octapharma

# Statistical Analysis Plan

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| Study ID | GAM10-08 |
| Study title | Prospective, double-blind, randomized, phase III study evaluating efficacy and safety of Octagam 10% in patients with dermatomyositis |
| Study phase | III |

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|---|---|
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| Protocol version this SAP is based upon | Version 12, dated 18-JUN-2019 |

Approved by

| *Name*<br>*Function, affiliation* | *Date and signature* |
|---|---|
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## Document History

| Version | Date | Author | Description |
|---|---|---|---|
| Final v1.0 | 29-Mar-2016 | [redacted] | New Document |
| Final v2.0 | 18-Jul-2016 | [redacted] | Clarification of treatment group assignment, Primary analysis of the primary endpoint changed to full analysis set (ITT analysis), Definition of PP1 set rephrased, Discussion of patients with missing Week 16 score, Descriptive subgroup analyses added, Possible dose reduction to 1.0 g/kg in the extension phase, Requirement of confirmed deterioration emphasized, Infusions expanded to infusion cycles, Clarified that the modified CDASI (version 2) will be used, AEs of special interest (TEEs, HTRs) incorporated, Additional tests (Wells scores, Doppler scan, lab parameters), Available data on screening failures, References to week 6 changed to the next scheduled visit (week 8), Additional minor clarifications, cross-references, and rephrasing for clarity and consistency with the revised protocol |
| Final v3.0 | 03-JUL-2017 | [redacted] | Adapted to changes in the statistical section of study protocol, Update of definition of confirmed deterioration |
| Final 4.0 | 18-Jun-2019 | [redacted] | Adapted to changes in protocol version 12, in particular adjustments requested by authorities:<br>• Definition of the FAS analysis set changed to include all randomized subjects<br>• Wording of response definition unified across protocol and SAP |

## Abbreviations

| | |
|---|---|
| (e)CRF | (Electronic) Case Report Form |
| AE | Adverse Event |
| ALAT | Alanine Aminotransferase |
| ASAT | Aspartate Aminotransferase |
| BMI | Body Mass Index |
| CDASI | Cutaneous Dermatomyositis Disease Area and Severity Index |
| CI | Confidence Interval |
| CK | Creatine Kinase |
| CSM | Core Set Measure |
| CSR | Clinical Study Report |
| DM | Dermatomyositis |
| DVT | Deep Vein Thrombosis |

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|---|---|
| IMACS | International Myositis Assessment and Clinical Studies Group |
| IMP | Investigational Medicinal Product |
| ITT | Intention-To-Treat |
| IVIG | Intravenous Immunoglobulin |
| LDH | Lactate Dehydrogenase |
| MDAAT | Myositis Disease Activity Assessment Tool |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMT | Manual Muscle Testing |
| PE | Pulmonary Embolism |
| PP | Per Protocol |
| PT | Preferred Term |
| QoL | Quality of Life |

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|---|---|
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GDA | Global Disease Activity |
| HAQ | Health Assessment Questionnaire |
| HTR | Hemolytic Transfusion Reaction |
| ICH | International Conference on Harmonisation |
| IgG | Immunoglobulin G |
| IGIV | Immunoglobulin Intravenous |

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|---|---|
| SAE | Serious Adverse Event |
| SAF | Safety Set |
| SAP | Statistical Analysis Plan |
| SF-36v2 | Short Form 36 Items Health Status Version 2 |
| SOC | System Organ Class |
| TEAE | Treatment Emergent Adverse Event |
| TEE | Thromboembolic Event |
| TIS | Total Improvement Score |
| VAS | Visual Analog Scale |

# Table of Contents

# 1. Preface

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Octapharma Protocol GAM10-08: *Prospective, double-blind, randomized, phase III study evaluating efficacy and safety of Octagam 10% in patients with dermatomyositis.*

This phase III study is conducted to provide confirmatory data on the beneficial effect of Octagam 10% every four weeks compared to placebo in patients with active dermatomyositis (DM). It is designed as prospective, parallel group, double-blind, randomized, multicenter study with a 16-week efficacy period, followed by a 24-week open-label extension period.

The primary endpoint measures for each subject will be assessed at the end of the blinded efficacy period, before the subject may enter the open-label extension period.

The open-label extension period will allow to evaluate the sustained benefit as well as the safety and tolerability of Octagam 10% over an extended period of time.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1].

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol GAM10-08, Version 12, dated 18-JUN-2019

The reader of this SAP is encouraged to also read the clinical protocol for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant for the specification of the planned analyses.

[1] International Conference on Harmonization. (1998). Guidance on Statistical Principles. ICH Topic E9 (Statistical Principles for Clinical Trials) (p. 37). London: International Conference on Harmonization.

# 2. Purpose

This SAP outlines all statistical analyses to be performed on data collected in study GAM10-08, and the resulting output that will be compiled to support the completion of the Clinical Study Report (CSR).

The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed that are not identified in this SAP will be clearly identified in the respective CSR.

The statistical output provided to the medical writer of the CSR will closely follow the ICH guideline for industry on topic E3 (Structure and Content of Clinical Study Reports[2]) to facilitate the subsequent compilation of the CSR.

