# Statistical Analysis Plan

Version No.: FINAL v1.0

Study Title: 205MS305 (SUSTAIN)

Name of Study Treatment: DACLIZUMAB

Protocol No.: 205MS305/NCT02881567

Study Phase: PHASE IIIB

# APPROVAL

This document has been reviewed and approved by:

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A Phase 3b, 12-month, Open-label, Multicenter Study to Evaluate the Efficacy and Safety of BIIB019, Daclizumab beta, in Subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) Switching from Natalizumab (SUSTAIN)

# Protocol 205MS305

**Study Phase: 3b**

**Product Studied:** Daclizumab

**Date of Protocol:** 06 July 2011 (version 1.0 )

**Date of SAP:** 14 June 2018

**Key words**: (Open-label, multicenter, clinical relapses, confirmed disability progression, MRI, adverse events)

**Written By:** [redacted], PhD
[redacted]

**Compliance**: The study described in this report was performed according to the principles of Good Clinical Practice (GCP)

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# 1 STUDY OBJECTIVES AND ENDPOINTS

## 1.1 Primary Objective and Endpoint

**The primary study objective** is to evaluate the effects of treatment with daclizumab beta on proportion of subjects relapse-free at Month 6, in RRMS subjects who switched from treatment with natalizumab to daclizumab beta due to safety concerns.

**The primary endpoint** in relation to this objective is the proportion of subjects relapse-free at Month 6, in RRMS subjects treated with daclizumab beta who switched from treatment with natalizumab.

## 1.2 Secondary Objectives and Endpoints

**The secondary objectives** are to evaluate the effects of daclizumab beta on the following:

- Multiple Sclerosis (MS) relapse activity including annualized relapse rate (ARR) and the proportion of subjects experiencing relapses requiring hospitalization and/or steroid treatment.
- MS-related outcomes measured using magnetic resonance imaging (MRI).
- Safety and tolerability in subjects previously treated with natalizumab.

**The secondary endpoints** are:

- The proportion of subjects relapse-free at Month 12.
- The proportion of subjects experiencing relapse requiring hospitalization and/or steroid treatment at Month 12.
- The ARR at Month 12.
- The number of new gadolinium enhanced (Gd+) and T1 hypointense lesions at Month 6 and Month 12 on MRI.
- The number of new or newly enlarged T2 hyperintense lesions at Month 6 and Month 12 on MRI.
- The permanent discontinuation rate of daclizumab beta at Month 12.
- The incidence of adverse events (AEs) and serious adverse events (SAEs) including clinically relevant.

## 1.3 Exploratory Objectives and Endpoints

**The exploratory objectives** of this study in this study population are to evaluate the effects of daclizumab beta on the following:

- [redacted]

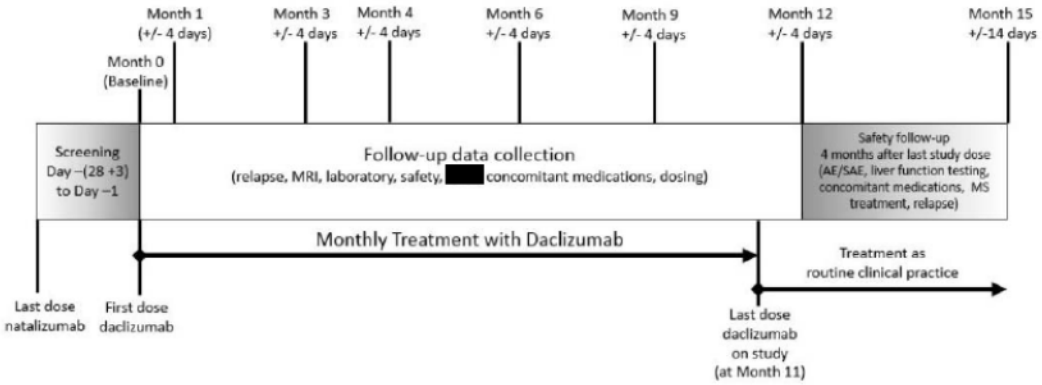
- [redacted]
- [redacted]
- [redacted]

**The exploratory endpoints** of the study are:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

## 2 STUDY DESIGN AND SAMPLE SIZE

This is a multicenter, open-label study of daclizumab monotherapy in subjects with RRMS who were previously treated with natalizumab for at least 12 months. Subjects will be enrolled over an approximately 12-month period. Subjects discontinuing from natalizumab treatment due to safety concerns will commence treatment with daclizumab beta following consent and evaluation of eligibility. Subjects will initiate treatment with daclizumab beta at 28 (+3) days following the last infusion of natalizumab. Assessments will be completed at enrollment, baseline, Month 1, Month 3, Month 4, Month 6, Month 9 and Month 12.




