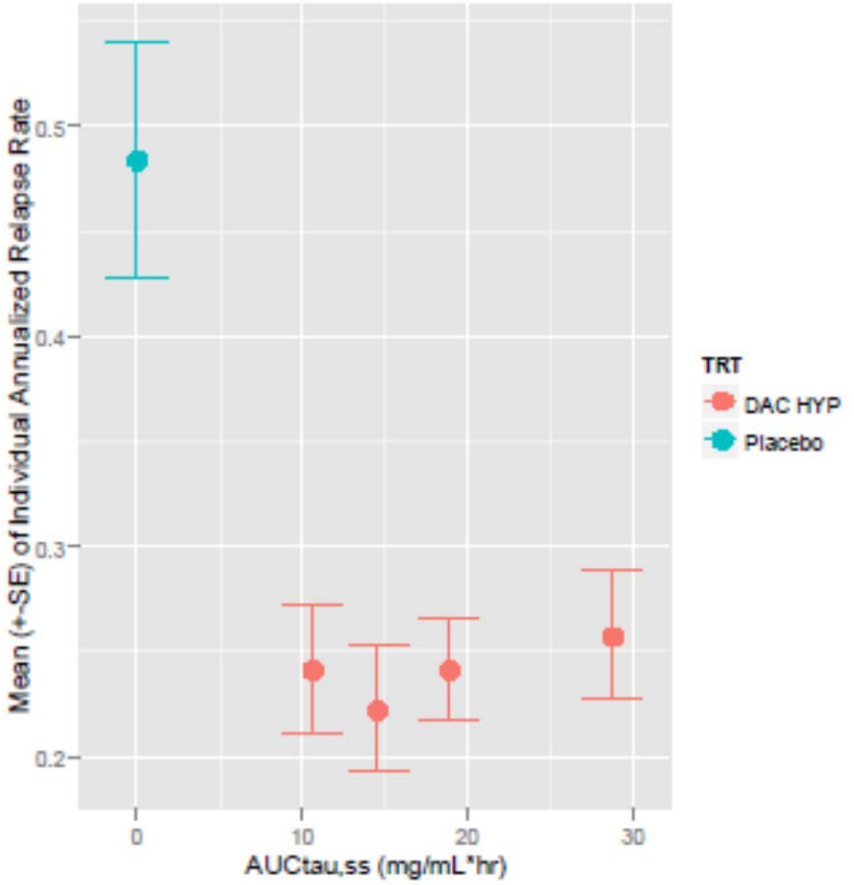
1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 What are the characteristics of the exposure-response (E-R) relationships for efficacy?

The E-R relationship for efficacy was evaluated in subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) from Phase 2 (205MS201[SELECT], 205MS202[SELECTION]) and Phase 3 (205MS301[DECIDE], 205MS302[OBSERVE]) studies. The results suggest a flat E-R relationship in the range of exposures associated with the 150 mg and 300 mg doses. Figure 1 shows that no correlation between DAC exposure and the annualized relapse rate (ARR) can be discerned, which is consistent with the dose-response relationship observed in study 205MS201 as shown in Table 1. In addition, a flat E-R relationship for the secondary efficacy endpoints including new or newly enlarging T2 lesion count and new Gd+ lesion count was observed in the range of exposures associated with the 150 mg and 300 mg doses (Figure 2, Figure 3). One possible explanation for such findings is that the exposures associated with both 150 mg and 300 mg every 4 weeks regimens are at the plateau of the E-R curve for ARR, new or newly enlarging T2 lesions and Gd-enhancing lesions.

Figure 7. Mean ARR by Placebo and DAC HYP AUCss subgroups



Source: study report CPP-14008-BIIB019 page 18

Table 1. Primary Efficacy Results in Study 205MS201

Study 205MS201			
	Placebo	150mg DAC HYP	300mg DAC HYP
n	196	201	203
ARR (95% CI)	0.458 (0.370, 0.566)	0.211 (0.155, 0.287)	0.230 (0.172, 0.308)
p-value		<0.0001	0.0002

Figure 8. Annualized New or Newly Enlarging T2 Lesion Count at Final Visit vs. DAC HYP AUCss Subgroups

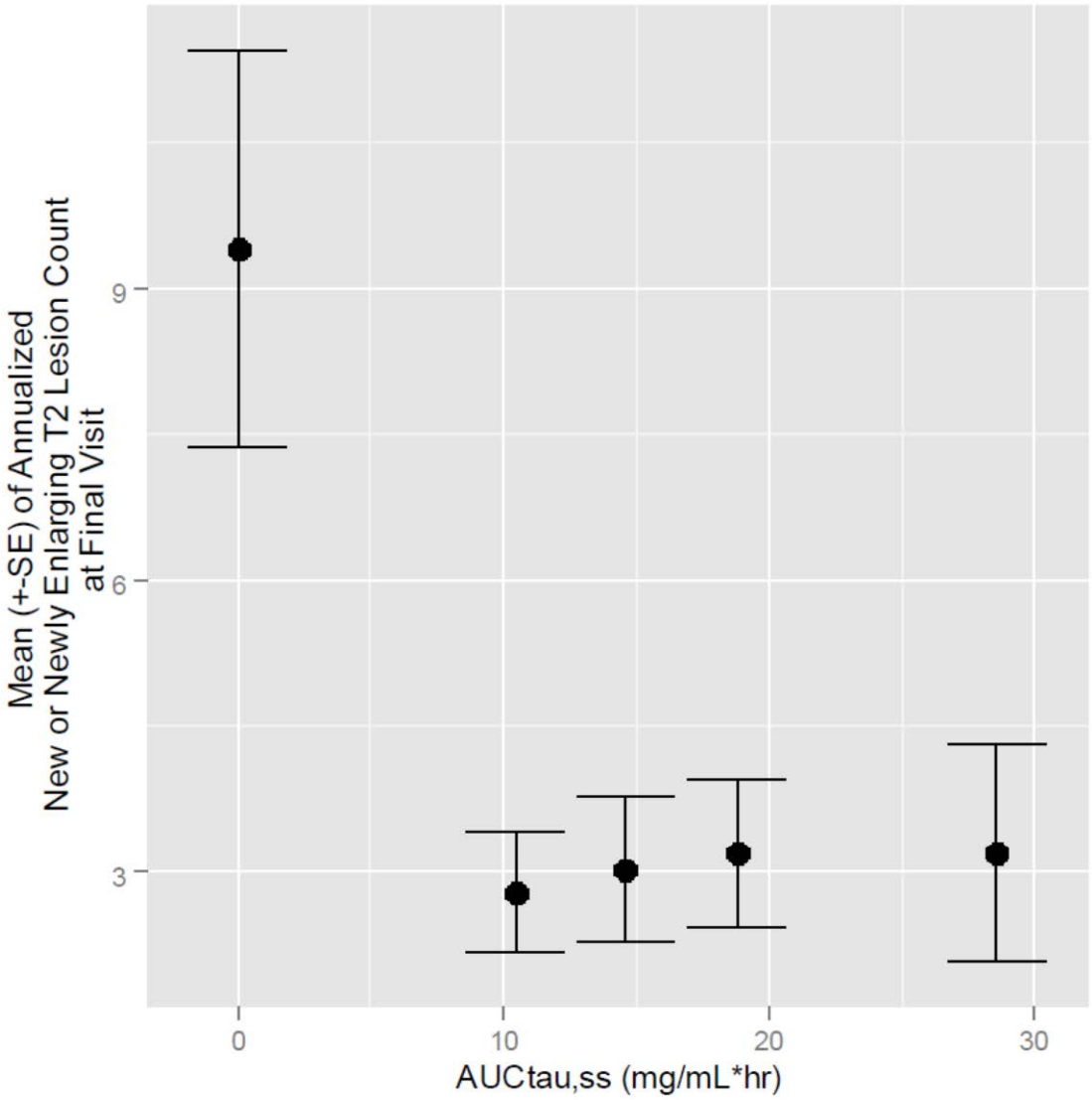


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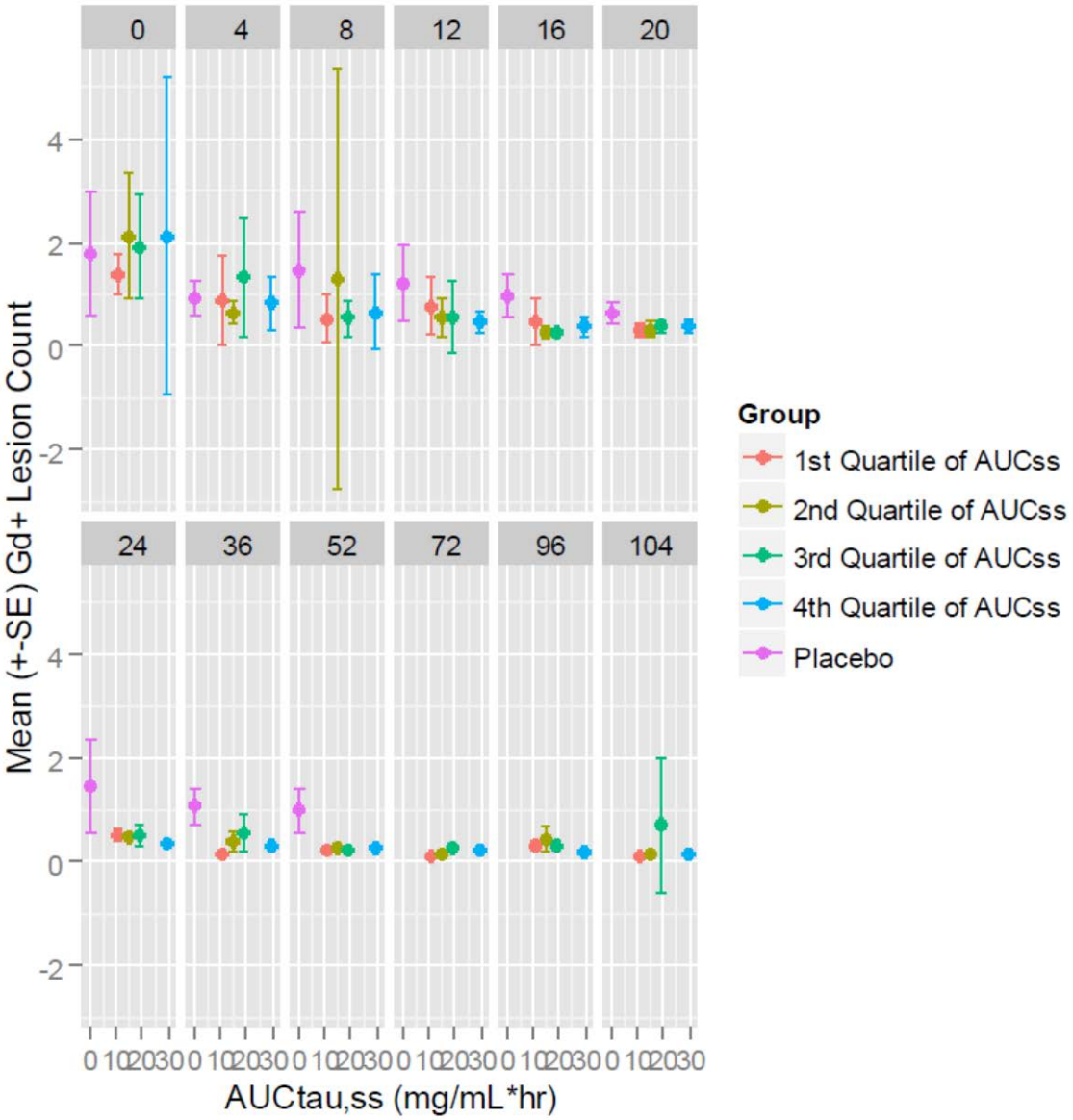
Figure 9. Mean Gd+ Lesion Count over Time by Week and DAC HYP AUCss Subgroups



