Statistical Analysis Plan

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Document History

Version	Date	Author	Description
Final 1.0	24-May-2017	[redacted]	New Document
Final 2.0	13-Jun-2017	[redacted]	Update to match version 2 of the study protocol, in particular the revised definition clinically important deterioration.
Final 3.0	04-Jul-2017	[redacted]	Minor additions (urinalysis, physical examination frequency) to match version 3 of the study protocol.
Final 4.0	09-Jan-2018	[redacted]	Incorporation of changes triggered by FDA feedback and as reflected in protocol version 5, most important the removal of the low-dose arm and the adjustment of the sample size calculation.
Final 5.0	20-Jul-2018	[redacted]	Wording revised to make clear that patients discontinued before week 32 are also included in the analyses of secondary endpoints; incorporation of changes triggered by VHP questions and as reflected in protocol version 6 and 7.

Abbreviations

AE	Adverse Event	ITT	Intention-To-Treat
ATC	Anatomical Therapeutic Chemical	LOCF	Last Observation Carried Forward
BMI	Body Mass Index	MedDRA	Medical Dictionary for Regulatory Activities
CDASI	Cutaneous Dermatomyositis Disease Area and Severity Index	MMT	Manual Muscle Testing
CI	Confidence Interval	PE	Pulmonary Embolism
CRO	Contract Research Organization	PP	Per Protocol
CSM	Core Set Measure	PT	Preferred Term
CSR	Clinical Study Report	QoL	Quality of Life
DB	Database	SAE	Serious Adverse Event
DM	Dermatomyositis	SAF	Safety Set
DVT	Deep Vein Thrombosis	SAP	Statistical Analysis Plan
ECG	Electrocardiogram	SCIG	Subcutaneous Immunoglobulin
FAS	Full Analysis Set	SF-36v2	Short Form 36 Items Health Status Version 2
FDA	Food and Drug Administration	SOC	System Organ Class
HAQ	Health Assessment Questionnaire	TEAE	Treatment Emergent Adverse Event
HTR	Hemolytic Transfusion Reaction	TEE	Thromboembolic Event
ICH	International Conference on Harmonization	TIS	Total Improvement Score
IgG	Immunoglobulin G	VAS	Visual Analog Scale
IGIV	Immunoglobulin Intravenous	WHO	World Health Organization
IRT	Interactive Response Technology		

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1. Preface

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Octapharma Protocol SCGAM-02: *Double-blind, randomized, placebo-controlled phase III study evaluating efficacy and safety of subcutaneous human immunoglobulin (octanorm) in patients with dermatomyositis*.

This phase III study is conducted to determine the efficacy of subcutaneous immunoglobulin *octanorm* in the maintenance treatment of patients with dermatomyositis (DM) who have previously responded to IGIV therapy. It is designed as parallel group, double-blind, randomized, multicenter study with up to 2 weeks for screening, followed by a 32-week treatment period and 1 week of safety follow-up.

Patients eligible after screening will be randomized 1:1 to receive infusion cycles of either *octanorm* 0.5 g/kg/week or placebo every week for 32 weeks. The weekly infusion will be performed in two separate sessions, either on the same day or on two consecutive days or with maximum one day in between two sessions.

The primary endpoint is defined as the occurrence of a clinically important deterioration during the treatment period. The safety follow-up will ensure a complete record on all safety assessments, including adverse events and changes in concomitant medications.

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 SCGAM-02, Version 07, dated 16-Jul-2018

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.

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[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 the statistical analyses to be performed on data collected in study SCGAM-02, 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 submissions 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.

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[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 this study is to determine the efficacy of subcutaneous immunoglobulin *octanorm* in the maintenance treatment of DM patients who have previously responded to IGIV therapy.