This statistical output will consist of tables, figures and listings, including

- Tables, figures and listings used or referenced in, or appended to the CSR as detailed in the remainder of this SAP (section 14 of the CSR)
    - Demographic data summary figures and tables
    - Efficacy data summary figures and tables
    - Safety data summary figures and tables
- Listings provided as appendices to the CSR
    - Patient data listings (section 16.2 of the CSR)
    - Individual patient data listings (section 16.4 of the CSR) will be covered by inclusion of SAS datasets into the electronic submission to the authorities

A detailed list of all tables, figures and listings will be supplied in a separate document later when all feedback from authorities will be available.

[2] International Conference on Harmonization. (1996). Structure and Content of Clinical Study Reports. Structure and Content of Clinical Study Reports (Guideline for Industry) (S. 37). London: International Conference on Harmonization.

# 3. Study Objectives and Endpoints

## 3.1. Study Objectives

### 3.1.1. Primary Objective

The primary objective of the study is to provide confirmatory data on the beneficial effect of 2.0 g/kg Octagam 10% given every four weeks compared with placebo in patients with active dermatomyositis (DM) based on the percentage of responders at Week 16.

### 3.1.2. Secondary Objectives

The secondary objectives of the study are:

- to evaluate the beneficial effect of Octagam 10% in patients with active DM by assessing different parameters and scores at Week 16 and Week 40;
- to confirm the sustained benefit of treatment with Octagam 10% by assessing the primary response measures also at Week 40;
- to evaluate the safety and tolerability of Octagam 10% in patients with DM.

## 3.2. Study Endpoints (Target Variables)

This section defines the target variables collected or derived for the evaluation of the endpoints; please refer to sections 8 to 12 for analysis details.

### 3.2.1. Primary Target Variables

The evaluation of the primary endpoint will be based on the newly developed Total Improvement Score (TIS), a scale from 0 to 100, with 20-39 points being minimal improvement, 40-59 points being moderate improvement, and ≥60 points being major improvement (Aggarwal et al., 2017, please refer to the protocol for details).

In the context of this study, subjects need to have at least minimal improvement at Week 16 (i.e. TIS ≥ 20) to qualify as responders.

The primary endpoint is defined as the proportion of responders in the 2.0 g/kg Octagam 10% and placebo arms at Week 16, a responder being defined as a subject with an increase from baseline (Week 0) of ≥ 20 points on the Total Improvement Score (TIS) and who has not met "Confirmed Deterioration" criteria at 2 consecutive visits as defined in Section 8.4 up to (including) Week 16.

The TIS is based on the assessment of six core set measures (CSMs):

1. Physician Global Activity: Global Disease Activity (GDA), assessed by the investigator on a Visual Analog Scale (VAS)
2. Patient Global Activity: GDA, assessed by the patient on a VAS
3. Manual muscle testing: MMT-8 Muscle Grading and Testing
4. Health Assessment Questionnaire (HAQ): Standard HAQ used by the International Myositis Assessment and Clinical Studies Group (IMACS)
5. Enzymes: Aldolase, CK, ALAT, ASAT, LDH
6. Extra muscular activity: Evaluated as part of Myositis Disease Activity Assessment Tool [MDAAT]

Please refer to the protocol for further details and references on these CSMs. The CSMs will be assessed at Screening, at each visit of the first period, at Visit 9 (Week 28), and at the Termination Visit.

The TIS is calculated as a sum of sub-scores as detailed below. The level of improvement will always be based on the comparison of the current CSMs compared to the baseline (Week 0) values.

| *Core set measure* | *Level of improvement* | *Level score* |
|---|---|---|
| Physician Global Activity | Worsening to 5% improvement | 0 |
| | >5% to 15% improvement | 7,5 |
| | >15% to 25% improvement | 15 |
| | >25% to 40% improvement | 17,5 |
| | >40% improvement | 20 |
| Patient Global Activity | Worsening to 5% improvement | 0 |
| | >5% to 15% improvement | 2,5 |
| | >15% to 25% improvement | 5 |
| | >25% to 40% improvement | 7,5 |
| | >40% improvement | 10 |
| Manual muscle testing (MMT) | Worsening to 2% improvement | 0 |
| | >2% to 10% improvement | 10 |
| | >10% to 20% improvement | 20 |
| | >20% to 30% improvement | 27,5 |
| | >30% improvement | 32,5 |
| Health Assessment Questionnaire (HAQ) | Worsening to 5% improvement | 0 |
| | >5% to 15% improvement | 5 |
| | >15% to 25% improvement | 7,5 |
| | >25% to 40% improvement | 7,5 |
| | >40% improvement | 10 |
| Enzyme (most abnormal)* | Worsening to 5% improvement | 0 |
| | >5% to 15% improvement | 2,5 |
| | >15% to 25% improvement | 5 |
| | >25% to 40% improvement | 7,5 |
| | >40% improvement | 7,5 |
| Extra muscular activity | Worsening to 5% improvement | 0 |
| | >5% to 15% improvement | 7,5 |
| | >15% to 25% improvement | 12,5 |
| | >25% to 40% improvement | 15 |
| | >40% improvement | 20 |
| | **Improvement category** | **Total Improvement Score** |
| Adult thresholds | Minimal | 20 |
| | Moderate | 40 |
| | Major | 60 |

- *The most abnormal muscle enzyme is the enzyme at baseline (Week 0) with the highest ratio compared to its upper limit of normal.