Source: study report CPP-14008-BIIB019 page 22

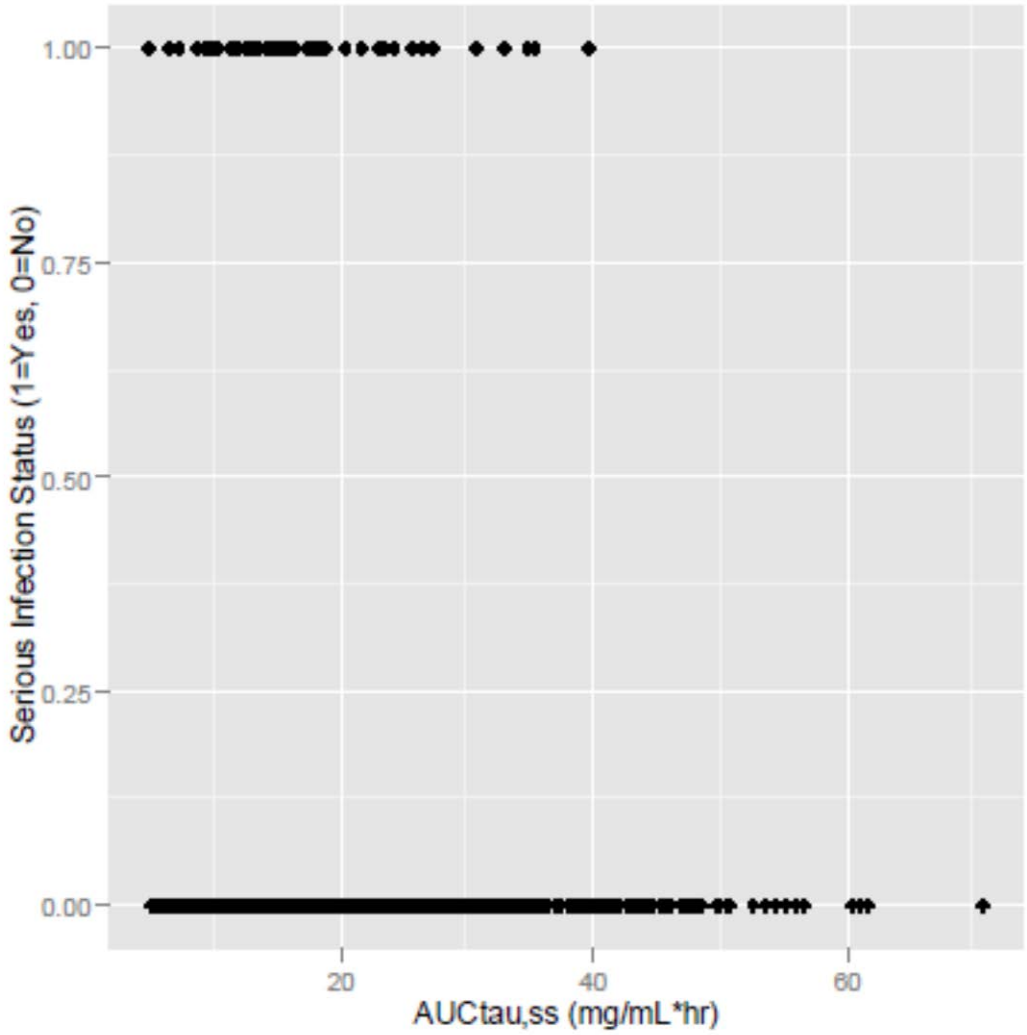
1.1.2 What are the characteristics of the exposure-response (E-R) relationships for safety?

The E-R relationship for several safety endpoints (Serious infection, moderate and severe cutaneous adverse events, and liver enzyme abnormalities) was evaluated in subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) from Phase 2 (205MS201[SELECT], 205MS202[SELECTION]) and Phase 3 (205MS301[DECIDE], 205MS302[OBSERVE]) studies. The results suggest that the risk of serious infection, cutaneous AE and liver enzymes (AST/ALT) elevation are unlikely directly related to the level of exposure of DAC HYP in the 150 mg and 300 mg dose range. The serious infection status (1 and 0

representing yes and no, respectively), the cutaneous AE status (1 and 0 representing with or without moderate or severe cutaneous adverse event), and liver enzyme abnormality status were plotted against DAC HYP AUCss in Figure 4, Figure 5, and Figure 6, respectively and no clear pattern was observed.

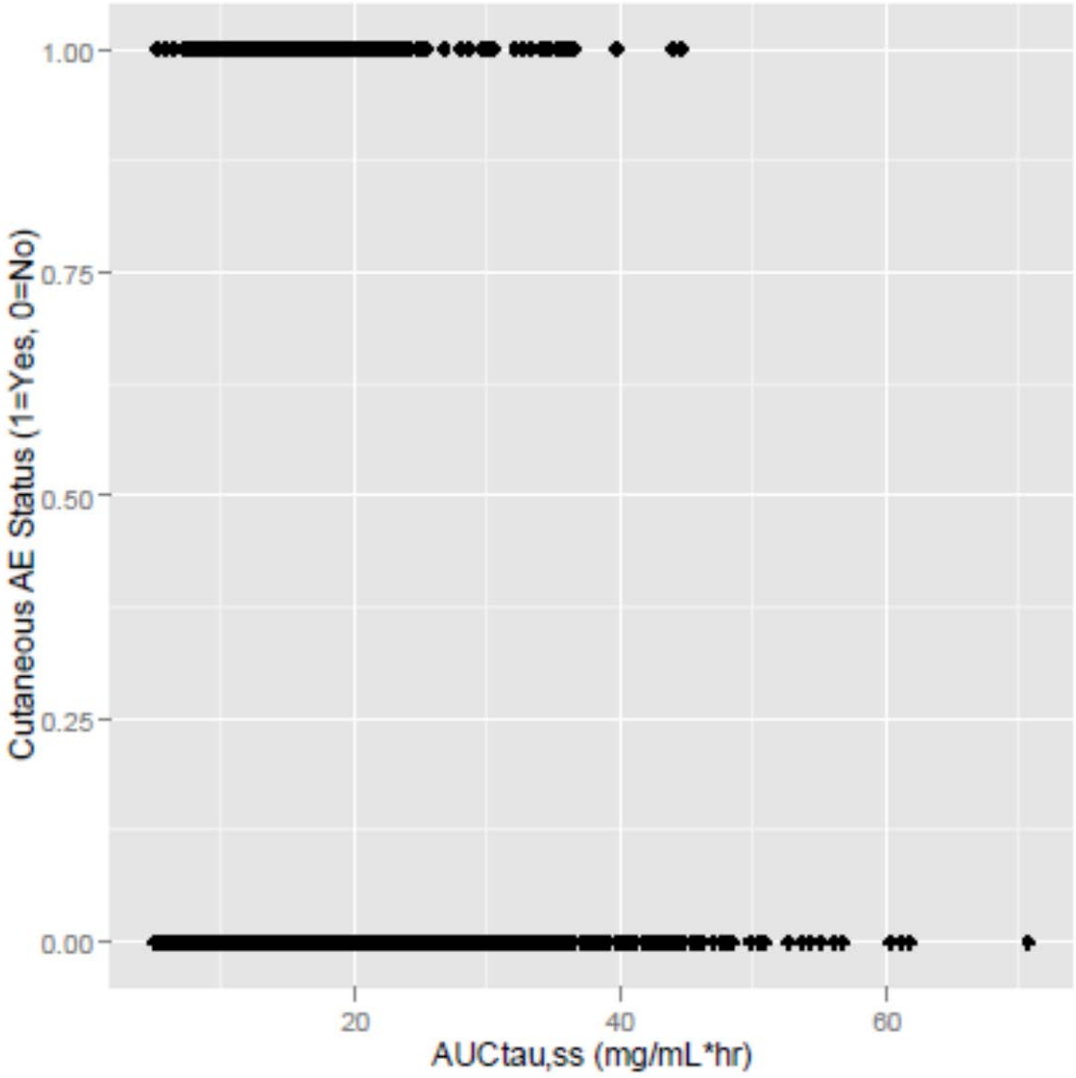
Autoimmune hepatitis, a life threatening AE, occurred in 3 subjects in the DAC HYP treatment groups (1 subject on 150 mg and 2 subjects on 300 mg) and 1 case resulted in death according to the sponsor's report. The relationship between DAC exposure and autoimmune hepatitis was not evaluated due to the limited number of cases in the whole clinical program. Therefore, whether the autoimmune hepatitis event is related to the DAC exposure levels cannot be concluded.

Figure 10. Serious Infection Status vs. DAC HYP AUCss



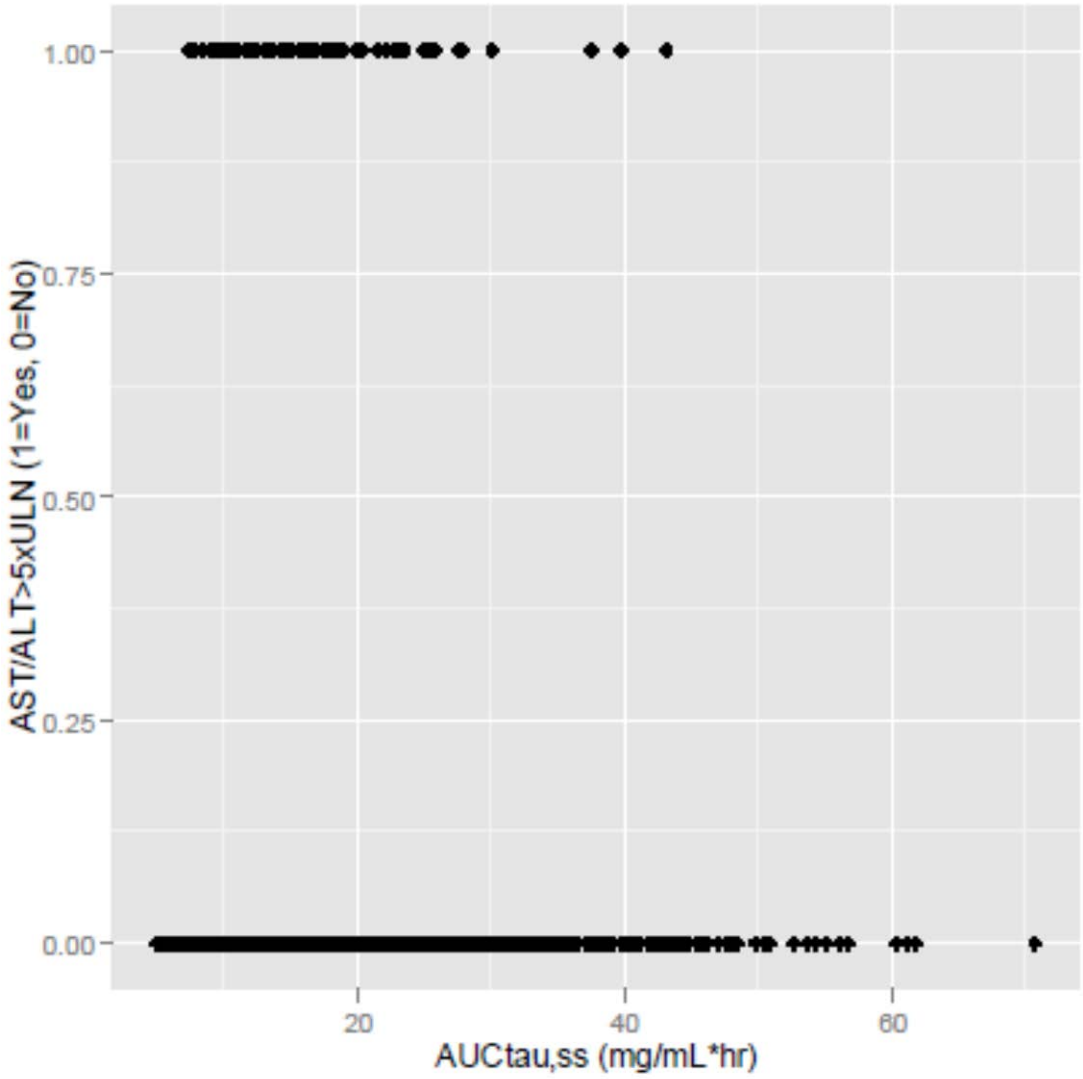
Source: study report CPP-14008-BIIB019 page 26

Figure 11. Cutaneous AE Status vs. DAC HYP AUCss



Source: study report CPP-14008-BIIB019 page 28

Figure 12. Liver Enzyme Abnormality Status vs. DAC HYP AUCss



Source: study report CPP-14008-BIIB019 page 32

1.1.3 Does the exposure-response (E-R) relationship for efficacy and safety support the proposed 150 mg once a month dose?