**Abbreviations:** AE: adverse event; [redacted] MRI: magnetic resonance imaging; MS: Multiple Sclerosis; SAE: serious adverse event.

The duration of subject participation will be up to 16 months, including a 28 (+3) day screening period, treatment with daclizumab beta for up to 12 months, and an additional safety follow-up visit performed remotely 4 months after last study treatment dose. Subjects having tentative disability progression near the end of the core study (e.g., Month 12) will attend additional follow-up visits 12 and 24 weeks later to confirm progression. This study will enroll approximately 100 subjects. The sample size is estimated based on the proportion of subjects who are relapse-free at Month 6.

On March 2, 2018, daclizumab beta has been voluntarily withdrawn from the global market and the drug supply to patients has been stopped. As a result SUSTAIN has been terminated. An abbreviated clinical study report will be developed based on the patient data available upon the withdrawal and from the safety follow-up.

# 3 ANALYSIS POPULATIONS

The full analysis set (FAS) will include all subjects who receive at least one dose of daclizumab. This dataset will be used for all analyses.

# 4 GENERAL CONSIDERATIONS

The SUSTAIN study was terminated early by sponsor upon the withdrawal of daclizumab from the global market after approximately 30 subjects were enrolled in study. Because the study was not fully enrolled and there was limited follow-up time, some endpoints will no longer be analyzed and some endpoints and outcomes will be summarized in listings rather than data tabulations. Missing data in this study will not be imputed.

## 4.1 Treatment Period Definitions

Based on the schedule of assessment, we have the following definitions:

- **the first dosing date** is the date when the subject is first dosed;
- **the last dosing date** is the date of the last date the subject is dosed;
- **The end of study date** is the last visit date;

- **Treatment period, or, time on (study) treatment**, is defined as the time between the first dosing date and the last dosing date; it is calculated as the last dosing date minus the first dosing date + 1; also known as the time exposed to study drug;
- **Time on study, or study period**, is defined as the time between the first dosing date and the end of study date, calculated as the last visit date – the first dosing date + 1.

### 4.2 Accounting of Subjects

Disposition of the subjects will be summarized. The key contents include number (and percentage) of subjects, number of subjects dosed, median follow-up time, median time on study treatment, the number of subjects who completed study follow-up. In addition, along with reasons, numbers (and percentage) of subjects discontinued treatment and withdrawn from the study will be presented. Listings of these subjects and reasons for discontinuation/withdrawal will be presented

### 4.3 Demographics and Baseline Characteristics

Demographic data, including age (years), age category (<18, 18-19, 20-29, 30-39, 40-49, 50-55, and >55, also $\leq 35$ , $> 35$), gender, race category, baseline height (cm) and weight (kg) will be summarized.

Baseline data are defined as data collected on the closest date prior to or on the first dosing date. Baseline disease characteristics will be summarized. These include years since disease (MS) onset, years since diagnosis, McDonald criteria, number of relapses in the past 12 months and in the past 3 years, [redacted], baseline MRI, prior MS treatment history, medical history, tobacco use, and status of interferon binding and neutralizing antibodies. Additional variables may be included where applicable.

All demographic and baseline data will be summarized for the full analysis set.

### 4.4 Study Drug Compliance

Study drug compliance will be summarized, including the total number of injections of daclizumab beta, the percentage of the treatment injections received.

### 4.5 Concomitant Medications and Non-drug Therapies

Concomitant medication is defined as prescribed or over-the-counter medication used during the study (e.g. either started prior to the study and continued during the study or started after the first dose of study drug). The WHO dictionary will be used for coding concomitant medication. MedDRA is used for coding concomitant non-drug therapies.

Number and percentage of subjects taking concomitant medication and non-drug therapies will be summarized. In addition, number and percentage of subjects taking (switching to) alternative medication will also be summarized.

### 4.6 General Information on Statistical Analysis

Summary statistics will be generated for all efficacy, safety, PK/PD parameters, demographic/baseline variables and other variables where applicable. For the continuous endpoints, the summary statistics will generally include number of subjects, mean, standard deviation, median, $25^{th}$ and $75^{th}$ percentile, minimum and maximum. For categorical endpoints, the summary statistics will generally include number of subjects in corresponding analysis population, number and the percentage of subjects in each category.

In general, all efficacy endpoint analyses where applicable will include the baseline covariates; the covariates included in the statistical models for efficacy endpoints are selected to be consistent with analysis models in other previously reported Phase 3 MS studies.

All statistical tests will be 2-sided with an overall type I error rate of 0.05; no multiple testing adjustment will be performed in this study.