3.1.2. Secondary Objectives

The secondary objectives of the study are:

- To assess other efficacy outcomes at the end of study (week 32 or earlier drop-out visit)
- To assess the effect of *octanorm* on Quality of Life (QoL) measures
- To assess the treatment compliance of home treatment with *octanorm*
- To evaluate the safety and tolerability of *octanorm* in subjects 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 occurrence of clinically important deteriorations during the treatment period in the *octanorm* arm and the placebo arm until week 32.

Clinically important deterioration is defined as

1) MMT-8 worsening ≥ 6 points (scale of 150) OR CDASI (Global Disease Activity) worsening ≥ 5 points, AND
2) A Physician's Global Disease Activity VAS worsening ≥ 2 cm.

Please refer to the protocol for further details on these assessments of disease status and progress.

3.2.2. Secondary Target Variables

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

- The modified Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI): Mean change from baseline (Week 0, defined as end of IGIV therapy) to end of the treatment period (Week 32 or earlier drop-out visit)
- Six Myositis core set measures (CSMs) used for calculation of the Total Improvement Score (TIS), i.e. MMT-8, Physician's Global Disease Activity, Patient's Global Disease Activity, Extra-Muscular Disease Activity, Muscle enzymes, and Health Assessment Questionnaire (HAQ): Mean change from baseline to end the treatment period
- SF-36v2 Health Survey: Mean change from baseline to end the treatment period
- TIS: Mean change from baseline to end the treatment period
- Time to clinically important deterioration during the treatment period
- Number and type of deviations from protocol requirements relating to home treatment (dosing, timing)

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For Safety, target variables will be:

Throughout the entire Period:

- Occurrence of all adverse events with particular emphasis on thromboembolic events (TEEs) and hemolytic transfusion reactions (HTRs)
- Local injection site reactions
- Vital signs (blood pressure, heart rate, body temperature and respiratory rate)
- Physical examination
- Laboratory parameters (hematology, clinical chemistry, urinalysis)

At Baseline and end of Treatment Period:

- Tests for viral safety
- Pregnancy test, if applicable

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4. Study Methods

4.1. Overall Study Design and Plan

Study SCGAM-02 is designed as a prospective, parallel group, double-blind, randomized, multicenter phase III study in adults of both genders with definite or probable DM according to the criteria of Bohan and Peter who have previously responded to IGIV therapy.

It is expected that a number of patients will also have participated in study GAM10-08 (a currently ongoing phase III study on efficacy and safety of Octagam 10% in DM patients). As DM is a rare disease, this should facilitate recruitment; for the same reason we plan for about 45 sites to participate in countries worldwide with emphasis on European countries and North America, and do not expect that any single center will enroll a decisive proportion of the overall study population.

The duration of the entire study for each subject will be up to 35 weeks, consisting of up to 2 weeks for screening, 32 weeks of double-blind treatment (*octanorm* 0.5 g/kg/week or placebo), and a 1 week safety follow-up period.

For patients from GAM10-08 study who directly enter this study, the GAM10-08 Termination Visit is supposed to coincide with the SCGAM-02 Baseline Visit; the GAM10-08 Week 40 test results will be used for SCGAM-02 Baseline Visit evaluations.

Eligible subjects after screening will be randomized 1:1 to receive up to 32 infusion cycles of either *octanorm* 0.5 g/kg/week or placebo every week. An infusion cycle comprises two infusion sessions administered over 1 to 3 days for a given weekly administration.

In case of clinically important deterioration during the SCIG treatment period, subjects will be discontinued from the study and undergo a drop-out visit. Such patients may optionally receive Octagam 10% as IGIV rescue medication (2g/kg BW one time, provided or reimbursed by the sponsor) or rescue treatment according to standard of care at the site by the treating physician. Such patients will be regarded as completers, as those patients reached the primary endpoint and thus completed the study as intended.

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 (Baseline) will be block randomized to one of the 2 treatment arms: *octanorm* 0.5 g/kg/week or placebo (0.9% sodium chloride) in a balanced ratio of 1:1 by means of a permuted block randomization scheme; varying block sizes may be used to facilitate balanced enrolment.

