CLINICAL STUDY PROTOCOL

DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED PHASE III STUDY EVALUATING EFFICACY AND SAFETY OF SUBCUTANEOUS HUMAN IMMUNOGLOBULIN (OCTANORM) IN PATIENTS WITH DERMATOMYOSITIS

Investigational Product:	*octanorm* (human normal immunoglobulin G with 16.5% protein content)
Indication:	Dermatomyositis (DM)
Study Design:	Double-blind, randomized, placebo-controlled, parallel group, multicentre, comparative efficacy and safety study.
Sponsor:	Octapharma Pharmazeutika Produktionsges.m.b.H. Oberlaaer Str. 235, 1100 Vienna, Austria
Study Number:	SCGAM-02
EudraCT and/or IND Number:	EudraCT: 2017-002710-31 / IND: 17515
Development Phase:	Phase 3
Planned Clinical Start:	Quarter 3, 2018
Planned Clinical End:	Quarter 2, 2020
Date of Protocol:	16-July-2018
Version:	Version 07
Co-ordinating Investigator:	[redacted] REVMATOLOGICKÝ ÚSTAV Na Slupi 450/4, Prague, 128 50 Czech Republic

STUDY OUTLINE

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H., 1100 Vienna, Austria	
Name of Investigational Product: *octanorm*	**Protocol Identification Code:** SCGAM-02
Name of Active Ingredient: Human Normal Immunoglobulin	**Date of Final Protocol:** 16-July-2018

Title of Study:

Double-blind, Randomized, Placebo-Controlled Phase III Study Evaluating Efficacy and Safety of Subcutaneous Human Immunoglobulin (*octanorm*) in Patients With Dermatomyositis (SCGAM-02)

Indication:

Dermatomyositis (DM).

Number of Study Centre(s):

Approximately 45 selected study sites worldwide.

Objectives:

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.

Secondary Objectives:

The secondary objectives of this study are:

- to assess other efficacy outcomes at the end of study (Week 32 or 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.

Study Design:

Double-blind, randomized, placebo-controlled, parallel group, multicenter, comparative efficacy and safety study.

Number of Subjects/Patients:

A minimum of 78 adult subjects of both genders are to be enrolled.

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Subject/Patient Selection Criteria:

Inclusion Criteria:

1. Subjects with diagnosis of definite or probable DM according to the Bohan and Peter criteria.
2. Subjects who have responded to IGIV treatment as assessed by the treating physician and being on a stable dose for at least 3 months on 2 g/kg bodyweight (+/- 10%) prior to study enrolment.
3. For subjects being on other medication(s) for the treatment of DM (immunosuppressants, corticosteroids): a) subject was on such medication(s) at the start of IGIV treatment in the first place, and b) received such medication(s) for at least 3 months prior to study enrolment and at a stable dose for at least 4 weeks prior to study enrolment at the maximally allowed conditions as per Table 2 (see section 4.2.1).
4. MMT-8 score ≥144, with at least 3 other CSM to be normal or near normal as per the following criteria: Visual Analogue Scale [VAS] of patient global disease activity ≤2 cm, physician's global disease activity ≤2 cm, extra-muscular disease activity ≤2 cm; no muscle enzyme >4 times upper limit of normal due to myositis, Health Assessment Questionnaire [HAQ] ≤0.25.
5. Males or females ≥ 18 to <80 years of age.
6. Voluntarily given, fully informed written consent obtained from subject before any study-related procedures are conducted.
7. Subject must be capable and willing to understand and comply with the relevant aspects of the study protocol.

Exclusion Criteria:

1. Cancer-associated myositis, defined as the diagnosis of myositis within 2 years of the diagnosis of cancer (except basal or squamous cell skin cancer or carcinoma in situ of the cervix that has been excised and cured - at least 1 year for basal or squamous cell skin cancer and 5 years for carcinoma in situ of the cervix must have passed since excision).
2. Evidence of active malignant disease or malignancies diagnosed within the previous 5 years (including hematological malignancies and solid tumors) or breast cancer diagnosed within the previous 10 years. Subjects >5 years (>10 years for breast cancer) of cancer diagnosis who have been treated and are in remission are allowed.
3. Subjects with overlap myositis (except for overlap with Sjögren's syndrome),

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connective tissue disease associated DM, inclusion body myositis, polymyositis, juvenile dermatomyositis or drug-induced myopathy.