### 3.2.2. Secondary Target Variables

For Efficacy and Quality of Life (QoL), secondary endpoints will be:

- Proportion of TIS responders by improvement category (minimal, moderate, major) at Week 16 and Week 40.
- Mean change from baseline (Week 0) to end of First Period (Week 16) in modified Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI)
- Mean change from end of First Period (Week 16) to end of Extension Period (Week 40) in modified CDASI.
- Mean change from Baseline (Week 0) to end of First Period (Week 16) and Extension Period (Week 40) in:

    - SF-36v2 Health Survey;
    - Individual 6 Core Set Measures (CSM) used for TIS calculation.
- Mean TIS from Baseline (Week 0) to end of First Period (Week 16) and from Baseline (Week 0) to end of Extension Period (Week 40).
- Time to minimal, moderate and major improvement in TIS.
- Time to confirmed deterioration (defined on basis of the CSM assessments, see section 8.4 for details) in the First Period and overall.
- Proportion of subjects in each treatment arm who met "confirmed deterioration" criteria up to (including) Week 16

For Safety, target variables will be:

- Occurrence of adverse events (AEs) with an emphasis on thromboembolic events (TEEs) and hemolytic transfusion reactions (HTRs)
- Wells probability scores for deep vein thrombosis (DVT) and pulmonary embolism (PE), and Doppler scan (if indicated)
- Occurrence of all adverse drug reactions (ADRs) and suspected ADRs
- Vital signs (blood pressure, heart rate, body temperature and respiratory rate)
- Physical examination (at Screening and every 12 weeks from Week 4 on)
- Laboratory parameters (hematology, clinical chemistry, IgG, enzymes, viral markers, Coombs' test [plus specific antibodies if positive], D-dimers)
- Pregnancy test

# 4. Study Methods

## 4.1. Overall Study Design and Plan

Study GAM10-08 is designed as a prospective, parallel group, double-blind, randomized, multicenter phase III study with a 16-week efficacy period followed by a 24-week open-label extension period.

As DM is a rare disease, about 55 sites are projected to participate in countries worldwide with emphasis on (Eastern) European countries and North America. For the same reason, it is not expected that single centers will enroll more than about 5 subjects.

The duration of the entire study for each subject will be up to 43 weeks and consists of the following segments:

- approximately 3 weeks for Screening
- 16 weeks of double-blind treatment
- 24 weeks of open-label treatment with Octagam

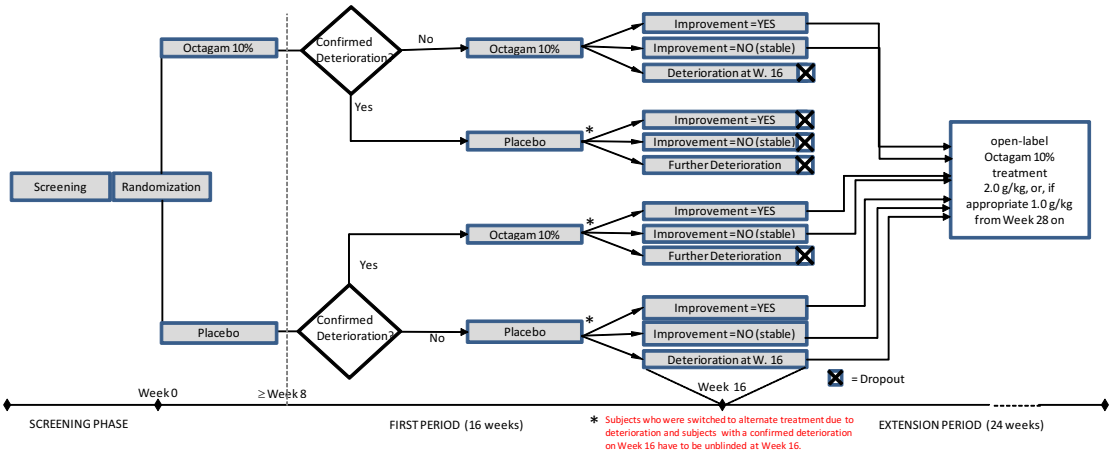
Eligible subjects after screening will be randomized 1:1 to receive up to four infusion cycles of either 2.0 g/kg Octagam 10% or placebo every 4 weeks during the 16-week First Period. An infusion cycle will consist of 2 to 5 days over which the study drug will be administered.

Subjects, who deteriorate[3] in this phase, will be crossed-over to the alternate treatment from week 8 on.

After response assessment at Week 16, the following subject groups will continue in the 6-months open-label Extension Period and receive 2.0 g/kg Octagam 10% given over 2 days (if tolerated by the patient) at 4 week intervals:

- Subjects randomized to Octagam without confirmed deterioration during the First study period including Week 16.
- Subjects randomized to placebo without confirmed deterioration prior to Week 16.
- Subjects randomized to placebo who switched to Octagam and show no further deterioration at Week 16

The rest of the subjects will not continue the study, but Week 16 will be considered as their termination visit:




[3] For a definition of confirmed deterioration, please refer to section 8.4.