From the efficacy perspective, the proposed 150 mg once a month dose is supported by the exposure/dose-efficacy relationship. Results from study DAC-1012, which is a Phase 2, randomized, double-blind, placebo-controlled, proof-of-concept/dose-ranging study using the DAC Penzberg formulation, demonstrated that a dose of 2 mg/kg DAC Penzberg SC every 2 weeks (equivalent to 300 mg once a month DAC HYP dose) produced statistically significant reductions in new or enlarged Gd+ lesion counts, while a dose of 1 mg/kg DAC Penzberg SC every 2 weeks (equivalent to 75 mg once a month DAC HYP dose) did not result in statistically significant reductions in new or enlarged Gd+ lesion counts. Therefore, 150 mg and 300 mg monthly doses were selected for the subsequent clinical development. Results from study 205MS201 show that both 150 mg and 300 mg once a month doses demonstrated significantly improved efficacy comparing

to placebo and similar benefit was observed between 150 mg and 300 mg dose groups. This is consistent with the E-R analysis result, which shows a flat E-R relationship in the range of exposures associated with the 150 mg and 300 mg doses. The 150 mg once a month dose was further evaluated in the phase 3 study 205MS301 and showed superior efficacy comparing to the active control (Interferon β-1a 30 μg IM once weekly).

From the safety perspective, although E-R analyses show that the risk of serious infection, moderate or severe cutaneous AE and liver enzymes (AST/ALT) elevation are unlikely directly related to the level of exposure of DAC HYP in the 150 mg and 300 mg dose range, safety concerns, i.e. increased risk of fetal autoimmune hepatitis, do exist. Given the limited number of autoimmune hepatitis cases, no dose/exposure response relationship can be concluded. Whether lowering the dose would reduce the risk of autoimmune hepatitis (or other serious adverse reactions) remains a question. It might be possible that the risk of autoimmune hepatitis is lower at a dose level below 150 mg. However, there is no data to support this hypothesis in the current submission.

1.1.4 What are the characteristics of the relationship between PD markers, i.e. $CD56^{bright}$ NK cells and FoxP3+ regulatory T cells, and AEs of interest including drug induced liver injury (DILI), colitis, and lymphadenopathy?

No relationship between $CD56^{bright}$ NK cell counts and FoxP3+ regulatory T cell counts and the AEs of interest was identified based on the data from this submission. Exploratory analysis was conducted by the pharmacometric reviewer to evaluate he relationship between $CD56^{bright}$ NK cell counts and FoxP3+ regulatory T cell counts and the AEs of interest, i.e. DILI, colitis, and lymphadenopathy, using the list of patients with the AEs of interest provided by the safety reviewer. The time courses of the $CD56^{bright}$ NK cell counts and FoxP3+ regulatory T cell counts of subjects with and without the AEs of interest were visualized and compared. No consistent trend of changes in $CD56^{bright}$ NK cell counts and FoxP3+ regulatory T cell counts in subjects with the AEs of interest was observed. Figure 7 and Figure 8 show the time courses of $CD56^{bright}$ NK cell counts of subjects with and without DILI in Study 205MS301. Figure 9 and Figure 10 show the time courses of FoxP3+ regulatory T cell counts of subjects with and without DILI in study 205MS301. Similar patterns were observed in other studies for DILI and for colitis and lymphadenopathy. Therefore, the results from this analysis were inconclusive regarding the relationship between $CD56^{bright}$ NK cell counts and FoxP3+ regulatory T cell counts and the AEs of interest. The results should be interpreted with caution due to limitations of the analysis. First, the number of samples for the $CD56^{bright}$ NK cell counts and FoxP3+ regulatory T cell counts is limited and does not cover the whole study period in some subjects, especially in subjects with the AEs of interest. Second, the time when the AEs was diagnosed may not be accurate and there might be lags between the true time when the AEs happened and the diagnostic time (please refer to Dr. Lourdes Villalba's safety review for detailed information).

Figure 13. Time courses of $CD56^{bright}$ NK cell counts of subjects with and without DILI in Study 205MS301. (Blue lines represent $CD56^{bright}$ NK cell count profiles of subjects without DILI; red line represents the mean $CD56^{bright}$ NK cell count profile

of subjects without DILI; Black lines represent the CD56^{bright} NK cell count profiles of subjects with DILI.)

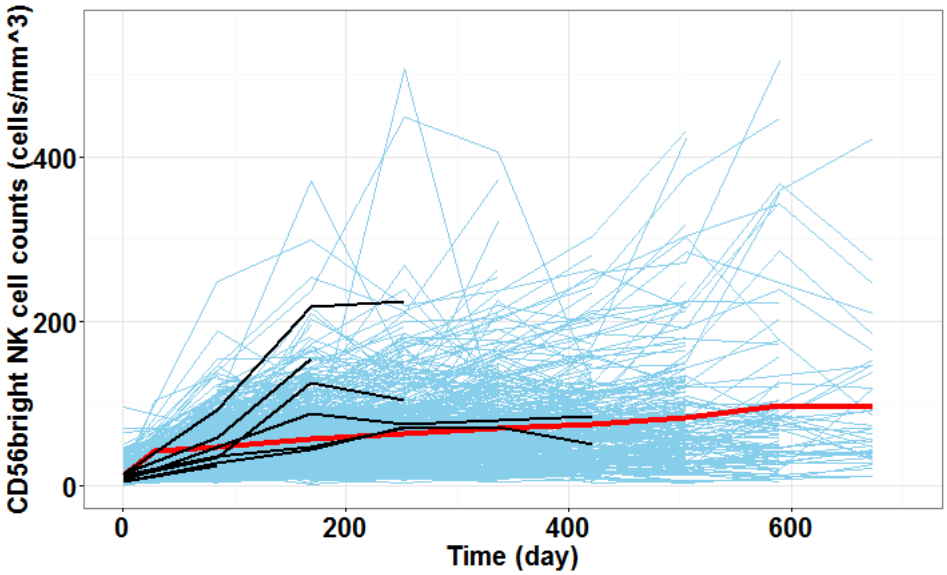


Figure 14. Individual plots of CD56^{bright} NK cell count profiles in subjects with DILI in Study 205MS301. (Blue lines or dots represent the individual CD56^{bright} NK cell count profile of subjects with DILI; Red line represents the mean CD56^{bright} NK cell count profile of normal subjects without DILI; Black vertical lines indicate the time when DILI was observed.)

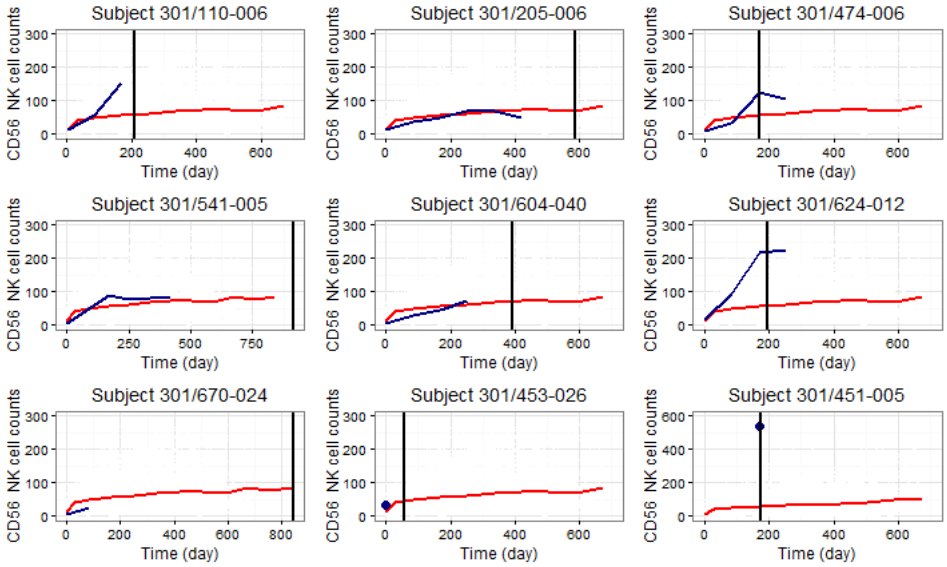


Figure 15. Time courses of FoxP3+ regulatory T cell counts of subjects with and without DILI in Study 205MS301. (Blue lines represent FoxP3+ regulatory T cell count profiles of subjects without DILI; red line represents the mean FoxP3+ regulatory T cell count profile of subjects without DILI; Black lines represent the FoxP3+ regulatory T cell count profiles of subjects with DILI.)

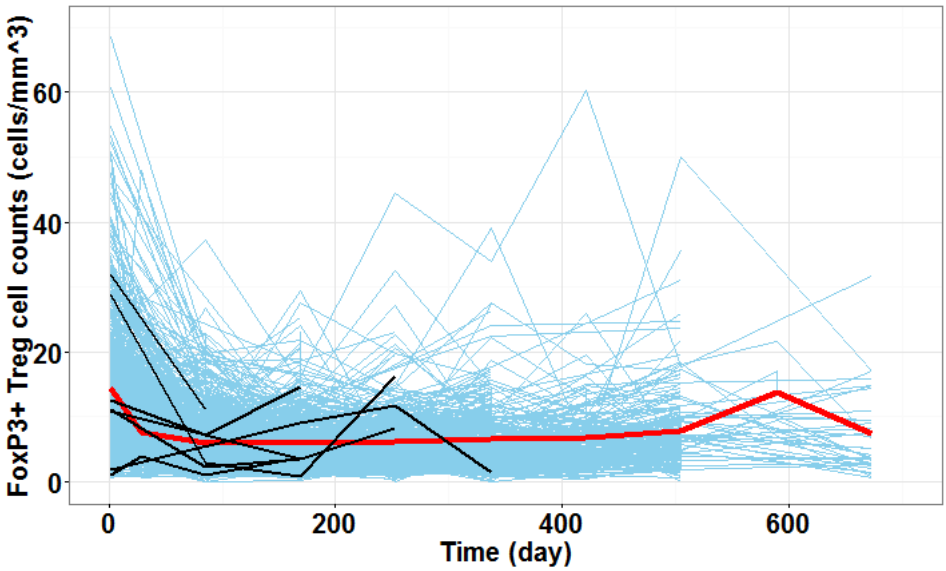
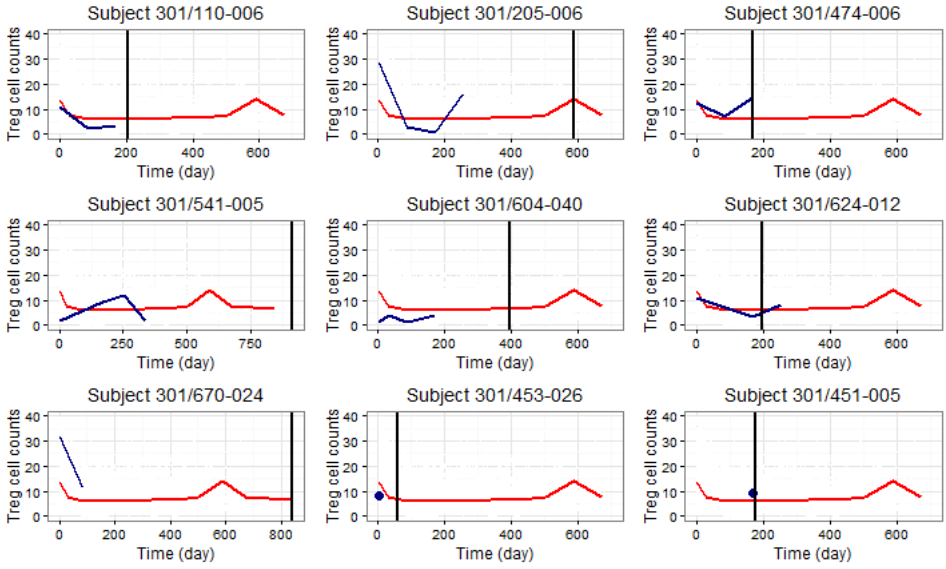


Figure 16. Individual plots of FoxP3+ regulatory T cell count profiles in subjects with DILI in Study 205MS301. (Blue lines or dots represent the individual FoxP3+ regulatory T cell count profile of subjects with DILI; Red line represents the mean FoxP3+ regulatory T cell count profile of normal subjects without DILI; Black vertical lines indicate the time when DILI was observed.)