4. Subjects with immune-mediated necrotizing myopathy with absence of typical DM rash.
5. Subjects with generalized, severe musculoskeletal conditions other than DM that prevent a sufficient assessment of the subject by the physician.
6. Subjects who received blood or plasma-derived products (other than IGIV) or plasma exchange within the last 3 months before enrolment.
7. Subjects with administration of permitted concomitant medications exceeding the maximally allowed conditions as per section 4.2.1.
8. Subjects with administration of forbidden concomitant medications within the washout periods as defined in Table 3: see section 4.2.2.
9. Subjects starting or planning to start a physical therapy–directed exercise regimen during the trial. Subjects on stable physical therapy for >4 weeks are allowed but the regimen should remain the same throughout the trial.
10. Cardiac insufficiency (New York Heart Association III/IV), cardiomyopathy, significant cardiac dysrhythmia requiring treatment, unstable or advanced ischemic heart disease.
11. Severe liver disease, with signs of ascites and hepatic encephalopathy.
12. Severe kidney disease (as defined by estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2).
13. Known active or chronic hepatitis B, hepatitis C or HIV infection. Past hepatitis B or C infection that has been cured is allowed.
14. Subjects with a history of deep vein thrombosis within the last year prior to study enrolment or pulmonary embolism ever.
15. Body mass index >40 kg/m2 and/or body weight >120 kg.
16. Medical conditions whose symptoms and effects could alter protein catabolism and/or IgG utilization (e.g. protein-losing enteropathies, nephrotic syndrome).
17. Known IgA deficiency with antibodies to IgA.
18. History of hypersensitivity, anaphylaxis or severe systemic response to immunoglobulin, blood or plasma derived products or any component of *octanorm* 16.5% such as polysorbate 80 or to sodium chloride.
19. Known blood hyperviscosity, or other hypercoagulable states.
20. Subjects with a history of drug abuse within the past 5 years prior to study enrolment.
21. Participating in another interventional clinical study with investigational treatment

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within 3 months prior to study enrolment. Subjects who participated in the Octagam 10% Dermatomyositis Study (GAM10-08) can be included.

22. Women who are breast feeding, pregnant, or planning to become pregnant, or are unwilling to apply an effective birth control method (as per protocol section 7.3.9 b) up to four weeks after the last IMP infusion received.

Test Product, Dose, and Mode of Administration:

octanorm 16.5%, human normal immunoglobulin for subcutaneous (SC) administration. *octanorm* 16.5% is delivered in vials and must be stored and transported light-protected at 2 °C to +8 °C (36 °F to 46 °F) and must not be frozen.

Subjects are randomly assigned to either one of the following treatment arms

- 0.5 g/kg/week *octanorm*
- Placebo

octanorm or placebo (see below) has to be administered subcutaneously every week (±2 days) using a syringe driver for precise infusion rates. The total dose/volume of a weekly infusion will be calculated on the basis of the body weight. The weekly infusion will be performed in two separate sessions (= 1 infusion cycle for a given weekly administration). An infusion cycle comprises both sessions to be administered on 1 or 2 days, either on the same day or on two consecutive days or with maximum one day in between two sessions.

Up to 6 injection sites and up to 2 syringe drivers can be used simultaneously in one session. In case the allowed flow rate cannot be reached with the 2 syringe drivers because of currently approved/available syringe drivers in a particular country – up to 4 syringe drivers can be used, although the number of simultaneous injection sites remains maximum 6. Up to 12 injection sites can be used consecutively during a single session. Injection sites should be at least 2 inches (approx. 5 cm) apart. The actual sites of injection should be changed with each administration.

In the first two weeks (infusion cycles 1-2), 20 mL per injection site should not be exceeded. In the next two weeks (infusion cycles 3 – 4), max. 25 mL per injection site are permitted. In infusion cycles 5 – 12, this may gradually be increased to 35 mL/site. Starting with infusion cycle 13 and when the previous volumes were well tolerated, increases of ≤ 10 mL/site per infusion cycle can be made up to a maximum of 60 mL/site.

The initial flow rate in the first two weeks is 20 mL per hour per site. For subsequent infusions, the flow rate may gradually be increased to a maximum of 30 mL/hr/site as tolerated. The maximum flow rate for all sites combined should not exceed a total of 180 mL per hour.

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For safety or tolerability reasons, the above infusion volumes per site and flow rates can be lowered as per discretion of the investigator; any such changes need to be recorded.