At Week 28, subjects who are stable on 2.0 g/kg Octagam 10% can be switched to 1.0 g/kg Octagam 10%, at the discretion of the investigator.

Please refer to the study protocol for a detailed flowchart of planned study events and assessments.

## 4.2. Selection of Study Population

The study population consists of adult patients of both sexes with a diagnosis of definite or probable dermatomyositis according to the Bohan and Peter criteria (1975); please refer to the protocol for a complete list of inclusion/exclusion criteria.

## 4.3. Randomization, Stratification and Blinding

All subjects qualified to participate in the study at Visit 2 will be randomized to one of the two treatment arms – Octagam 10% or Placebo – in a ratio of 1:1. The randomization scheme will be stratified according to the seriousness of disease before enrollment: Mild | Moderate | Severe.

The Physician's Global Disease Activity assessment will determine the correct stratum for each subject as follows: GDA value of 0-3 [mild], 4-6 [moderate], 7-10 [major]

Within the strata, the same fixed block size will be used for a balanced randomization.

This design will ensure the desired overall randomization ratio and avoid random differences between the treatment groups with respect to the seriousness of DM prior to enrollment.

The randomization scheme will only be available to the statisticians responsible for creating it, and the programmer implementing the scheme into the IRT system. No information on treatment assignment will be communicated to the sponsor or any CRO personnel responsible for the conduct of the study or the analysis of data, with the following exceptions:

- The result of randomization, i.e. the treatment group assignment of individual subjects will be reported to the hospital pharmacist or designee by a dedicated email that no other trial personnel will have access to.
- Subjects with confirmed deterioration who were crossed-over during the First Period and subjects with confirmed deterioration at Week 16 will be unblinded at Week 16 as their further continuation in the Extension Period depends on their initial assignment as described in section 4.1 above. In the analysis of the primary endpoint these subjects will be considered as non-responders in the group they were randomized to.
- In case of medical emergencies as described in the protocol (section 5.6)

Only after completion of all procedures related to data cleaning, the medical review of the data, the finalization of the statistical analysis plan, the agreement on the final subject disposition, and the formal database lock the blind will be broken and the individual treatment assignment will be added to the clinical database for analysis

# 5. Sequence of Planned Analyses

## 5.1. Final Analyses and Reporting

As stated in section 4.1, this study consists of a double-blinded period, followed by an open-label extension period. The blind will however be maintained throughout the complete study to the extent possible; only for subjects who were switched during the first study period and show no further deterioration at Week 16 and for those subjects with confirmed deterioration at Week 16, the decision whether a subject is allowed to continue into the open-label period will imply whether the subject was initially treated with Octagam (Subject has to drop out) or Placebo (Subject continues). Otherwise the blind will not be broken before all subjects have completed the entire study and the final database has been locked and released for analysis according to the applicable standard operating procedures.

This process includes a data review, the identification and classification of any protocol deviations as detailed in section 7, and thus the subject disposition with respect to the analysis populations. All final, planned analyses identified in the protocol and in this SAP will be performed only after the last subject has completed the study, the subject disposition has been agreed and documented, and the final SAP has been approved.

Key statistics and study results will be made available to the study team following database lock and prior to completion of the final CSR by means of tables, figures and listings.

Any, post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in the final SAP, will be documented and reported in the CSR or its appendices. Any results from such unplanned analyses will also be clearly identified in the text of the CSR.

No interim analysis is planned.

# 6. Sample Size Determination

The sample size calculation is based on the target parameters for the evaluation of the primary endpoint, i.e. the proportions of responders in the Octagam 10% and the placebo group at the end of the 16 week efficacy period (First Period).

A total sample size of 84 subjects is required to show a significant difference in the proportion of responders between Octagam and placebo group with a power of 80%, under the assumption that the true proportions of responders are 0.6 in the Octagam group and 0.3 in the placebo group. The sample size calculation is based on Pearson's chi square test using a two-sided alpha level of 0.05.

A stratified analysis using Cochran-Mantel-Haenszel test will finally be applied as primary analysis, to account for the stratification of the randomization.

To have some additional safety margin with respect to unexpected drop-outs and with respect to the use of a stratified analysis, it is therefore planned to enroll a total of 94 evaluable subjects into the study.

The abovementioned assumptions for the true proportions of response were thoroughly discussed and agreed with an advisory board, consisting of several experts in this field.

## 6.1. Subject Replacement Policy

Not applicable. Withdrawals will not be replaced.

## 6.2. Premature Termination of the Study

Both, the responsible Investigators and the Sponsor, reserve the right to terminate the study as a whole or centre-wise at any time. Should this be necessary, the procedures will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests. Premature termination will be notified in accordance with applicable regulatory requirements. Please refer to the protocol (section 6.2.3) for further details on premature termination, in particular for the exact stopping criteria triggering the early termination of the entire study for safety reasons (6.2.3.1).