1.2 Recommendations

If the proposed 150 mg once a month dose is determined to be acceptable, no dose adjustment would be necessary for intrinsic or extrinsic factors including body weight, sex and age.

A dose lower than 150 mg once a month might have a better benefit/risk profile, but E-R relationships in the current submission provide limited ability to extrapolate efficacy/safety at a lower dose. Therefore, both efficacy and safety for the hypothetical dose will need to be established, if a lower dose is considered.

1.3 Label Statements

No changes to the label are proposed.

2 PERTINENT REGULATORY BACKGROUND

Daclizumab is a humanized monoclonal antibody (mAb) of the human immunoglobulin G1 (IgG1) isotype that binds to CD25, the alpha subunit (interleukin [IL]-2Rα) of the human highaffinity IL-2 receptor (IL-2R), and modulates IL-2 signaling. Daclizumab (ZENAPAX) was approved by the FDA in 1997 for the prophylaxis of acute organ rejection in patients receiving renal transplants. DAC HYP is a form of the daclizumab antibody co-developed by AbbVie and Biogen Idec as a therapeutic agent for relapsing forms of MS, manufactured using a NS0 sub-strain transfected cell line (b) (4) (b) (4).

DAC HYP has been classified as a new molecular entity.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Summary of study report CPP-14-010-BIIB019

3.1.1 Population Pharmacokinetic Modeling

A population pharmacokinetic analysis of Daclizumab HYP (DAC HYP) was conducted using data in healthy volunteers and multiple sclerosis patients from Phase 1 to Phase 3 clinical trials.

3.1.2 Data

PK concentration-time data collected in three Phase 1 (DAC-1014, DAC-1015, DAC-1018), two Phase 2 [205MS201/202 (SELECT/SELECTION)] and two Phase 3 [205MS302 (OBSERVE), 205MS301 (DECIDE)] were used for the population pharmacokinetic analysis. Studies included in this population PK analysis are summarized in Table 1. Table 2 summarizes the PK sampling schedule for each study. The final population PK dataset includes 1670 subjects and 17139 post-dose DAC HYP concentrations. Post-dose BLQ samples accounted for approximately 9% of the total post-dose PK samples and were excluded from the modeling dataset.

Table 2. Studies Included in the Population PK Analysis

Study	Phase	Population	Number	Treatment Regimen
DAC-1014	1	HV	32	SC, multi-dose q2wk x 9 200 mg (n = 12); 200 mg loading dose + 100 mg q2wk x 8 (n = 12); Placebo (n = 8)
DAC-1015	1	HV	34	SC, single dose 50 mg (n = 7); 150 mg (n = 8); 300 mg (n = 8) Placebo (n = 10)
DAC-1018	1	HV	31	IV, single dose 200 mg (n = 12); 400 mg (n = 12); Placebo (n = 7)
205MS201 (SELECT)	2	MS patients	621	SC, multi-dose 150 mg q4wk x 13 (n = 208); 300 mg q4 wk x 13 (n = 209); Placebo (n = 204)
205MS202 (SELECTION)[1]	2	MS patients	517	SC, multi-dose 150 mg q4wk x 13 (n = 172); 300 mg q4wk x 13 (n = 171) Placebo q4wk x 5, then 150 (n = 86) or 300 mg (n = 88) q4wk x 8
205MS302 (OBSERVE)	3	MS patients	113	SC, multi-dose 150 mg q4wk up to 188 wks
205MS301[2] (DECIDE)	3	MS patients	919	SC, multi-dose 150 mg q4wk for 96 to 144 wks

[1] SELECTION is the extension of SELECT.
[2] Phase 3 DECIDE data were not included during base and covariate model development.

Source: popPK report CPP-14-010-BIIB019 page 12

Table 3. PK sampling schedule

Study	PK sampling schedule
1014 (multi-SC)	Days 0 (pre-dose and 4h), 1, 3, 7, 10, 14 (pre-dose), 28 (pre-dose), 42 (pre-dose), 47, 56 (pre-dose), 112 (pre-dose and 2h; last dose), 115, 119, 126, 140, 168, 196 and 252.
1015 (single SC)	predose, 4 h, Day 1, 3, 7, 10, 14, 28, 42, 56, 70, 84, and 126.
1018 (single IV)	predose, 30 min, 2h, 4h, Day 1, 3, 7, 14, 28, 56, 70, 84, and 126 or early termination.
205MS302 (OBSERVE)	Intensive PK subgroup: predose, 8h, 24h, 72h, 120h, Day 7, 10 , 14 , 21, and postdose at Week 20 Non-intensive PK subgroup: Week 0, 2, 4, 8, 12, 16, 20, 24, (28, 32, 36, 44, 188)[1]
205MS201 (SELECT)	Week 0, 4, 8, 16, 24, 32, 40, 48, (52, 56, 64, 72)[2]
205MS202 (SELECTION)	Week 0, 4, 8, 12, 16, 20, 24, 32, 40, 52, (72)[3]
205MS301 (DECIDE)	Week 0, 4, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 164

[1] Follow-up visits
[2] Patients who don't roll-over to 205MS202, follow-up period
[3] Patients who don't roll-over to 205MS203 (Selection extension), follow-up period

Source: popPK report CPP-14-010-BIIB019 page 14

3.1.3 Structural Model

A two-compartment model with first-order absorption and elimination, IIV on CL, V2, and Ka best described the PK of DAC HYP in both healthy volunteers and MS patients. Ka was constrained to be larger than the terminal elimination constant Ke for all the

individuals to avoid the flip-flop, which significantly improved model fit. In addition, inclusion of absorption lag time further improved the model fit.

3.1.4 Covariate Model

Intrinsic and extrinsic factors evaluated in the current analysis include body weight, age, race, sex, dose group, Neutralizing antibody (NAb), Non-neutralizing antibody (NNAb), baseline percentages of $CD4_+$ T cells staining positive for CD25 as well as baseline absolute $CD25_+CD4_+$ T cell counts. Based on exploratory graphical analysis, i.e. ETA-covariate plots for the base model, effects of body weight, NAb and NNAb, baseline percentage of CD25+CD4+ T cells and baseline absolute CD25+CD4+ T cell counts, sex, and 50 mg dose group on CL, body weight and 50 mg dose group on V2, body weight, sex and 50 mg dose group on Ka, and 50 mg dose group on F were selected for further covariate analysis. After a full stepwise forward addition ($P \leq 0.005$) and backward elimination ($P \leq 0.001$) procedure, body weight as covariate on CL and V2, time-varying NAb status as covariates on CL, dose level (50 mg versus higher doses) as covariate on F were included in the final model.

3.1.5 Final Model Results

Parameter estimation results of the final model as well as the bootstrap results were provided in Table 4. Goodness-of-fit plots are shown in Figure 11.

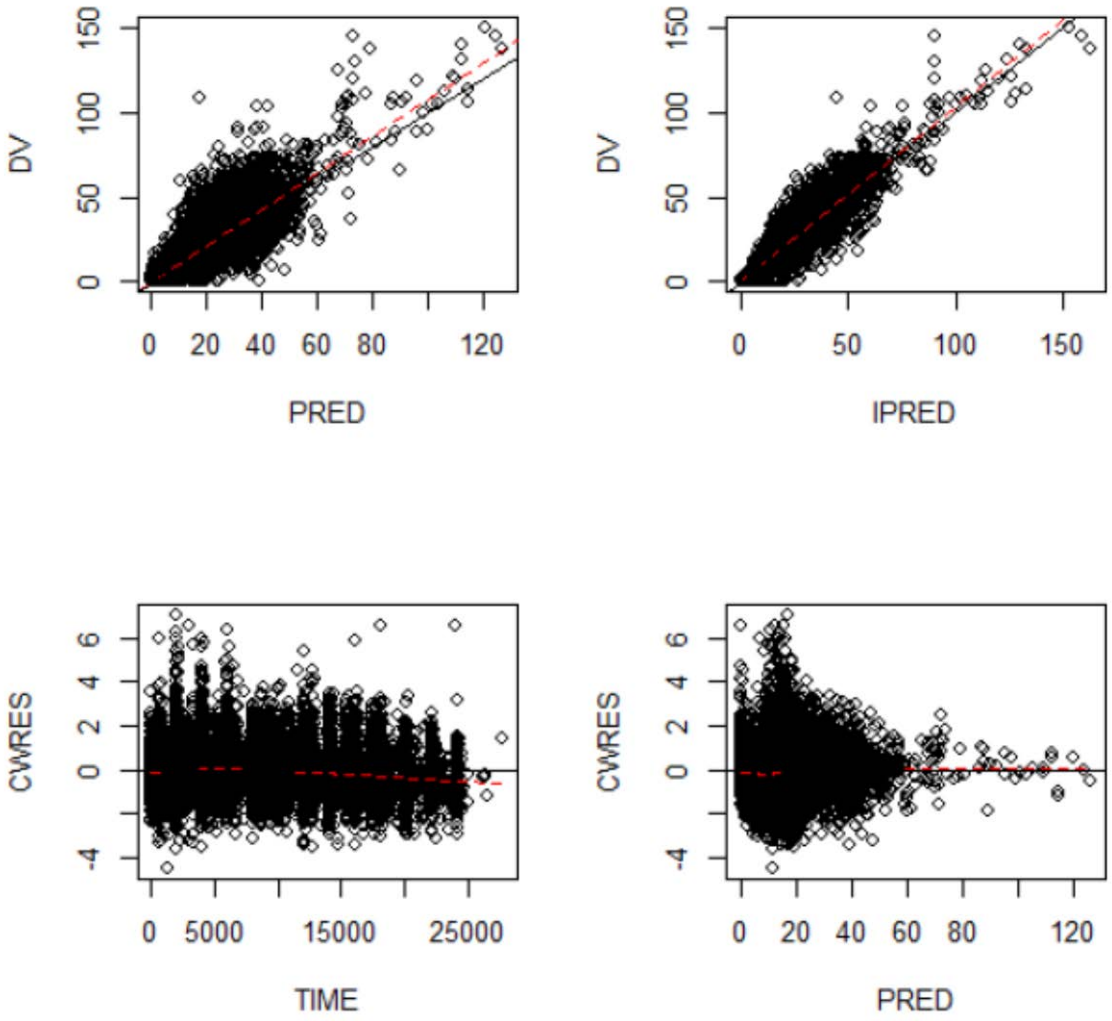
Table 4. Summary of the final model

Parameter	Final Model with Inclusion of Phase 3 DECIDE (Full-40F6DECIDE)	Bootstrap (N=772) Median (2.5^{th}, 97.5^{th})
CL (L/day) IIV (%)	0.212 27.2	0.211 (0.196, 0.222) 26.9 (24.7, 29.6)
V2 (L) IIV (%)	3.92 50.9	3.86 (3.31, 4.36) 51.0 (42.8, 60.7)
Q (L/day)	0.977	0.977 (0.802, 1.17)
V3 (L)	2.42	2.44 (2.12, 2.74)
THETA5 (/day) IIV (%)	0.107 94.4	0.109 (0.077, 0.162) 91.2 (61.6, 114)
Ka (/day)[1]	0.139	
F (bioavailability)	0.55 (50 mg) 0.88 (100 – 300 mg)	0.56 (0.42, 0.67) 0.88 (0.82, 0.93)
Absorption lag time (h)	1.61	1.63 (0.91, 2.11)
WT exponent on CL	0.87	0.87 (0.80, 0.95)
Additive ratio of CL for NAb positive records	0.19	0.19 (0.12, 0.28)
WT exponent on V2	1.12	1.13 (0.93, 1.35)
Residual Error (Proportional), %	25.5 (SC) 12.6 (IV)	25.5 (24.9. 26.2) 12.3 (9.49, 15.3)
Residual Error (Additive), mg/L	0.562 (SC) 0.291 (IV)	0.562 (0.464, 0.673) 0.297 (0.173, 0.449)

[1] Ka = Ke + THETA (5)