Duration of Treatment:

The duration of the entire study for each subject will be up to 35 weeks and consists of the following segments: up to 2 weeks for Screening, then 32 weeks of double-blind treatment period, followed by a 1 week safety follow-up period.

For patients from GAM10-08 study screening for SCGAM-02 should be performed within 2 weeks prior to GAM10-08 Week 40 Termination Visit, to determine eligibility. For them GAM10-08 Week 40 Termination Visit will be SCGAM-02 Baseline Visit. GAM10-08 patients not able to follow this schedule, and if they receive other IGIV in between, can be included as well if they fulfil the selection criteria.

Reference Therapy, Dose, Mode of Administration:

0.9% sodium chloride.

Subjects randomized to receive placebo will receive the same volume of 0.9% sodium chloride as if the subject would have been randomized to 0.5 g/kg *octanorm* 16.5%.

Study Outcome Parameters (Primary and Secondary Endpoints):

Efficacy Endpoints:

Primary

- Proportion of patients with clinically important deterioration during the treatment period up to Week 32. A patient with clinically important deterioration is defined as a patient with 1) MMT-8 worsening ≥ 6 points (scale of 150) OR CDASI (Total Activity Score) worsening ≥ 5 points, AND 2) a Physician's Global Disease Activity VAS worsening ≥2 cm.

Secondary

- Mean change from baseline (Week 0-defined as end of IGIV therapy) to end of the treatment period (Week 32 or Drop-Out Visit) in:
  - Modified Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI);
  - Six Myositis CSM: MMT-8, Physician's Global Disease Activity, Patient's Global Disease Activity, Extra-Muscular Disease Activity, Muscle enzymes,

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Health Assessment Questionnaire (HAQ);
- SF-36v2 Health Survey.

- Mean change in TIS from Baseline (Week 0) to end of treatment period (Week 32 or Drop-Out Visit).
- Time to clinically important deterioration during the treatment period.
- Number and type of deviations from protocol requirements relating to home treatment (dosing, timing).

Safety Parameters:

Safety (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).

Safety:

- Tests for viral safety (at Baseline and end of Treatment Period)
- Pregnancy test, if applicable (at Screening and end of Treatment Period).

Study Procedures:

Screening procedures must be performed within two weeks prior to the planned Baseline Visit; the Baseline Visit is to be performed 4 weeks (+/- 4 days) after the last pre-study IGIV treatment. For patients from Study GAM10-08 screening for SCGAM-02 should be performed within 2 weeks prior to GAM10-08 Week 40 Termination Visit, to determine eligibility. For them GAM10-08 Week 40 Termination Visit will be SCGAM-02 Baseline Visit. GAM10-08 Week 40 test results will be used for SCGAM-02 Baseline Visit evaluations. GAM10-08 patients not able to follow this schedule, and if they receive other IGIV in between, can be included as well if they fulfil the selection criteria.

Subjects eligible after screening will be randomized 1:1 to receiving up to 32 infusion cycles of either *octanorm* 0.5 g/kg/week or placebo every week for 32 weeks.

During the first four weeks (first 4 infusion cycles from Visit 2 to Visit 3), all infusions will be administered at the study site. Apart from Visit 3, where at least the first session of an infusion cycle will also be administered at the site, the next two weeks can be performed

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either at the patient´s home by the mobile healthcare research nurses or at the site (decision to be taken by Investigator and patient based on previous experience). Thereafter, SCIG infusions will be administered at home by mobile healthcare research nurses, apart from Visits 4-9, where at least the first session of an infusion cycle will be administered at the site. Before starting home treatment, a diary will be provided to the patients for documenting AEs and local tissue reactions at injection sites, body temperature around 1 hour after the end of the infusion, and any changes in concomitant drug and non-drug therapies between visits. The date of home treatments, batch numbers, number of vials, volume and speed of infusion, number and location of injection sites will be recorded by the mobile nurses. Based on the Investigator´s decision a home infusion can be replaced with an on-site infusion if considered medically relevant.

In case of clinically important deterioration during the treatment period, subjects will be discontinued from the study, will undergo a termination visit and may optionally receive Octagam 10% as IGIV rescue medication (2g/kg BW one time, provided by the sponsor) or rescue treatment according to standard of care at the site by the treating physician. Octagam 10% or any other commercially available IGIV as optional IGIV rescue medication can be also reimbursed by the sponsor (2g/kg BW one time). IGIV as rescue medication should be administered with infusion rate not higher than 0.04 mL/kg/min (240 mg/kg/h).Subjects dropping out due to clinically important deterioration anytime during the treatment period will in any case be classified as patient with deterioration in the statistical analysis.