In case the study is terminated prematurely, the SAP will be revised to address all issues arising from such special circumstances, and to confirm or redefine the scope of the analysis.

# 7. Analysis Populations

The following populations will be considered for the statistical analysis:

The safety analysis set (SAF) consists of all subjects who received at least part of one infusion of Octagam or placebo.

The full analysis set (FAS) is defined according to the intention-to-treat principle and consists of all randomized subjects. It is expected that the FAS will coincide with the safety set.

The per-protocol set 1 (PP1) consists of all subjects of the FAS excluding those with significant protocol deviations that occurred before the Week 16 assessments, and which may have an impact on the analysis of the primary endpoint. This is the set of subjects for whom the primary endpoint can be evaluated as planned; it also includes subjects who deteriorated at 2 consecutive visits up to (including) Week 16 and that are therefore counted as non-responders, and also subjects that were withdrawn from the study for any AEs or insufficient response before Week 16. Protocol deviations in the open-label extension period are irrelevant for the definition of this population.

The per-protocol set 2 (PP2) consists of all subjects of the FAS who received at least part of one infusion of Octagam, excluding those with significant protocol deviations which may have an impact on the evaluation of the treatment effects of Octagam. This set of subjects is defined to allow the assessment of Octagam throughout the study and will not be used for comparisons with the Placebo group.

Only significant protocol deviations with the potential to affect the study results significantly, or to invalidate the interpretation of the data obtained, will lead to exclusion of subjects from the PP sets; protocol deviations to be considered will include (but will not be limited to):

- Violations of the study entry criteria
- Withdrawal criteria that developed during the study
- Wrong treatment or incorrect dose
- Prohibited concomitant medication (e.g. IGIV other than Octagam)

Analysis of the safety endpoints will be based on the safety set.

The primary endpoint will be evaluated on basis of the FAS and the PP1 set. The intent-to-treat analysis of the FAS population is considered the primary study outcome, and will be presented first in the statistical output. The primary analysis in the FAS will also include those subjects with significant protocol deviations that are unrelated to disease progression or lack of efficacy, but that have the potential to distort the TIS assessment. This would e.g. include subjects that start an intensive exercise during the first study period.

Because the PP1 set will include all subjects that deteriorated or dropped out for clinical reasons as described above, the difference between the FAS and the PP1 is expected to be small.

All other analyses will be based on the FAS set and/or the appropriate PP set; this will be specified in detail in the list of all tables, figures and listings.

Repetition of an analysis in the PP set might be skipped in case the PP population differs from the FAS by no more than 5 subjects; this does however not apply for the primary endpoint evaluation.

In general baseline tables will summarize data by randomized treatment. Tables by visit will summarize data by randomized treatment, but values obtained after the switch of treatment in first period will be excluded. Adverse events tables will summarize data according to actual treatment at time of AE, i.e. any adverse event will be considered to be associated with the most recent treatment administered, Octagam or Placebo, when summarizing the data. Patients who are switched to the other treatment during the first study period will therefore be considered to be at risk for adverse events in both treatment groups.

The membership of each subject in the respective analysis populations will be determined before the statistical analysis in a data review meeting by a panel consisting of a medical expert from the sponsor, the clinical project manager, the data manager and the study statistician.

All protocol deviations documented during the conduct of the study or identified at the data review process prior to DB lock will be reviewed and classified as minor or major and with respect to their significance for the planned analyses. Only significant protocol deviations with the potential to affect the study results or to invalidate the interpretation of the data obtained will lead to exclusion of subjects from the PP sets. This classification of protocol deviations is the joint responsibility of the clinical study manager, the study statistician, and Octapharma's responsible medical expert, and will be performed and documented before the database is locked and the statistical analyses are performed.

# 8. General Issues for Statistical Analysis

The main analysis will be the comparison between Octagam 10% and placebo on basis of the efficacy measures assessed in the 16 week efficacy period.

To evaluate the sustained benefit of treatment with Octagam 10%, and also the safety and tolerability of Octagam 10% in subjects with DM, all data collected during treatment with Octagam 10% throughout the study period will be used.

In addition to the confirmatory evaluation of the primary endpoint, descriptive summaries will be presented for each of the primary and secondary target variables. In general, these summaries will be presented for all patients overall and by treatment group, for each of the 3 strata (GDA at screening mild|moderate|severe), as totals and by treatment group within each stratum.

Descriptive subgroup analyses will be performed with respect to age, sex, race, and region (U.S. vs. Non-U.S.).

Depending on the number of infusions with reduced dose of 1.0 g/kg in the extension period, measures and events associated with this dose regimen will be contrasted with the regular 2.0 g/kg dose scheme.

Continuous, quantitative variable summaries will in general include the number of subjects with non-missing values (N), mean, standard deviation, median, minimum and maximum, 1st and 3rd quartile.

Categorical, qualitative variable summaries will include the frequency and percentage of subjects who are in the particular category. In general the denominator for the percentage calculation will be based upon the total number of subjects in the analysis population unless otherwise specified.

## 8.1. Analysis Software

Statistical analyses will be performed using SAS Software version 9.3 or higher.