Source: popPK report CPP-14-010-BIIB019 page 31

Figure 11. Goodness-of-fit plot for the final model

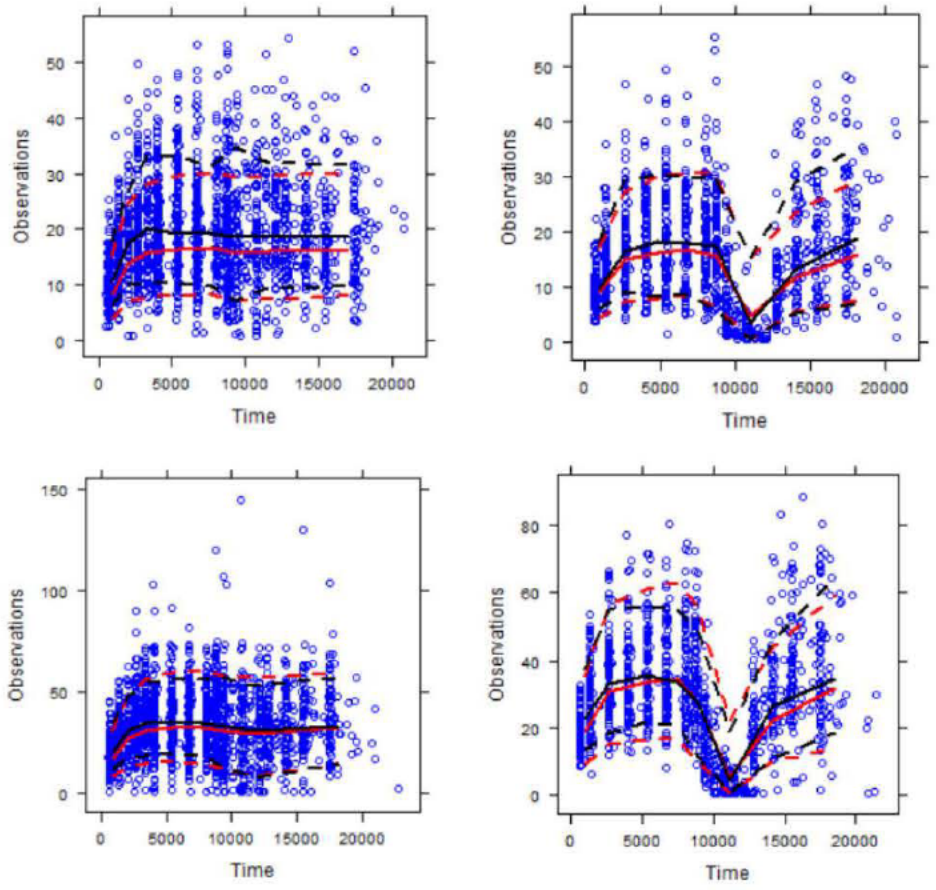


Source: popPK report CPP-14-010-BIIB019 page 32

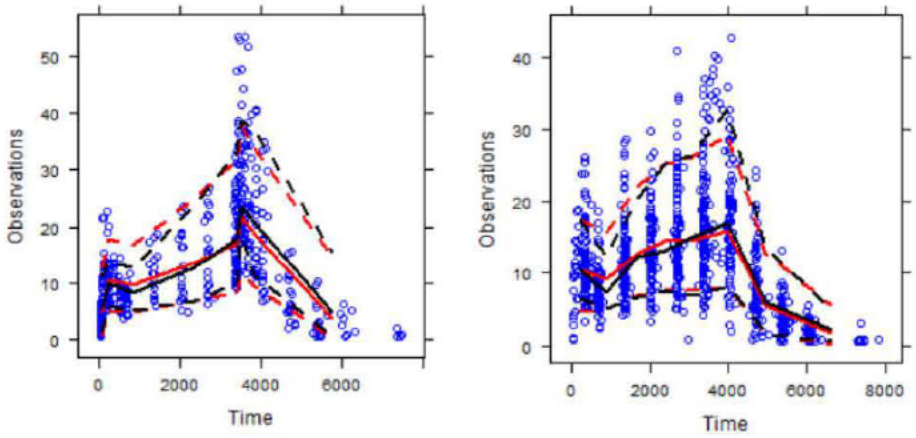
VPC results stratified by study, dose group and the presence or absence of washout in SELECTION are presented in Figure 12 and Figure 13.

Figure 12. VPC for the final model

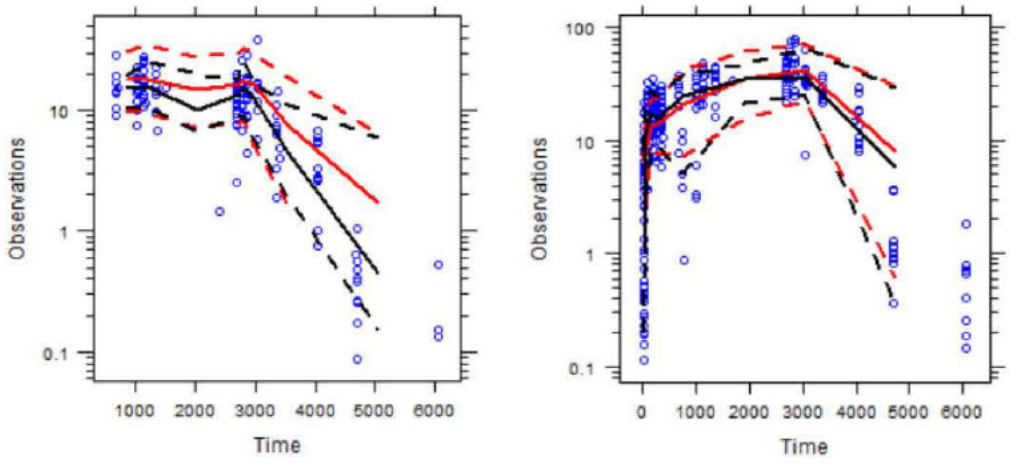
A. SELECT/SELECTION (Upper left: 150 mg no washout; Upper right: 150 mg washout; Lower left: 300 mg no washout; Lower right: 300 mg washout)



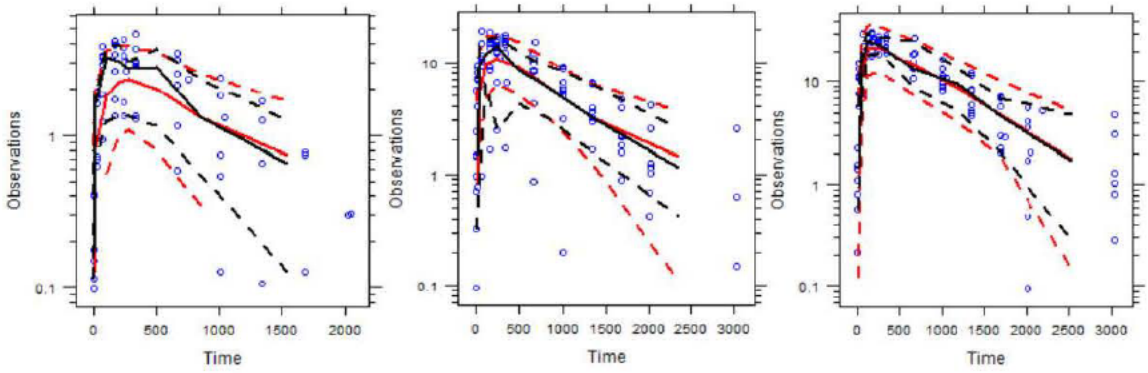
B. OBSERVE (Left: intensive; Right: non-intensive)



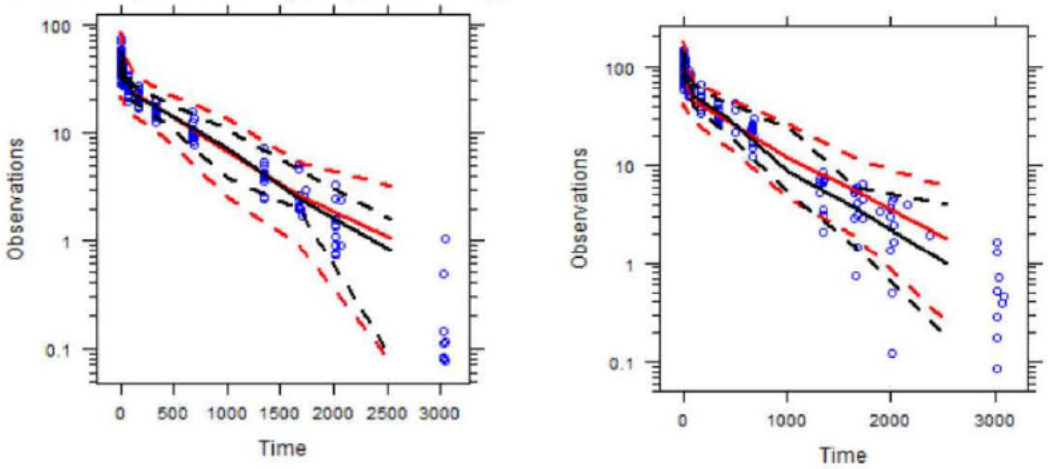
C. 1014 (Left: 100 mg; Right: 200 mg)



D. 1015 (Left: 50 mg; Middle: 150 mg; Right: 300 mg)

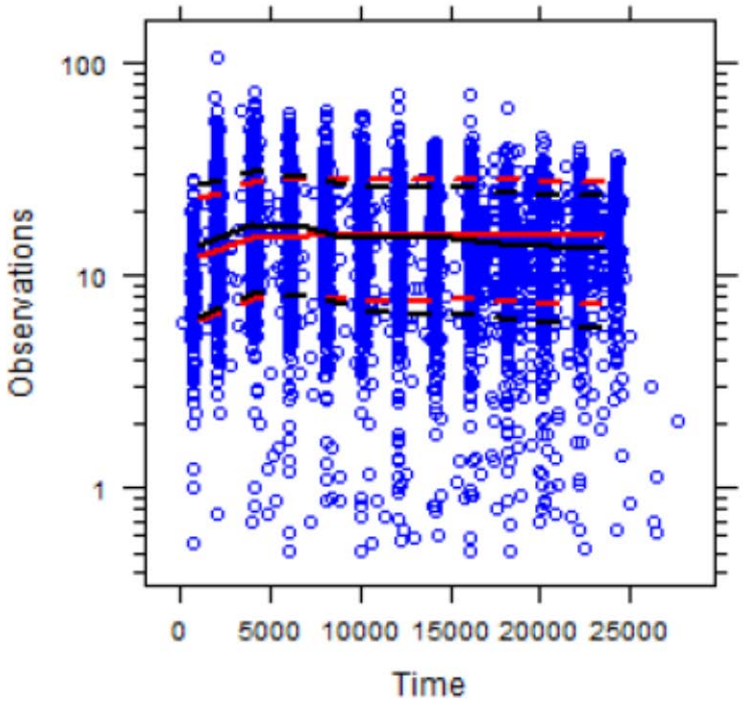


E. 1018 (Left: 200 mg; Right: 400 mg)



Source: popPK report CPP-14-010-BIIB019 page 27-28

Figure 13. VPC for the Phase 3 DECIDE



Source: popPK report CPP-14-010-BIIB019 page 29

Reviewer's comments: A population PK analysis for DAC HYP was conducted to characterize DAC HYP PK from 1670 healthy volunteers and MS subjects using 17139 post-dose DAC HYP concentrations from three Phase 1, two Phase 2 and two Phase 3 clinical trials. A two-compartment model with first-order absorption and elimination described DAC HYP PK well in both healthy volunteers and MS patients. Goodness-of-fit plots and VPC were used for model evaluation and results suggest reasonable model fit and predictability of the final model. Bootstrap analysis results show that model parameter estimates are similar to the bootstrap estimates, suggesting that the final model is reasonably stable.

Statistically significant covariates for DAC HYP PK identified include body weight and neutralizing antibody. Time-varying neutralizing antibody positive status increased the DAC HYP CL by an average of 19%. Body weight was a significant covariate on CL and V2 with exponents of 0.87 and 1.12, respectively. The IIV of CL decreased from 34.6% in the base model to 27.2% in the final model. Subgroup analysis was conducted for both efficacy and safety in the Phase 3 study DECIDE and results show that no meaningful differences in clinical efficacy (ARR of 0.192, 0.25, 0.191, and 0.206 in the 4 weight quartiles, respectively) or safety (AE incidence of 90%, 88%, 91%, 95% in the 4 weight quartiles, respectively) were observed among the subgroups of MS patients by weight quartile. Therefore, the proposed flat dosing regimen (150 mg once a month), rather than weight based dosing, is reasonable.