### 4.7 Protocol Deviations

Protocol deviations identified during site monitoring will be captured in a protocol deviation log and categorized as major or minor deviations. These deviations will be listed.

### 4.8 Alternative Multiple Sclerosis Medications

In this study, alternative MS medications refers to a list of medications including but not limited to methotrexate, glatimer acetate, mycophenoloate mofetil, azathioprine, natalizumab, alemtuzumab, teriflunomide, mitoxantrone, fingolimod, dimethyl fumarate, rituximab, ocrelizumab, laquinimod, and interferon beta throughout this document. Patients who take alternative MS medications during the study will be listed.

## 5 STATISTICAL ANALYSES

### 5.1 Primary Analysis

**Definition of relapses.** Relapses are defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the Examining Neurologist. Protocol-defined relapses up to the end of treatment period visit will be included in the primary analyses. New or recurrent neurological symptoms that occurred less than 30 days following the onset of a protocol-defined relapse will be considered part of the same relapse (i.e., relapses with onset days $\leq$29 days of one another, will be counted as 1 relapse).

**Censoring.** If a subject prematurely discontinues the treatment and the subject does not experience a protocol-defined relapse prior to discontinuation, the subject will be censored on the last dosing date.

**Analysis method.** The number of relapses per subject will be summarized. The proportion of subjects who are relapse-free at 6 months will be estimated as 1 minus the cumulative

probability of relapses from the Kaplan-Meier product limit method. The time to relapse is the number of days from the first dosing date to the date of first relapse, or end of treatment period, whichever comes first. Time to first relapse will be summarized by $10^{th}$, $25^{th}$ and $50^{th}$ percentile.

## 5.2 Secondary Analysis

Due to the early termination of the study, the permanent discontinuation rate of daclizumab is not analyzed.

### 5.2.1 Analysis for the proportion of subjects experiencing relapse requiring hospitalization and/or steroid treatment at Month 12

Relapses requiring hospitalization and/or steroid treatment will be listed by subject with relapse evaluation date and onset date.

### 5.2.2 Analysis for Annualized Relapse Rate (ARR)

ARR will be analyzed for both treatment period and study period. Please see section 4.1 for their definitions.

The number of relapses observed during the treatment period (or during the study period) will be summarized as a categorical variable (number of relapse being 0, 1, 2, 3 and ≥4). The unadjusted relapse rate will be calculated as the total number of relapses observed divided by the total number of days on treatment (or on study) multiplied by 365.25.

If there is sufficient data, the adjusted mean annualized relapse rate and its 95% confidence interval (CI) during the treatment period will be estimated by a negative binomial model; proper covariates are adjusted in the model. The logarithmic transformation of the number of days in the study will be included in the model as the "offset" parameter. If the data is under-dispersed or if the negative binomial regression model does not converge, a Poisson model will be used instead of the negative binomial regression model. Dispersion will be evaluated from the Pearson Chi-Square statistic. If the ratio of the Pearson Chi-Square statistic to the degrees of freedom is < 1 then a Poisson regression model will be used.

### 5.2.3 Analysis for MRI endpoints

MRI is measured from all subjects in this study.. Records up to 28 days after the first dose can be used as baseline assessments. If there are multiple records, then the one closest to the first dosing date will be selected; if tied, then the record prior to the first dose will be defined as baseline.

At each visit where MRI data is available, the number of Gd+ lesions , the number of T1 hypointense lesions, and the number of new or newly enlarged T2 hyperintense lesions, will be summarized both as continuous variables and as categorical variables (number of lesions being 0, 1, 2, 3 and ≥4).

## 5.3 Exploratory Analyses

Because the study is not fully enrolled due to the global withdrawal of daclizumab, the [redacted]

### 5.3.1 Analysis for disability progression

Due to the early termination of this study, [redacted]

- [redacted]
- [redacted];
- [redacted]
- [redacted].

### 5.3.2 Analysis for exploratory biomarkers

[redacted]

[redacted]

[redacted]

## 5.4 Safety Analysis

Safety analysis will be performed with data from the entire study period.

### 5.4.1 Clinical Adverse Events

**Treatment-emergent** adverse event (TEAE) is defined as an adverse event having onset date on or after the first dosing date and prior to the 180 days after the last dosing date, or if it was present prior to start of study treatment and subsequently worsened. If it cannot be determined whether an event is treatment emergent due to a missing or partial date, then the event will be tabulated as treatment emergent. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Only treatment-emergent adverse events (TEAE) will be presented in the summary tables.