## 8.2. Withdrawals

Subjects who withdraw from the study prematurely will be considered in all data presentations for which they contribute data.

## 8.3. Handling of Missing Data

In general, missing data will not be imputed, with a few exceptions. For ANCOVA analysis of changes from baseline to week 16, LOCF will be used in main model in case of missing values (e.g. due to early termination) and in case of switch to the alternate treatment group (as values obtained after the switch will not be included in the analysis).

For missing weight measurements the last available body weight will be used for all calculations related to dosing; in individual patient data listings missing data will however not be replaced by imputed values.

No analyses of the patterns of missing data will be done.

For adverse events the following will be applied:

An Adverse Event (AE) is defined as treatment-emergent, if first onset or worsening is after start of the first infusion of Octagam 10% or placebo.

If the start date and time of an AE are partially or completely missing, the AE will be assumed to be treatment-emergent if it cannot be definitely shown that the AE did not occur or worsen during the treatment emergent period (worst case approach). Missing dates and times will not be replaced.

For medications the following will be applied: A medication will be assumed to be concomitant if it cannot be definitely shown that the medication was not administered during the treatment period as defined in section 8.4 below. Missing dates will not be replaced.

## 8.4. Derived and Computed Variables

The following derived and computed variables have been initially identified as important for the analysis of the primary and secondary target variables. It is expected that additional variables will be required. The SAP will not be amended for additional variables that are not related to the primary target or key secondary target variables. Any additional derived or computed variables will be identified and documented in the SAS programs that create the analysis files. If the SAP is not amended, further derivations related to primary and secondary target variables will be described in the CSR.

- **Age** will be derived according to the usual definition that a person is n years old until she or he has completed her or his $(n+1)^{th}$ year of life, using the date of informed consent as the reference date. This is also the definition that will be applied for evaluation of the age related inclusion criteria. [Unit: years]
- **Body Mass Index**: BMI = (Body weight) / Height$^2$ [Unit: kg/m$^2$]
- The **treatment period** is defined as the period between the day of first treatment with study drug (Octagam or placebo) to the end of the observation period. This will usually be the termination visit.
- **Confirmed Deterioration** is defined as follows:
    - Physician's Global Disease Activity VAS worsening ≥ 2cm and MMT-8 worsening ≥ 20% on 2 consecutive visits,

  or

    - global extra-muscular activity worsening ≥ 2cm on the MDAAT VAS on 2 consecutive visits,

  or

    - any 3 of 5 CSM (excluding enzymes) worsening by ≥ 30% on 2 consecutive visits.

  For all criteria worsening will be determined by comparing to baseline values (Week 0).

# 9. Study Subjects and Demographics

## 9.1. Disposition of Subjects and Withdrawals

All subjects screened for the study will be accounted for. For screening failures only the reasons for not being enrolled in the study will be listed and summarized.

For all subjects enrolled in the study, descriptive summaries of population data will be provided overall and by treatment group; these will include

- The frequency and percent of subjects in each study period and analysis population by country and overall
- Number of subjects enrolled, number of subjects treated, number of completers
- Study withdrawals by reason of withdrawal

## 9.2. Protocol Deviations

Protocol deviations will be checked on complete data for all subjects prior to defining the analysis populations. The final decision regarding inclusion/exclusion of subjects from the analysis sets will be taken based on data listings and reports during data review meetings before database lock, data release and final analysis, applying the definitions in section 7.

Patients that have baseline scores but no score at 16 Weeks will in general be considered as non-responders in their respective (randomized) treatment group. If a Week 16 score is available, but not within the planned time window of 4 weeks ±4 days after the preceding infusion, the decision of whether a particular score can be used for analysis will be made at the data review meeting.

Major and significant protocol deviations will be summarized by type of deviation. Individual subjects with these protocol deviations will be listed.

A dedicated listing will cover the use of forbidden concomitant medication as detailed in the protocol, section 4.2.2.

## 9.3. Demographics and Other Baseline Characteristics

Descriptive summaries of the demographic and other baseline characteristics will be completed for the populations specified below, overall and by treatment group and stratum as applicable; these include:

- Demographics (Age, Gender, Race/Ethnicity, Height, Weight, BMI (calculated))

  (SAF, FAS, PP1, PP2)

- Medical History (SAF)

  *Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA, according to the version specified in the Data Management Plan). Incidences of findings in medical history will be summarized by MedDRA system organ class (SOC) and preferred term (PT)*

- Prior and Concomitant Medications (SAF)

  *Medications will be coded using the WHO Drug Dictionary (according to the version specified in the Data Management Plan). Incidences of prior and concomitant medications will be summarized by ATC level 2 and ATC level 4*

- Baseline Physical Examination, including vital signs (SAF)
- Baseline ECG

## 9.4. Measurement of Treatment Compliance

The following parameters will be listed and summarized per subject and/or per infusion cycle:

- Body weight
- Actual dose (total and per kg body weight, based on the latest available weight measurement)
- Total dose administered
- Total number of infusions administered
- Total volume of solution administered
- Number of infusions
- Infusion times
- Use of premedication
- Overall amount of product administered (only included in data listings)

Deviations from the planned treatment schedule will be summarized by counting the number of infusion cycles that deviate from the scheduled intervals by more than the allowed intervals, and by listing all cases with more than two days deviation individually.