In addition, more than dose proportionality was observed from 50 mg to 100 mg, which is consistent with NCA analysis result from a phase 1, randomized, double-blind, placebo-controlled, single-dose, dose-escalation study of SC DAC HYP in healthy volunteers (DAC-1015). Results from study DAC-1015 show that CL/F and V/F are similar in the 150 mg dose group(11 mL/hr and 8826 mL) and the 300 mg dose group(11.2 mL/hr and 9026 mL), but lower than those in 50 mg dose group (19.7 mL/hr and 13393 mL). During the process of popPK model development, inclusion of dose level as a covariate (50 mg versus higher doses) was found to be a significant covariate on either CL or F. Inclusion of dose as a covariate on F resulted in a slightly bigger drop of OFV compared with inclusion of dose as a covariate on CL. So the sponsor included dose as a covariate on F. Given a very limited number of subjects on the 50 mg dose (7 out of 1670 subjects in the final popPK dataset), it would not make any significant difference to the overall model fitting by including dose as a covariate on either CL or F.

3.1 Summary of study report CPP-14-008-BIIB019

3.2.1 PK-PD analysis

A PK-PD (E-R) analysis was performed to quantify the relationship between DAC HYP exposure and several clinical efficacy/safety endpoints, including annualized relapse rate (ARR), new or newly enlarging T2 hyperintense lesion counts, new Gadolinium-enhancing lesion counts, serious infection, moderate and severe cutaneous adverse events, and liver enzyme abnormalities, from Phase 2 and 3 Studies.

3.2.2 Data

Data from two Phase 2 (205MS201, 205MS202) and two Phase 3 (205MS301, 205MS302) studies were included in the analysis. The study descriptions are presented below.

Study 205MS201 (SELECT) was a phase II, multicenter, double-blind, placebo-controlled, dose-ranging study to determine the safety and efficacy of DAC HYP as a monotherapy treatment in subjects in RRMS. In this study, a total of 621 subjects were randomized in a 1:1:1 ratio to receive 1 of the following treatments:

- Group 1: placebo SC injections every 4 weeks for a total of 13 doses
- Group 2: DAC HYP 150 mg SC injections every 4 weeks for a total of 13 doses
- Group 3: DAC HYP 300 mg 3 SC injections every 4 weeks for a total of 13 doses

Study 205MS202 (SELECTION) was a phase II, double-blind, multicenter, extension study to evaluate the safety and efficacy of DAC HYP in subjects with multiple sclerosis who have completed treatment in study 205MS201. The Week 52 visit from Study 205MS201 served as the baseline visit for this study. A total of 517 subjects were randomized in this study. The study included a 52-week treatment period. Subjects who did not consent to rolling over to Study 205MS203 remained in follow-up until Week 72. Treatment groups were determined by their original treatment allocation during Study 205MS201. Subjects previously randomized to placebo in study 205MS201 were randomized in a 1:1 ratio to either DAC HYP 150 mg SC every 4 weeks for a total of 13

doses, or DAC HYP 300 mg SC every 4 weeks for a total of 13 doses. Subjects previously randomized to DAC HYP 150 mg SC every 4 weeks in study 205MS201 were randomized in a 1:1 ratio to either placebo SC every 4 weeks for a total of 5 doses followed by DAC HYP 150 mg SC every 4 weeks for a total of 8 doses, or continued DAC HYP 150 mg SC every 4 weeks for a total of 13 doses. Subjects previously randomized to DAC HYP 300 mg SC every 4 weeks in study 205MS201 were randomized in a 1:1 ratio to either placebo SC every 4 weeks for a total of 5 doses followed by DAC HYP 300 mg SC every 4 weeks for a total of 8 doses, or continued DAC HYP 300 mg SC every 4 weeks for a total of 13 doses.

Study 205MS301 (DECIDE) was a phase III, multicenter, double-blind, randomized, parallel-group, monotherapy, active-control study to determine the efficacy and safety of DAC HYP versus Avonex in patients with RRMS. In this study, approximately 1800 patients were randomized in a 1:1 ratio to receive either DAC HYP 150 mg SC once every 4 weeks plus Avonex placebo IM once weekly for 96 to 144 weeks, or Avonex IM injection 30 mcg once weekly plus DAC HYP placebo SC once every 4 weeks for 96 to 144 weeks.

Study 205MS302 (OBSERVE) was a multicenter, single-arm, open-label, study to evaluate the immunogenicity and pharmacokinetics of DAC HYP, prefilled syringe administered by subcutaneous injection in subjects with RRMS. All subjects received DAC HYP 150 mg SC injections using the PFS at the clinic every 4 weeks over an initial 24-week treatment period (for a total of 6 injections), followed by a 20-week washout period.

3.2.3 Methods

Most subjects in these studies had only trough concentrations being measured, and these data do not support estimation of Cmax as this parameter would require reliable estimate of absorption rate, volume of distribution for both central compartment and peripheral compartment at individual level. However, individual Empirical Bayesian Estimate (EBE) of apparent clearance can be reliably obtained. Based on these considerations, the AUCss for one dosing interval (4 weeks) was selected as the predictor to evaluate the relationship between PK exposure and efficacy/safety endpoints.

Since OBSERVE study was not intended for efficacy evaluation, no efficacy endpoints (relapse, Gadolinium-enhancing lesion or T2 lesion) from this study was included in the analysis.

For the efficacy endpoints, a negative binomial model was used to fit the relapse count, the T2 count data and the Gd-enhancing lesion count data. An Emax function was used to describe the relationship between mean parameter of the negative binomial model and steady state AUC.

For the safety endpoint, a logistic regression model was used to evaluate the relationship between serious infection, cutaneous adverse event and liver enzyme elevations and steady state AUC.

3.2.4 Results

Annualized Relapse Rate
The individual AUCss were divided into quartiles. The mean ARR was plotted against the median AUCss in each quartile along with the placebo group as shown in Figure 2, which demonstrates that the mean ARR is highest in the placebo group, but very similar across subgroups of different median AUCss levels. Two models, where the number of relapse per individual was assumed to follow a negative binomial distribution, were also fit to the data. The first model assumed the mean of the negative binomial distribution is an Emax function of AUCss and proportional to duration of exposure. This model was fit to data from both placebo and active treatment groups. The result shows that a reliable estimate for EC50 could not be obtained. The second model assuming a log linear relationship was fit to data on active treatment only, the estimated slope of AUCss (in the unit of mg/mL*hr) was 0.0044 with a p-value of 0.4862, indicating the slope was not significantly different from zero.

New or Newly Enlarging T2 Lesion Count
Mean annualized new or newly enlarging T2 lesion count at final MRI scan was plotted against median AUC in each subgroup of AUCss and the result shows that while all the subgroups on active treatment had lower annualized count than the placebo group, there was no clear difference among AUCss subgroups (Figure 2).

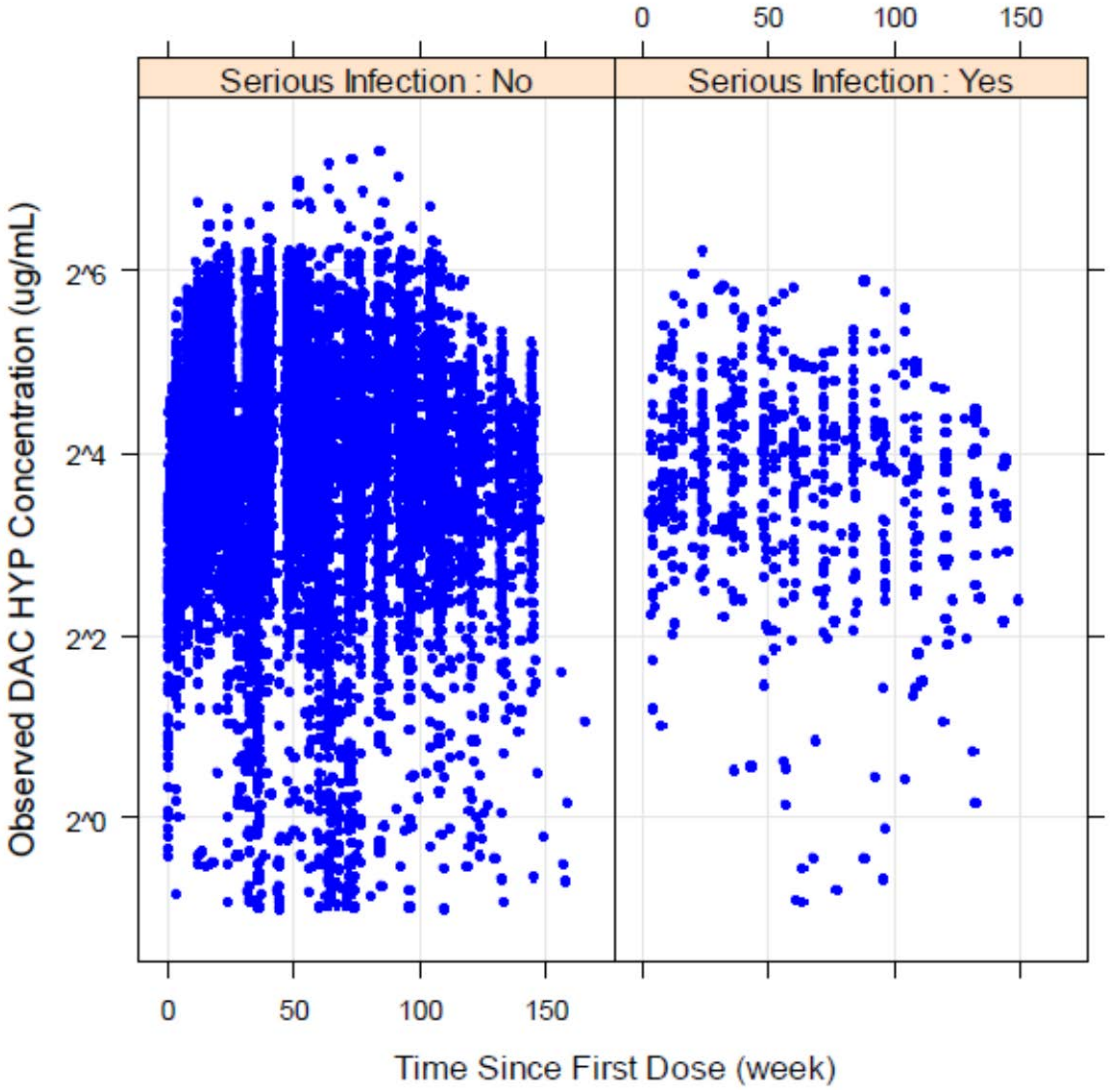
New Gadolinium-enhancing Lesion Count
The mean Gd-enhancing lesion count was plotted against AUCss subgroup over time in Figure 3. While placebo group had significantly higher mean lesion count over time compared to active treatment groups, no significant difference can be identified among the subgroups with different AUCss levels. Several models assuming different relationships between Gd-enhancing lesion count and AUCss were tested, including Emax and Sigmoid Emax models. While all models indicated the AUCss has a significant effect on the reduction of Gd-enhancing lesion count over time, the EC50 in the Emax model cannot be reliably estimated and there was no clear difference among AUCss subgroups at each visit.

Serious Infection
A total of 21 subjects experienced serious infections while on the 205MS201 and 205MS202 study, 14 of them received DAC HYP 150 mg (5%), and 7 received DAC HYP 300 mg (2.5%). There were 40 (4%) subjects in the DAC HYP 150 mg every 4 weeks group experienced serious infection in the 205MS301 study. Only 1 out of 113 (0.9%) in the OBSERVE study experienced serious infection. The observed DAC HYP concentrations over time were plotted by whether a subject experienced serious infection during the study (Figure 14). No clear pattern can be observed from this graph. The serious infection status (1 and 0 representing yes and no, respectively) was plotted against DAC HYP AUCss in Figure 4.