The block size and the randomization scheme will only be available to the statisticians responsible for creating it, and the programmer implementing the scheme into the Interactive Response Technology (IRT) system. No information on treatment assignment will be communicated to study site personnel or to the sponsor or any CRO personnel responsible for the conduct of the study or the analysis of data, with the exception of medical emergencies as described in the protocol (section 5.6).

Each weekly infusion cycle will consist of 2 infusion sessions as described above. If a subject is randomized to placebo, the same volume with the same infusion rate will be applied as if the subject would have been randomized to *octanorm*.

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In order to maintain the blind, IgG plasma level results performed at the central laboratory will not be revealed to the Sponsor, the Investigator and other blinded personnel at the study site.

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.

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5. Sequence of Planned Analyses

5.1. Final Analyses and Reporting

As described above, all patients should be followed for 32 weeks of SCIG treatment or until a clinically important deterioration occurs. The blind will be maintained throughout the complete study, including patients withdrawn from the study for deterioration and treated with IGIV as a rescue treatment. Only in case of a medical emergency individual patients may be unblinded; 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.

Deviations from the analyses described in the protocol, this SAP or its appendices will be described and justified in a protocol amendment and/or in the final CSR.

No interim analysis is planned.

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6. Sample Size Determination

The sample size calculation is based on the target parameter for the evaluation of the primary endpoint, i.e. the proportions of patients with clinically important deterioration in the active treatment arm (*octanorm* 0.5 g/kg/week) and the placebo arm until the end of the 32 week treatment period. Patients who drop out prematurely or receive rescue treatment for any reason will also be analyzed as patients with clinically important deterioration.

The following assumptions for the true proportion of patients to be analyzed as patients with clinically important deterioration, which will include all dropouts, were chosen for the sample size calculation after thorough discussion with Steering Committee members involved in the treatment of DM patients:

- *Octanorm* arm: 27% (this corresponds to a failure rate of 18.89% in patients randomized to *octanorm* who completed the study per protocol plus a 10% drop-out rate)
- Placebo arm: 58% (this corresponds to a failure rate of 53.33% in patients randomised to Placebo who completed the study per protocol plus a 10% drop-out rate)

The pair of hypotheses tested is: H_0: $P_O = P_P$ vs. H_A: $P_O \neq P_P$

where P_O and P_P denote the proportions of patients with clinically important deterioration in the *octanorm* and placebo arm respectively.

With these assumptions, a sample size of 39 patients per treatment arm will be needed to achieve a power of 80% to detect a difference between the group proportions, using the Pearson Chi-square Test for Proportion Difference at a significance level of α=0.05. It is therefore planned to enroll a minimum of 78 patients, randomized to the two treatments groups in a balanced 1:1 ratio.

6.1. Subject Replacement Policy

Patients withdrawn from the study because of safety or efficacy reasons will not be replaced; these premature terminations will in any case establish clinically important deteriorations and be analyzed as such. Patients withdrawn from the study for any other reason, e.g. major protocol violation, pregnancy or administrative reasons will also not be replaced. However, if there is a substantial number of withdrawals, the Sponsor and the Coordinating Investigator will consult with the IDMC (without breaking the blind), and decide on a possible replacement policy.

6.2. Premature Termination of the Study

Both, the responsible Investigators and the Sponsor, reserve the right to terminate the study 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.

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7. Analysis Populations

The following populations will be considered for the statistical analysis:

The all patients enrolled set includes all patients with a non-empty case report form who signed the informed consent.

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

The full analysis set (FAS) is defined according to the intention-to-treat (ITT) principle and consists of all randomized subjects of the SAF who satisfy all major eligibility criteria and for whom any post screening data are available. It is expected that the FAS will coincide with the safety set, only patients who could otherwise only be regarded as artefacts in the final ITT analysis would be excluded from the FAS. Examples for such special circumstances would include a wrong diagnosis (if it turns out that a patient does in fact not suffer from dermatomyositis) or if the patient was in fact not previously treated with IgG. Also the exclusion of patients without any data post randomization will help to avoid artefacts that cannot contribute any meaningful data to the analysis; this cannot introduce any bias due to the blinded design of the study.