# 10. Efficacy Analysis

## 10.1. Primary Endpoint

The primary endpoint measure 'response' will be assessed at Week 16 on bases of the TIS score detailed in section 3.2.1: a subject is defined as responder if

(i) the subject has a TIS score of ≥20 points at Week 16 and
(ii) the subject has not met "Confirmed Deterioration" criteria at 2 consecutive visits as defined in Section 8.4 up to (including) Week 16

Otherwise the subject will be counted as a non-responder in the treatment group he was randomized to Thus subjects who discontinued from the study prior to Week 16 will also be considered as non-responders.

The proportion of responders within both treatment groups will be compared by Cochran-Mantel-Haenszel test, stratified by global disease activity (randomization stratum), using two-sided alpha level of 0.05.The primary analysis will be considered as success if the proportion of responders is significantly higher in the Octagam group compared to the placebo group.

Moreover, an exact two-sided 95% confidence-interval will be constructed for the overall difference in the proportion of responders between Octagam and placebo group, using the 'exact riskdiff' option of the SAS FREQ procedure.

In a sensitivity analysis for the primary endpoint, a logistic regression model will be applied, including global disease activity and further baseline variables as applicable as covariates.

## 10.2. Secondary efficacy endpoints

All secondary efficacy endpoints will be analyzed and presented in full detail by means of descriptive statistics and inferential analyses as appropriate.

For TIS response at Week 16 by improvement category, the proportion of subjects with at least moderate improvement and the proportion of subjects with major improvement will be calculated together with subject counts and the associated 2-sided 95% confidence interval (CI) for the difference in the proportion of patients with improvement. Moreover, both treatment groups will be compared using a Cochran-Mantel Haenszel test, analogously as for the primary endpoint. The proportion of subjects in each treatment arm who meet confirmed deterioration criteria up to (including) Week 16 will be presented in the same way.

All mean changes to be evaluated as secondary endpoints (listed in section 3.2.2) will be presented by a full set of descriptive parameters: number of subjects with non-missing values, mean, standard deviation, median, minimum and maximum, 1st and 3rd quartile, 95% CI. Moreover, for all continuous secondary endpoints, an analysis of covariance (ANCOVA) will be used to analyze changes from baseline to Week 16. For patients who are switched to the alternate treatment before Week 16, the last value prior to switch will be carried forward to Week 16 and used to calculate change from baseline to Week 16. The model will include treatment and global disease activity as a fixed factor. Center will be included as random factor. The baseline value of the variable to be analyzed will be included as a covariate. Least square means will be derived and presented together with 95%-confidence intervals by treatment group. Moreover, two-sided 95% confidence intervals will be derived for the overall difference in least square means between Octagam and placebo treatment. As sensitivity analysis, a modified ANCOVA model will be used, where the changes from baseline to Week 16 are calculated based on Week 16 values, even if a patient is switched to the alternate

treatment before Week 16. To incorporate the switch into the model, the variable crossover (yes/no) which indicates if there was a switch to the alternate treatment will be included as additional factor into the ANCOVA model, as well as the treatment-by-cross-over interaction term.

In case the proportion of patients with missing values is greater than 10%, or if the modified ANCOVA detailed above gives a signal of divergence, the concerned data will be further reviewed and analyzed.

The time to at least minimal, at least moderate and major improvement in TIS, and the time to confirmed deterioration in the First Period and overall, will be summarized using based on Kaplan-Meier estimates that will also be presented graphically. For the analysis of improvement variables in the first period, the time to event will be censored at the time of switch to the alternate treatment group. A stratified log-rank test will be applied for time to event variables to compare both treatment groups. Cox regression models may be applied additionally to include randomization stratum and further baseline covariates in the analysis.

To also include all data from the extension period in such Kaplan-Meier analyses, we will look at the abovementioned events and their timely relationship to the first infusion of Octagam.

To confirm the sustained benefit of treatment with Octagam 10% , response rates at Week 40 and changes from baseline to Week 40 will be presented descriptively (overall and by randomized treatment), including 95% confidence intervals.

All individual core set measures (CSMs) used for the TIS, and all other efficacy endpoints will be analyzed and presented in full detail by means of descriptive statistics, including summary and frequency tables, as well as graphs according to the general principles described in sections 8 and 12.

The development of each CSM over time will be presented graphically.

The detailed list of all tables, figures and graphs, and the analysis populations used for each analysis will be provided in a separate document later, when all feedback from authorities will be available.

# 11. Safety and Tolerability Analyses

The safety analysis will comprise descriptive statistics, tabulations and listings of all treatment emergent adverse events (TEAEs), safety laboratory results, viral markers, vital signs, Wells' scores, Doppler scan results, and physical examination findings.

## 11.1. Adverse Events

All reported AEs will be coded according to MedDRA.

An AE is defined as treatment-emergent, if first onset or worsening is during the treatment period. Only treatment-emergent AEs (TEAEs) are accounted for in the analysis.