A logistic regression was conducted to evaluate the relationship between AUCss and serious infection and the result shows an estimated slope of -0.0367. The total number of

doses was added to the logistic regression as a covariate to account for total duration a subject had been treated and its effect was not statistically significant. Above analyses suggested a lack of correlation between DAC HYP exposure and incidence of serious infection in the range of exposures observed in DAC HYP phase 2 and 3 studies.

Figure 17 Observed DAC HYP Concentration Profiles by Serious Infection Status



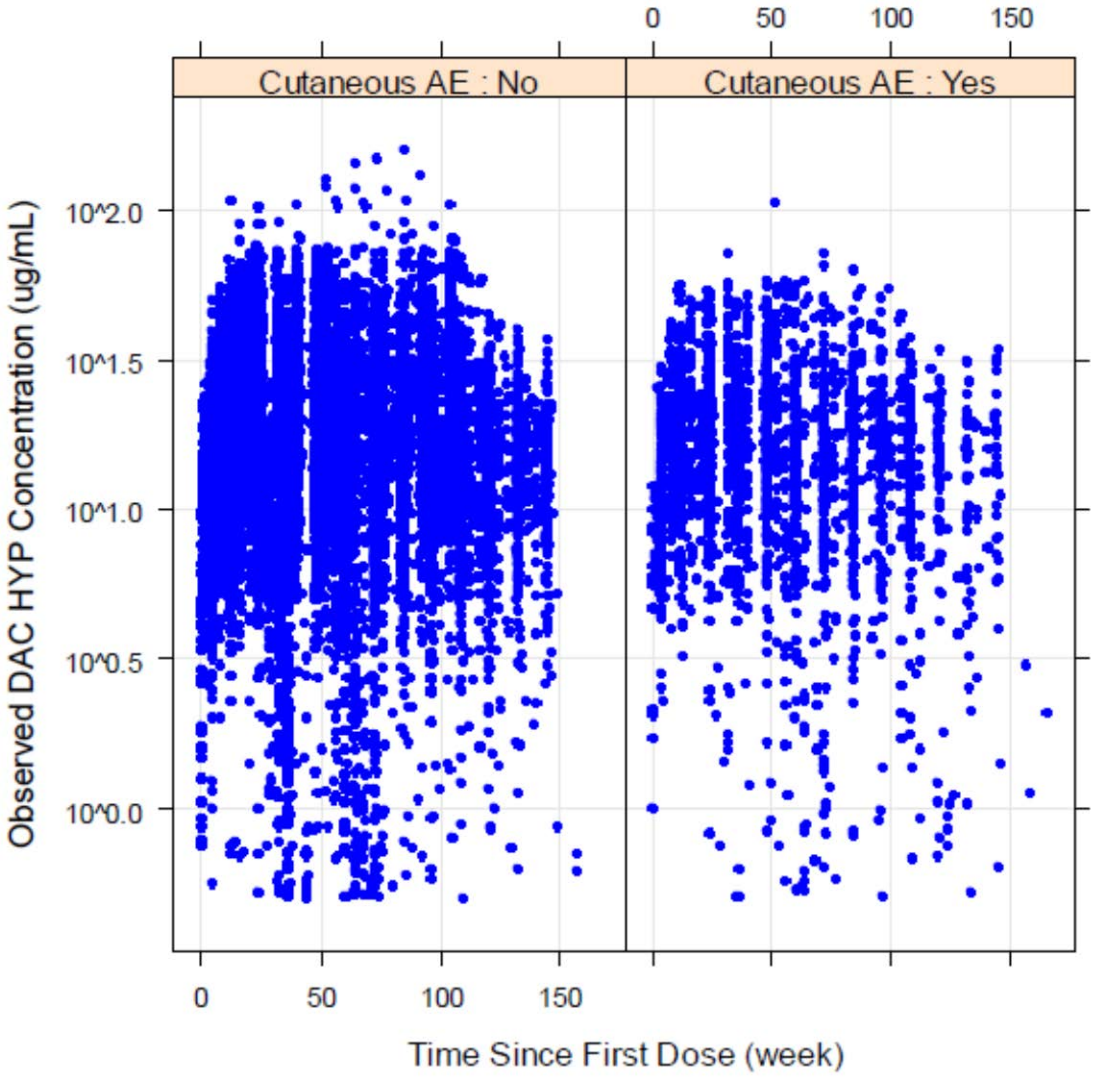
Source: study report CPP-14008-BIIB019 page 25

Cutaneous Adverse Events

In 205MS201 and 205MS202, 31 (11%) subjects on DAC HYP 150 mg and 28 (10%) subjects on DAC HYP 300 mg experienced cutaneous adverse event. In 205MS301, 152 (16.6%) subjects on DAC HYP 150 mg experienced cutaneous adverse event. In 205MS302, 8 (7.1%) subjects on DAC HYP 150 mg experienced the event. The observed DAC HYP concentrations over time were plotted by whether a subject experienced moderate or severe cutaneous AE during the study (Figure 15). The AE status (1 and 0 representing with or without moderate or severe cutaneous adverse event) was plotted against DAC HYP AUCss in Figure 5. No clear patterns can be observed from both plots.

A logistic regression was conducted to evaluate the relationship between AUCss and cutaneous AE and the result shows an estimated slope of -0.0229. The total number of doses was added to the logistic regression as a covariate to account for total duration a subject had been treated and its effect was not statistically significant. This analysis suggested a lack of correlation between DAC HYP exposure and incidence of cutaneous AE in the range of exposures observed in DAC HYP phase 2 and 3 studies.

Figure 18 Observed DAC HYP Concentration Profiles by Cutaneous AE Status



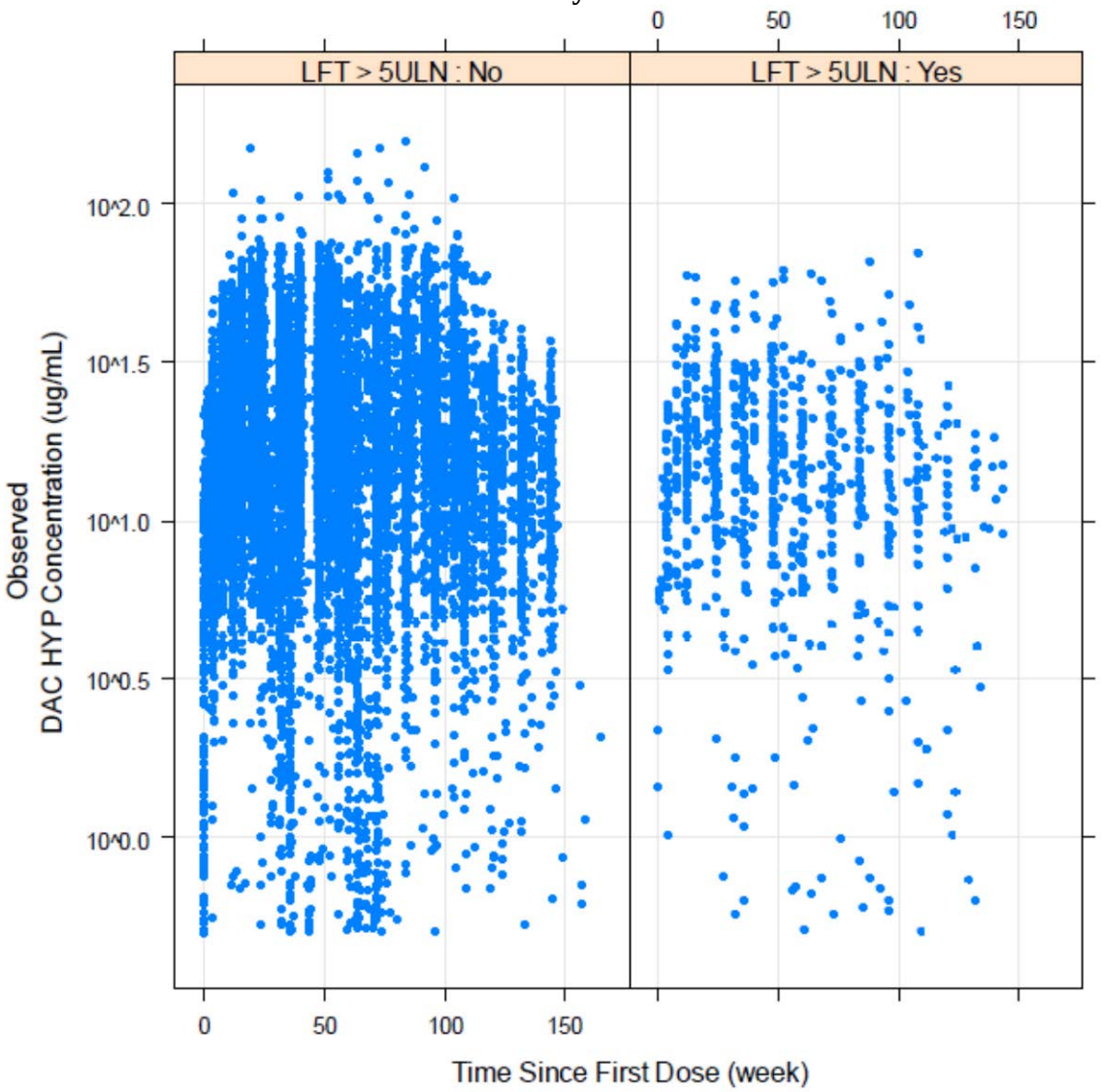
Source: study report CPP-14008-BIIB019 page 27

Liver Enzymes Abnormalities

In 205MS201 and 205MS202, 10 (3.5%) and 13 (4.6%) on DAC HYP 150 mg and 300 mg had liver transaminases (ALT and AST) > 5xULN. There were 58 (6.3%) and 4 (3.5%) subjects with such AE in the 205MS301 and 205MS302 studies, respectively. The observed DAC HYP concentrations over time were plotted by whether a subject

experienced liver enzyme abnormalities in Figure 12. In addition, Figure 6 presents liver enzyme elevation status against DAC HYP AUCss. No clear pattern can be observed from both plots.

Figure 19 Observed DAC HYP Concentration Profiles by Live Enzyme Abnormality Status



Source: study report CPP-14008-BIIB019 page 29

Reviewer's comments: E-R analyses were conducted by the sponsor to evaluate the relationship between DAC exposure and several clinical efficacy/safety endpoints, including annualized relapse rate, new or newly enlarging T2 hyperintense lesion counts, new Gadolinium-enhancing lesion counts, serious infection, moderate and severe cutaneous adverse events, and liver enzyme abnormalities, using data form phase 2 and phase 3 studies. For the efficacy endpoints, graphical analyses show that there is flat relationship between DAC AUCss and the efficacy endpoints in the active treatment groups. Effort was made to quantify such relationship by using models. However, key

model parameter such as EC50 cannot be reliably estimated. One possible explanation is that the exposures associated with both 150 mg and 300 mg every 4 weeks regimens are already at the plateau of the E-R curve for ARR, new or newly enlarging T2 lesions and Gd-enhancing lesions. Moreover, such E-R analysis findings are consistent with the dose response relationship.

For the safety endpoints, no apparent relationship between DAC exposure and the selected safety endpoints were observed from the graphical analyses. Logistic regression was employed to further evaluate the relationship and negative slopes for the relationship between DAC AUCss and serious infection and cutaneous adverse events. However, the negative slope in logistic regression estimate shouldn't be interpreted as reduced risk of serious infection or cutaneous adverse events with increased DAC HYP exposure.

4.3 Genomics and Targeted Therapy Group Review

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS and TARGETED THERAPY GROUP REVIEW

BLA Number	761029
Submission Date	07/24/2015
Applicant Name	Abbvie
Generic Name	Daclizumab
Proposed Indication	Treatment of Multiple Sclerosis
Primary Reviewer	Hobart Rogers Pharm.D, Ph.D.
Secondary Reviewer	Christian Grimstein Ph.D.

Review Question: Are there common underlying genetic causes that increase the risk of liver toxicity from daclizumab?

No. The sponsor's GWAS was adequately conducted and did not identify any statistically significant associations.