The following AEs are defined as Adverse Events of Special Interest (AESI): TEEs and HTRs. An Independent Data Monitoring Committee (IDMC) will be established to review all AESI in real time, to review relevant safety data periodically and to give advice on the continuation, modification, or termination of the study.

The study assessments and scheduled time points are summarized in the flowchart following this Study Outline.

Statistical Analysis Plan:

A formal statistical analysis plan describing all details of the analyses to be performed will be prepared by the study statistician and approved by the sponsor before the start of the statistical analysis.

The primary endpoint of clinically important deterioration will be evaluated at end of treatment (week 32 or Drop-Out visit), and the proportion of patients who deteriorated in the *octanorm* group will be compared to the proportion of such patients in the placebo group by means of a Chi-square test.

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The rates of patients to be analysed as patients with clinically important deterioration, which will include all dropouts, were set to 58% in the placebo arm (this corresponds to a failure rate of 53.33% in patients who completed the study per protocol plus a 10% drop-out rate), and to 27% in the octanorm group (this corresponds to a failure rate of 18.89% in patients who completed the study per protocol plus a 10% drop-out rate).

This yields a sample size of 39 patients per treatment arm needed to achieve a power of 80% to detect a difference between the group proportions at a significance level of α=0.05, and thus to a minimum of 78 subjects to be enrolled in this study.

The evaluation of the primary efficacy endpoint will be based on the full analysis set defined according to the intention-to-treat principle.

The analysis of safety will be based on the safety analysis set which includes all patients who received at least part of one infusion of *octanorm* or placebo.

Table 1: Flowchart of Assessments Performed During the Study

ASSESSMENTS	Screening[6]	Baseline[6]								Termination Visit Week 32 / Drop-out Visit	Safety Follow-up[8] Week 33	Throughout Un-scheduled Visit
Visit / Timepoints: weeks after 1st treatment	Visit 1 Week -2 to 0	Visit 2 Week 0	Visit 3 Week 4	Visit 4 Week 8	Visit 5 Week 12	Visit 6 Week 16	Visit 7 Week 20	Visit 8 Week 24	Visit 9 Week 28			
Informed consent	X[7]											
Eligibility criteria	X											
Demographic & baseline characteristics	X											
Medical history/Prior medication	X											
Standard ECG	X											
Pregnancy test (in WOCBP)	X									X		
Blood for viral markers		X								X		
Blood sample for D-dimers		X										
Randomization		X[2]										
Physical examination[2]	X	X	X	X	X	X	X	X	X	X	X[9]	X
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[2]	X	X			X			X		X		
Safety laboratory[2]	X	X	X	X	X	X	X	X	X	X	X[9]	X
Serum IgG[2]		X	X	X	X	X	X	X	X	X		X
Enzymes[2]	X	X	X	X	X	X	X	X	X	X	X[9]	X
Biomarkers blood sample	X				X			X		X		
Blood sample for additional safety lab[2]		X	(X)	(X)	X	(X)	(X)	X	(X)	X	X[9]	(X)
Direct Coombs' test[2]		X	(X)	(X)	X	(X)	(X)	X	(X)	X	X[9]	(X)
Urinalysis[2]		X			X			X		X	X[9]	
CSM[2]	X	X	X	X	X	X	X	X	X	X		X
CDASI[2]		X	X	X	X	X	X	X	X	X		X
SF-36 Health Survey[2]		X								X		
Wells score for DVT[4]	X	X	X	X	X	X	X	X	X	X	X	X
Wells score for PE[4]	X	X	X	X	X	X	X	X	X	X	X	X
Infusion of IMP[1]		X	X	X	X	X	X	X	X			
Local injection site reaction[5]		X	X	X	X	X	X	X	X	X		X
Patient diary check		X	X	X	X	X	X	X	X	X		X
Adverse event monitoring		Throughout the study										
Concomitant therapy		Throughout the study										

[1] *octanorm* or placebo has to be administered subcutaneously every week (±2 days) using a syringe driver for precise infusion rates. The total dose/volume of a weekly infusion will be calculated on the basis of the body weight. The weekly infusion will be performed in two separate sessions (= 1 infusion cycle for a given weekly administration). An infusion cycle comprises both sessions to be administered on 1 or 2 days, either on the same day or on two consecutive days or with maximum one day in between two sessions.