In general, AE tables include the following (but not limited to):

- incidence of treatment-emergent adverse events will be summarized overall and by severity (mild, moderate and severe);
- TEAE's will also be presented by system organ class (SOC) and preferred terms (PT) and sorted by decreasing frequency of PT within SOC, if there is sufficient data. If a patient experiences an event more than once with varying severity during the study, he/she will be counted only once with the maximum severity within each SOC and PT;
- the incidence of serious adverse events (SAE) will be summarized by system organ class (SOC) and preferred terms (PT) and sorted by frequency if there is sufficient data; otherwise listings for individual patients who experienced SAEs will be generated;
- any incidence of adverse events that lead to the dose interruption, discontinuation of study drug or premature withdrawal from the study will be presented; a listing of these adverse events may also be presented;
- any deaths that occurred during the study will be listed and relevant information including timing of the death relative to study treatment, reason of death, concomitant medications, the investigator assessment of the cause of death will be provided;
- incidences of adverse events of special interest (AESI) will also be presented, if there is sufficient data; otherwise listings of AESI will be generated. These adverse event of special interest categories are defined mainly based on Standardized MedDRA Queries (SMQs), SOC's, and/or PT's. The AEs of special interest categories may include but are not limited to the following:

    - Infections, including serious infections and potential opportunistic infections
    - Cutaneous events, including serious events
    - Hepatic disorders
    - Gastrointestinal events
    - Autoimmune disorders
    - Injection site reactions
    - Depression and suicide ideation
    - Malignancies, potential and those confirmed upon medical review

### 5.4.2 Clinical Laboratory Data

The following clinical laboratory parameters are assessed in the protocol:

- Hematology (CBC): hemoglobin, hematocrit, platelet count, red blood cell count, WBC count (with differential).
- Blood chemistry: sodium, potassium, chloride, alkaline phosphatase, lactate dehydrogenase, gamma glutamyl transferase, blood urea nitrogen, creatinine, bicarbonate.
- Liver function tests: serum transaminases (ALT and AST), and bilirubin levels.

**Hematology.** Clinically significant abnormalities for selected hematology parameters will be tabulated and listed; the number and percent of subjects for these abnormalities will be provided. The criteria of the potentially significant hematology laboratory abnormalities are provided below.

**Table 1** Criteria for Potentially Clinically Significant Hematology Abnormalities

| Test | Criteria |
|---|---|
| White blood cell count (10^9 cells/L) | <3.0; >=16.0 |
| Lymphocytes (10^9 cells/L) | <0.8; <0.5; >12.0 |
| Segmented neutrophils (10^9 cells/L) | <=1.0; <1.5; >=12.0 |
| Red blood cell count (10^12 cells/L) | <=3.3; >=6.8 |
| Hemoglobin (g/L) | <=100 |
| Platelets (10^9 cells/L) | <=100; >=600 |

Furthermore, selected hematology parameters will be listed and flagged by CTCAE grade, using the following categorization, if there is sufficient data.

**Table 2** Severity Grades for Hematology

| Test | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Hemoglobin (g/L) | [100, LLN) | [80, 100) | [65, 80) | <65 |
| Lymphocytes (10^9 cells/L) | [0.8, LLN) | [0.5, 0.8) | [0.2, 0.5) | <0.2 |
| Platelets (10^9 cells/L) | [75, LLN) | [50, 75) | [25, 50) | <25 |
| Segmented neutrophils (10^9 cells/L) | [1.5, LLN) | [1.0, 1.5) | [0.5, 1.0) | <0.5 |
| White blood cell count (10^9 cells/L) | [3.0, LLN) | [2.0, 3.0) | [1.0, 2.0) | <1.0 |

**Liver function tests (LFT).** Listings will be generated for alkaline phosphatase, ALT, AST, GGT and total bilirubin for each subjects by visit, where severity of abnormal values will be flagged based on the following table. Additionally, the incidence of ALT and/or AST elevations >=3X ULN by concurrently elevated total bilirubin will also be summarized.

**Table 3** Severity Grades for Liver Function Tests

| Test | Grade 1 | Grade 2 | Grade 3 | | Grade 4 |
|---|---|---|---|---|---|
| ALT | (1.0, 3.0) | [3.0, 5.0] | (5.0, 10.0] | (10.0, 20.0] | >20.0 |
| AST | (1.0, 3.0) | [3.0, 5.0] | (5.0, 10.0] | (10.0, 20.0] | >20.0 |
| Alkaline phosphatase | (1.0, 2.5] | (2.5, 5.0] | (5.0, 20.0] | | >20.0 |
| GGT | (1.0, 2.5] | (2.5, 5.0] | (5.0, 20.0] | | >20.0 |
| Total bilirubin | (1.0, 1.5] | (1.5, 3.0] | (3.0, 10.0] | | >10.0 |

### 5.4.3 Vital signs

Vital sign data will be listed for each subject by visit.