The sponsor conducted an exploratory GWAS to investigate liver adverse events encountered in their phase 2 (SELECT) and 3 (DECIDE) trials. The aim of the sponsor's analysis was to determine if common genetic variants were associated with adverse events in patients treated with daclizumab. DNA samples were obtained by patient's consent and genotyped using the HumanOmni25M-8v1-1_B array. The case-control GWAS tested 576 patient samples, including 54 cases and 522 controls. Cases were defined as any subjects who had ALT or AST serum levels greater than 5 times the upper limit of normal (ULN), at any time following the first dose of daclizumab within 180 days after the end of treatment. Subjects that had alcoholism or hepatitis were excluded. The control group was composed of the following subjects:

1. On treatment for at least 96 weeks
2. Did not have any ALT or AST serum level > 3xULN at any time during the study
3. Did not have the following safety events: Inflammatory Bowel Disease or moderate/serious/severe cutaneous event.
4. Did not have severe or serious GI events; in addition to excluding subjects with Inflammatory Bowel Disease.
5. Did not have severe or serious events in the hepatic standardized medra query (SMQ) at any time on/after the first dose of daclizumab.

According to the sponsor, after quality control measures, the GWAS yielded no significant ($p<5x10^{-8}$) findings (Figure 1, below). Given the sample size, there was sufficient power to detect associations of markers with an allele frequency of 5% or greater with an odds ratio greater than 10.

Reviewer Comment: *Overall, the sponsor's GWAS study was adequately powered to identify genome-wide significant associations between genetic markers with an allele frequency ≥ 5% and daclizumab-associated elevations in liver enzymes (serum ALT or AST >5xULN). Both, case and control definitions were adequate. None of the findings for any of the SNPs on the GWAS even approached the level of genome-wide significance ($p<5x10^{-8}$), hence it is unlikely that there is a robust genetic association between any common genetic variants and daclizumab-associated elevations in liver enzymes. Further refining the case control definitions is unlikely to yield any significant robust associations.*

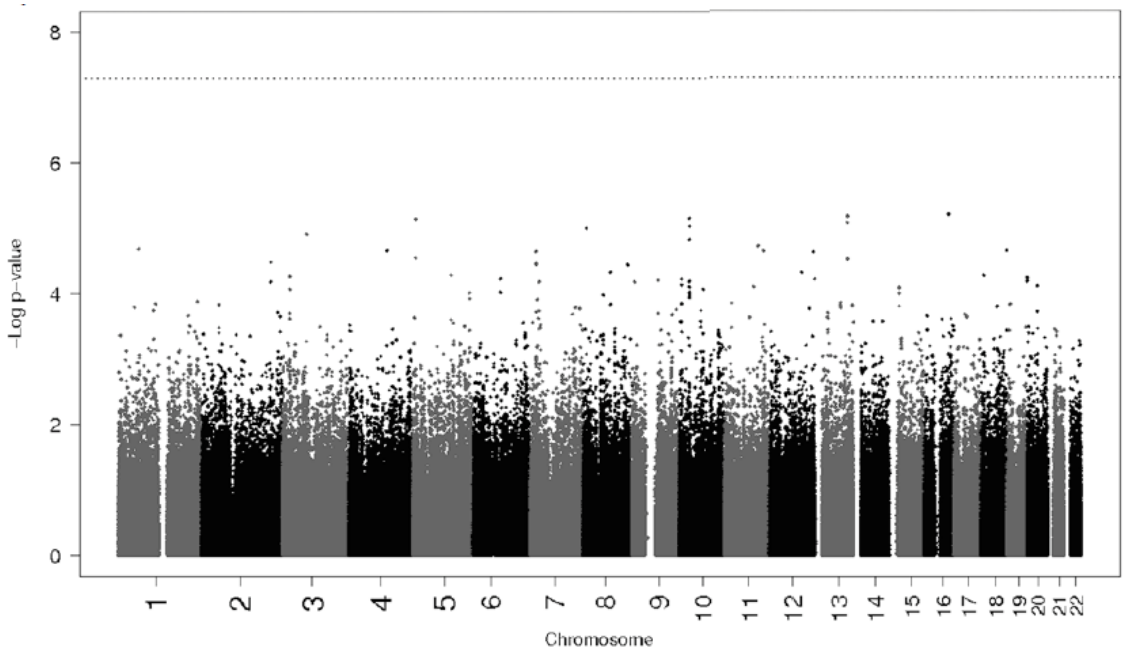


Figure 1. Single SNP GWAS with DAC Liver Adverse Events (dotted line represents $p<5x10^{-8}$)
Source: Sponsor's DAC HYP_GWAS report

4.4 OCP Filing/Review Form

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	BLA 761029 (0000)	**SDN**	1
Applicant	AbbVie Inc.	**Submission Date**	02/27/2015
Generic Name	Daclizumab	**Brand Name**	Z1NBRYTA
Drug Class	An anti-CD25 humanized monoclonal immunoglobulin G1 (IgG1) antibody		
Indication	Multiple Sclerosis		
Dosage Regimen	150 mg monthly		
Dosage Form	Subcutaneous (SC) injection liquid formulation (150 mg/mL of DAC HYP per vial) via prefilled syringe (PFS; 29G)		
OCP Division	DCP1, HFD-860	**OND Division**	HFD-120
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Ta-Chen Wu	Angela Men	
Pharmacometrics	Xiaofeng Wang	Kevin Krudys	
Genomics			
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	04/06/2015	**74-Day Letter Date**	04/28/2015
Review Due Date	(12/27/2015)	**PDUFA Goal Date**	02/27/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes [If the Applicant can provide the requested datasets and reports early]

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☑ Yes [The Information Request will be conveyed to the Applicant before the 74-day letter]

☐ No

If yes list comment(s)

Please provide the Agency with the following PK analysis datasets (RAW data and/or PK analysis) for the individual studies and bioanalytical reports for in-study assay performance. If you have submitted these reports, please point to the specific locations of the submission.

- Study 205MS201 -- both concentration-time data and PK parameters in SAS transport file (.xpt)
- Study 205MS202 -- both concentration-time data and PK parameters in SAS transport

file (.xpt)

- Study 205MS203 -- PK parameters in SAS transport file (.xpt)
- Study 205MS301 -- both concentration-time data and PK parameters in SAS transport file (.xpt)
- Study 205MS302 – PK datasets for the interim week 44 could not be opened. Since hyperlinks are not available, please clarify whether those datasets in Module 5 under Orphaned Files are the pertinent datasets for this study.
- The output listings for all models/analyses in Report CPP-14-008-BIIB019 in *.txt format.
- Please provide bioanalytical reports for the in-study assay performance for Studies DAC-1015 (listed in Reference #7-13), DAC-1012, 205MS301, 205MS302 Interim (clarify whether they are the same as those for 205MS302 Interim Week-44), and 205MS303 (when they become available). For clarity, please provide a tabular listing of all the in-study bioanalytical reports.

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No [No pivotal BE study for inspection]

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ NA	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		Cross-study Pop PK analysis (Report CPP-14-010-BIIB019): estimated 90%
☐ Relative Bioavailability		
☐ Bioequivalence		
☐ Food Effect		

☐ Other			
Human			
Healthy Subjects	☑ Single Dose	2	**DAC-1015**: Phase 1, safety, tolerability, PK/PD; DAC HYP 50 mg, 150 mg, 300 mg, placebo (sc) **DAC-1018**: Phase 1, safety, tolerability, PK/PD; DAC HYP 200 mg, 400 mg, placebo (iv) ***** See Intrinsic Factors (Race) for **205HV102**
	☑ Multiple Dose	1	**DAC-1014**: Phase 1, safety, tolerability, PK/PD; DAC HYP 200 mg every 2 weeks ×9 doses (200 mg loading dose + 100 mg every 2 weeks × 8 doses), placebo (sc)
Patients	☐ Single Dose		
	☑ Multiple Dose	7	**DAC-1012**: Phase 2, efficacy, PK and dose-ranging; DAC Penzberg daclizumab 1 mg/kg (max. 100 mg per dosing visit) every 4 weeks × 6 doses, alternating with SC placebo × 5 doses, daclizumab 2 mg/kg (max. 200 mg per dosing visit) every 2 weeks × 11 doses, placebo every 2 weeks × 11 doses; MS patients concurrently on IFN-β therapy **205MS201**: Phase 2, efficacy, safety and dose-ranging; DAC HYP 150 mg every 4 weeks × 13 doses, DAC HYP 300 mg every 4 weeks × 13 doses, placebo every 4 weeks × 13 doses (sc) **205MS202**: Phase 2 extension of 201, safety and immunogenicity; DAC HYP; PBO/DAC150 arm, PBO/DAC300 arm, DAC150/WO/150 arm, DAC150/150 arm, DAC300/WO/300 arm, DAC300/300 arm (13 doses per arm; sc) **205MS203**: Phase 2b extension of 201 and 202, safety; DAC HYP 150 mg every 4 weeks (sc); [ongoing/interim CSR] • Autoinjector PK substudy – PK comparison of prefilled pen (PFP or autoinjector) and manual PFS (Report CPP-13-006-BIIB019-amended). **205MS301**: Phase 3, Test superiority of DAC HYP compared with Avonex® (IFN β-1a); DAC HYP 150 mg SC every 4 weeks plus Avonex (IFN β-1a) placebo IM once weekly, IFN β-1a 30 µg IM once a week plus DAC HYP placebo SC once every 4 weeks **205MS302**: Phase 3, immunogenicity and PK; DAC HYP 150 mg every 4 weeks × 6 doses; Washout period: 20 weeks; Extension phase: 150 mg every 4 weeks (sc); [ongoing/interim CSR] • Intense PK substudy – DAC HYP administered by manual PFS. • TP-DI substudy – effect of DAC HYP on probe substrates (oral probe drug cocktail) for CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A)

		205MS303: Phase 3 extension of 301, safety and efficacy; DAC HYP 150 mg every 4 weeks (sc) [ongoing/interim CSR]
☐ Mass Balance Study		
☐ Other (e.g. dose proportionality)	(29)	• Bioanalytical validation reports: PK (4), PD (15), Immunogenicity (10) • Literature reference under m5.4: 326
Intrinsic Factors		
☑ Race	1	**205HV102**: PK of Japanese and Caucasian HV; DAC HYP SD 75 mg, 150 mg (sc)
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☑ Effects of Primary Drug		
Pharmacodynamics		
☑ Healthy Subjects		
☑ Patients		
Pharmacokinetics/Pharmacodynamics		
☑ Healthy Subjects		
☑ Patients		
☐ QT		
Pharmacometrics		
☑ Population Pharmacokinetics	2	Report CPP-14-010-BIIB019: data from Studies 201, 202, 302, and 301 (Pop PK) Report CPP-14-011-BIIB019: data from Studies 201, 202, 302, and 301 (Pop PK-PD)
☑ Exposure-Efficacy	1	Report CPP-14-008-BIIB019: data from Studies 201, 202, 302, and 301
☑ Exposure-Safety		Report CPP-14-008-BIIB019: data from Studies 201, 202, 302, and 301

Total Number of Studies	**In Vitro**		**In Vivo**	11 + 3(PM) + validation reports
Total Number of Studies to be Reviewed				(pending)

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit	☐Yes ☐No	PFS of 150mg/mL liquid formulation used in clinical trial

bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑N/A	Comparative BA between PFS and PEP as a substudy, but PEP is not part of the BLA filing (per the Applicant)
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	The exact metabolic pathway for DAC HYP has not been characterized. As an IgG1 monoclonal antibody, DAC HYP is expected to be metabolized into peptides and amino acids via catabolic pathway, not expected to undergo metabolism by hepatic enzymes such as CYP isoenzymes.
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐Yes ☐No ☐N/A	Yes, if the Applicant can provide the analysis datasets and reports (see Information Request)
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic	☑Yes ☐No ☐N/A	

submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?		
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☐Yes ☐No ☐N/A	See Information Request
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or	☐Yes ☐No ☑N/A	

pharmacodynamics?		
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☑No ☐N/A	

Filing Memo
This is optional, discuss with your TL content and format

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TA-CHEN WU
05/24/2016

KEVIN M KRUDYS
05/24/2016
I am also signing for Xiaofeng Wang, the primary pharmacometrics reviewer

HOBART ROGERS
05/24/2016

CHRISTIAN GRIMSTEIN
05/24/2016

YUXIN MEN
05/24/2016

MEHUL U MEHTA
05/24/2016