During the first four weeks (first 4 infusion cycles from Visit 2 to Visit 3), all infusions will be administered at the study site. Apart from Visit 3, where at least the first session of an infusion cycle will also be administered at the site, the next two weeks can be performed either at the patient´s home by the mobile healthcare research nurses or at the site (decision to be taken by Investigator and patient based on previous experience). Thereafter, SCIG infusions will be administered at home by mobile healthcare research nurses, apart from Visits 4-9, where at least the first session of an infusion cycle will be administered at the site. Before starting home treatment, a diary will be provided to the patients for documenting AEs and local tissue reactions at injection sites, body temperature around 1 hour after the end of the infusion, and any changes in concomitant drug and non-drug therapies between visits. The date of home treatments, batch numbers, number of vials, volume and speed of infusion, number and location of injection sites will be recorded by the mobile nurses. Based on the Investigator´s decision a home infusion can be replaced with an on-site infusion if considered medically relevant..

[2] If on day of IMP: before IMP administration;

[3] Measurements of the vital signs will be carried out before, at least once during, and 1 hour (+/- 10 min) after the end of the infusion session;

[4] If on day of IMP: at least 1 hour post-infusion (after the second infusion if both sessions are done on site);

[5] 1 hour (+/- 10 min) after the end of the infusion session;

[6] For patients from GAM10-08 study: GAM10-08 Week 40 Termination Visit will be SCGAM-02 Baseline Visit. GAM10-08 Week 40 test results will be used for SCGAM-02 Baseline Visit evaluations;

[7] For patients from GAM10-08 study: SCGAM-02 Informed consent to be provided to patient before GAM10-08 Week 40 visit;

[8] At minimum, all patients should be assessed for vital signs, adverse events and concomitant therapy. Other safety and/or efficacy laboratory assessments, and physical exam should be repeated only if found abnormal at the termination visit;

[9] Only parameters found abnormal at the termination visit will be re-assessed.

(X) To be performed whenever hemoglobin is found to have decreased by ≥ 2 g/dL from baseline.

PROTOCOL SIGNATURES

Signature of the Sponsor's Representative

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

[redacted] [redacted] [redacted]

International Medical Director Signature Date

on behalf of the Sponsor
Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
1100 Vienna, Austria

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Global Clinical Project Manager Signature Date
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Manager Biometrics Signature Date
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PROTOCOL SIGNATURES

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

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Date

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADR(s)	Adverse Drug Reaction(s)
AE(s)	Adverse Event(s)
AESI	Adverse Event of Special Interest
ALAT	Alanine Aminotransferase
ASAT	Aspartate Aminotransferase
BW	Body weight
CDASI	Cutaneous Dermatomyositis Disease Area and Severity Index
CRO	Contract Research Organization
CSM	Core Set Measures
DM	Dermatomyositis
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
EFNS	European Federation of Neurological Societies
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAQ	Health Assessment Questionnaire
HTR	Hemolytic Transfusion Reaction
IB	Investigator's Brochure
IDMC	Independent Data Monitoring Committee
IMACS	International Myositis Assessment and Clinical Studies Group
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IGIV	Immunoglobulin Intravenous
IIM(s)	Idiopathic Inflammatory Myopathy(ies)
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	Lactate Dehydrogenase
MDAAT	Myositis Disease Activity Assessment Tool
MedDRA	Medical Dictionary for Regulatory Activities
MMT	Manual Muscle Testing
NSAID	Non-Steroidal Anti-Inflammatory Drug

PE	Pulmonary Embolism
PM	Polymyositis
PP	Per Protocol
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCIG	Subcutaneous Immunoglobulin
SF-36v2	Short Form 36 Items Health Status Version 2
SOP	Standard Operating Procedure
TEAE(s)	Treatment Emergent Adverse Event(s)
TEE(s)	Thromboembolic Event(s)
TIS	Total Improvement Score
VAS	Visual Analogue Scale
WOCBP	Women of Childbearing Potential

1 INTRODUCTION

1.1 Immunoglobulins

Since more than 5 decades immunoglobulins have been used to provide antibodies for the prevention of viral and bacterial diseases (replacement therapy) in immunocompromised patients. Within the last 30 years intravenous immunoglobulins (IGIVs) have been proven to be useful in a wide variety of clinical conditions (other than classical replacement therapy), in which IGIVs exhibit an immunomodulatory effect. These include idiopathic thrombocytopenia in children and adults at high risk of bleeding or prior to surgery to correct the platelet count, Kawasaki disease and Guillain-Barré syndrome. More recently, single IGIV brands have also been licensed for chronic inflammatory demyelinating poly(radiculo)neuropathy and multifocal motor neuropathy. Experimental off-label use of IGIV in other neurological and dermatological indications is widespread.