For each TEAE, the time relative to the start of the infusion cycle will be calculated and the TEAE will be classified as infusional AE if the onset is during the infusion cycle or within 72 hours after the end of the last infusion episode of the respective infusion cycle/visit.

All reported events will be listed and tabulated in full detail; in particular the following key figures will be presented:

- Total number of TEAEs reported by severity and overall
- Number of related TEAEs by severity and overall
- Number of TEEs and HTRs
- Number of adverse drug reactions (ADRs) and suspected ADRs
- Number of infusional AEs by severity and overall
- Number of infusion cycles with infusional AEs

Narratives will be prepared describing each death, other SAEs, and other significant AEs that are judged to be of special interest because of clinical importance, including all TEEs and HTRs reported.

The number and percentage of patients with TEAEs and the number of TEAEs will be summarized by actual treatment, unless otherwise specified, i.e. any adverse event will be considered to be associated with the most recent treatment administered, Octagam or Placebo, when summarizing the data.

Patients who are switched to the other treatment during the first study period will therefore be considered to be at risk for adverse events in both treatment groups. AE tables for the first period will summarize data within the following four groups:

1. Octagam – before or no switch
2. Octagam – after switch from Placebo
3. Placebo – before or no switch
4. Placebo – after switch from Octagam

Moreover, exposure adjusted incidence rates of TEEs will be presented under Octagam and Placebo treatment. These rates will be calculated per 100 patient months on corresponding treatment, and will be presented together with 95% confidence intervals, based on Poisson distribution. Rates will be shown under Octagam and Placebo treatment in the first period and under Octagam treatment over the total study period and for the extension period only. Also all rates will calculated including only infusions before reduction of the infusion rate, those after reduction of the infusion rate, and including all infusions.

## 11.2. Clinical Laboratory Evaluations

All laboratory data will be converted to standard units during the Data Management process. The laboratory data will be listed with suitable flags indicating abnormal values (L=Lower than reference range, H=Higher than reference range).

Summary statistics for the laboratory values as well as their changes from baseline at each time will be tabulated for all laboratory parameters.

## 11.3. Viral Markers

Virology markers will be assessed at the screening visit and at the (early) termination visit; these data will be listed as well with suitable flags indicating positive results. Furthermore shift tables will be presented to show any changes in the viral status during the study.

## 11.4. Vital Signs

To evaluate short-term tolerance, monitoring of vital signs including blood pressure, body temperature, pulse and respiratory rate will be performed at all infusion visits. These parameters will be summarized by infusion and measurement time, using the standard set of summary statistics for both, absolute values and changes from baseline, where the baseline value is the pre-infusion measurement.

## 11.5. Further Safety Evaluations

### 11.5.1. Physical Examination

A general physical examination will be performed at the screening visit and all relevant abnormalities will be documented. The physical examination will be repeated at the termination visit (irrespective of whether termination is regular or premature), and any clinically relevant worsening from the status at screening will be documented as an AE.

### 11.5.2. Wells Scores

To identify all occurrences of DVT and PE, Wells' probability scores will be assessed at all visits. If the DVT score is likely for DVT (≥2 points), a Doppler scan is performed, and D-dimers are evaluated. These parameters will be combined into a dedicated listing to facilitate the assessment of these TEAEs of special interest.

# 12. Reporting Conventions

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize presentation with common notations.

## 12.1. General Reporting Conventions

- All tables and data listings will be developed in landscape orientation, unless presented as part of the text in a CSR.
- Figures will in general also be presented in landscape orientation, unless presented as part of the text in a CSR. Exceptions are the Trellis plots that will be presented in portrait orientation.
- Legends will be used for all figures with more than one variable or item displayed.
- Figures will be in black and white, unless color figures have been identified as useful for discriminating presentation in the figure. Lines in figures should be wide enough to view the line after being photocopied.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g., μ, α, β).
- The ICH numbering convention is to be used for all tables, figures and data listings.
- All footnotes will be left justified and placed at the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the table, figure, or data listing. If more than four footnote lines are planned then a cover page may be used to display footnotes.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A zero (0) may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as DDMMMYYYY (e.g., 29AUG2001) format.
- All observed time values will be presented using a 24-hour clock HH:MM format (e.g. 15:26).
- Time durations will be reported in HH:MM notation. The use of decimal notation to present (display) time durations should be avoided (e.g. 0.083h = 5min) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.
- All tables, figures and data listings will have the name of the program, and a date stamp on the bottom of each output.

## 12.2. Population Summary Conventions

- Population(s) represented on the tables or data listings will be clearly identified in the title as “Population: <name of population>” where <name of population> is any of the analysis population names or abbreviations defined in section 7 (safety analysis set (SAF), full analysis set (FAS), etc.).

- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., ITT Females, Per-Protocol Males >60 years of age) used for analysis in a table or figure.
- Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxx), where appropriate.
- Population sizes shown with summary statistics are the samples sizes (n) of subjects with non-missing values.
- All population summaries for continuous variables will include: N, mean, SD, median, Q1, Q3, minimum and maximum.
- All percentages are rounded and reported to a single decimal point (xx.x %).

# 13. Tables, Listings and Figures

To be supplied in a separate document later when all feedback from authorities will be available.