The per-protocol set (PP) consists of all subjects of the FAS excluding those with significant protocol deviations that 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.

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 set; 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
- Subjects who had no CSM or CDASI at Week 32

Protocol deviations during the safety follow up are irrelevant for the definition of the PP set.

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 PP 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 PP analysis will be conducted to assess the robustness of the result. The level of accordance between these two analyses will be discussed in the study report; in case the p-values obtained differ in terms of significance (i.e. above/below 0.05), this will be especially stressed.

All other analyses will be based on the FAS set and/or the PP set as appropriate; 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.

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

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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 agreed and documented before the database is locked and the statistical analyses are performed.

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8. General Issues for Statistical Analysis

The primary, confirmatory analysis will be the comparison between *octanorm* and placebo with respect to the proportion of patients with clinically important deterioration until week 32.

In addition to the confirmatory evaluation of the primary endpoint, all data collected will be listed and presented by means of descriptive statistics and comparisons between the treatment groups.

In general, statistical summaries will be presented for all patients overall and by treatment group in a side-by-side manner.

Descriptive subgroup analyses will be performed with respect to age, sex, race (if the study population is sufficiently diverse for meaningful comparisons), and region (U.S. vs. Non-U.S.); in particular the primary efficacy outcome will be presented for each of these subgroups.

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.

If appropriate, continuous variables may be categorized and additionally treated as ordinal variables.

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. Patients who drop out prematurely or receive rescue treatment for any reason prior to week 32 will also be analyzed as patients with clinically important deterioration in the evaluation of the primary endpoint.

8.3. Handling of Missing Data

In general, missing data will not be imputed, with a few exceptions. If a subject is prematurely withdrawn from the study, or misses data required for the evaluation of the primary endpoint, this subject will be analyzed as having a clinically important deterioration. For missing weight measurements the last available body weight will be used for all calculations related to dosing; in individual patient data listings such last observations carried forward (LOCF) will be tagged.

Missing data in other variables will not be replaced by any method of imputation; instead, the frequency of missing values will be presented.

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 *octanorm* 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.

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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 group:** For subgroup analyses related to age we initially plan for the following age groups: 18-39 years (young adults) / 40-65 years (middle-aged) / >65 years (elderly). In case the actual age distribution of the study population results in groups of very different sizes, these defining intervals might be adjusted in a subsequent SAP, but before the blind is broken.
- **Body Mass Index**: BMI = (Body weight) / Height^2 [Unit: kg/m^2]
- The **treatment period** is defined as the period between the first treatment with study drug (*octanorm* or placebo) to the end of the observation period. This will usually be the termination visit (Week 32 or earlier in case a patient is discontinued from the study).
- **Clinically important Deterioration** is defined as
    1) MMT-8 worsening ≥ 6 points (scale of 150) OR CDASI worsening ≥ 5 points, AND
    2) A Physician's Global Disease Activity VAS worsening ≥ 2 cm.

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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 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 analysis population by country and overall
- Number of subjects enrolled, randomized, treated, and the number of completers
- Study withdrawals by reason of withdrawal

Individual patient assignments to the analysis populations will be listed, including the reasons for any exclusion from an analysis population.

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 made based on data listings and reports during data review meetings before database lock, data release and final analysis, applying the definitions in section 7.

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; these include:

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

  (SAF, FAS, PP)

- 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
- Participation in study GAM10-08 (SAF)

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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 sessions that deviate from the scheduled intervals by more than the allowed intervals, and by listing all cases with more than two days deviation individually.

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10. Efficacy Analysis

10.1. Primary Endpoint

The primary endpoint measure 'clinically important deterioration' is medically defined in section 8.4, and will be assessed throughout the study until the last visit at Week 32. For the analysis of the primary endpoint, a patient will be considered to have a clinically important deterioration

(i) if the subject fulfills the definition given in section 8.4 at any time during the treatment period OR
(ii) if the subject was withdrawn from the study or received rescue treatment for any reason

If a subject is prematurely withdrawn from the study prior to week 32, or misses data required for the evaluation of the primary endpoint, this subject will be analyzed as a treatment failure, i.e. as having a clinically important deterioration. Because of the double-blind design of the study, and because there is no conceivable connection between the randomized treatment arm and events completely unrelated to study procedure (like e.g. relocation to another city or pregnancy), we trust that any such cases will be distributed uniformly between the treatment arms, and thus not distort the statistical evaluation.

However, to verify this assumption, each withdrawal will be assessed individually by an independent team of medical experts, in compliance with an EU Member State request, and the primary efficacy endpoint will also be analyzed on basis of their individual evaluation of treatment stops. This committee will assess for each patient individually whether she/he should be analyzed as failure or non-failure, based on the reason for treatment stop as well as all other relevant data available. The patients affected by this procedure will be listed with a brief statement justifying the individual classification. This analysis will be done for the FAS and the PP population, and any differences to the primary endpoint outcome will be discussed in the report.

The proportions of patients with clinically important deterioration within the *octanorm* and the placebo arm will be compared by means of the Pearson Chi-square Test for Proportion Difference as implemented in the SAS FREQ-procedure, when specifying the /chisq option for a 2x2 table statement. A confidence level of α=0.05 will be applied, and the associated 95% confidence limits for the proportion (risk) difference will be presented.

The pair of hypotheses tested is: H_0: $P_O = P_P$ vs. H_A: $P_O \neq P_P$

where P_O and P_P denote the proportions of patients with clinically important deterioration in the *octanorm* and placebo arm respectively.

The primary efficacy outcome will also be presented for the subgroups defined by age, sex, race (if feasible) and geographical region (North America / Europe). There will be no adjustments for covariates.

Individual patient data listings will be provided for the primary efficacy endpoint, including membership to the analysis sets, individual responses and response criteria fulfilled by visit.

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 CDASI, SF-36v2, TIS, and the individual CSMs the mean change from Baseline (Week 0) to the end of treatment 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.

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Moreover, for those continuous secondary endpoints, an analysis of covariance (ANCOVA) will be used to analyze changes from baseline to end of treatment (Week 32 or earlier end of treatment visit). The model will include treatment 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 Octanorm and placebo treatment.

The time to clinically important deterioration will be analyzed by the product-limit method for the analysis of survival data, and presented as Kaplan-Meir plots alongside a Log-Rank test for differences between treatment groups.

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.

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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.

The safety analysis will be made with the SAF population. Patients will be analyzed by actual treatment, data tabulations will present the treatment arms and the total count in a side-by-side manner.

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 exact time of onset will be recorded. A TEAE will be classified as infusional AE if the onset is during the first infusion session of a given infusion cycle, between the two infusion sessions of the same cycle, or within 72 hours after the end of the 2nd infusion session of the same infusion cycle.

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

- Total incidence and number of TEAEs reported by severity and overall
- Incidence and number of related TEAEs by severity and overall
- Incidence and number of TEEs and HTRs
- Incidence and number of SAEs
- Incidence and number of TEAEs leading to withdrawal
- Incidence and 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.

11.2. Local Injection Site Reactions

Local injection site reactions will be listed, and tabulated by treatment group and MedDRA preferred term for comparison of the total number of reactions, type of reaction, severity and time of occurrence (treatment week).

11.3. 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.

11.4. 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.

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11.5. 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.

11.6. Further Safety Evaluations

11.6.1. Physical Examination

A general physical examination will be performed at the screening and baseline visit and all relevant abnormalities will be documented. The physical examination will be repeated at each study visit, including 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.

11.6.2. 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.

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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.).

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- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., FAS 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%).

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13. Tables, Listings and Figures

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

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