However, immunoglobulins may also be administered by subcutaneous (SC) infusion. The administration via the SC route offers several advantages over IV infusion from a patient's and a physician's perspective. After the introduction of small, portable syringe drivers, this route of administration has gained even more popularity in several European countries and in the US as a practical, effective, and safe administration of treatment. In addition, home therapy can also be recommended with SC administration. An administration at home with small portable pumps can easily be learned by the patients or their caregivers. It may remarkably improve the patient's quality of life and compliance as it reduces the frequency of hospitalizations and the need for home care. Administration of IgG via the SC route provides more stable and well-balanced IgG plasma levels until the end of the treatment interval, in contrast with the peak IgG plasma concentrations attained with IGIV, which weaken at the end of dose. When effective IGIV therapy cannot be continued because of the lack of peripheral and central vein access, SC immunoglobulins (SCIG) might also be an alternative treatment option.

octanorm, the investigational medicinal product (IMP) in this study, is an immunoglobulin preparation from human normal plasma and is manufactured by Octapharma. It contains 16.5% (165 mg/mL) protein. The product is aimed for SC infusion by pump or syringe.

Further information on the IMP can be found in the Investigator's Brochure.

1.2 Idiopathic Inflammatory Myopathies

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of acquired, systemic connective tissue diseases characterized by chronic inflammation of striated muscles leading to predominantly proximal muscle weakness. They are best classified on the basis of their varying clinical characteristics into the most common subsets of IIM: adult dermatomyositis (DM) and polymyositis (PM), juvenile DM, necrotizing autoimmune myositis, myositis in overlap with cancer or another connective tissue disease, and inclusion body myositis.[1] IIMs are frequently associated with constitutional symptoms and commonly involve other organ systems including the skin, joints, lungs, gastrointestinal tract and heart. Patients with IIM have increasing difficulty with tasks requiring the use of proximal muscles, such as getting up from a chair, climbing steps, or lifting objects. In rare acute cases also respiratory muscles can be affected. Extra-muscular disease activity may manifest in systemic symptoms like fever, arthralgia, and Raynaud's phenomenon, cardiac arrhythmias or ventricular

dysfunction, and pulmonary complications, primarily due to interstitial lung disease (reported in 10-40% of patients).[1]

IIMs are rare with an estimated incidence of 4-10 cases/million population per year, and a bimodal incidence pattern reflecting childhood onset of juvenile DM and a later peak in adulthood.[2]

Each IIM subtype has a different prognosis and response to therapies so that the distinction from other diseases is very important. Although the precise pathogenesis is unknown, the IIMs likely result from immune-mediated processes initiated by environmental factors in genetically susceptible individuals.[3]

Although a spectrum of severity exists for DM, this entity is more likely to be associated with rapid and aggressive myositis. DM is seen in both, children and adults, and the early symptoms include distinct skin manifestations accompanying or preceding muscle weakness. The classic skin manifestations include periorbital heliotrope (blue–purple) rash with edema; erythematous rash on the face, knees, elbows, malleoli, neck, anterior chest (in a V-sign), and back and shoulders (in a shawl sign); and a violaceous eruption (Gottron's rash) on the knuckles, which may evolve into a scaling discoloration. The lesions are photosensitive and may be aggravated by ultraviolet radiation.[1]

The risk of cancer is increased in adults during the first 3-5 years after the onset of DM, with a reported frequency of 9-32%; necessitating a thorough annual workup in the first 3 years after disease onset. The most common forms are ovarian, breast, and colon cancer, melanoma, and non-Hodgkin's lymphoma.[1]

1.3 Rationale for Conducting the Study

During the last 20 years, several IgG preparations have been developed for intravenous (IV) and subcutaneous (SC) administration, and their use has further contributed to the successful treatment of patients requiring replacement therapy.

In addition to its use for the treatment of primary and secondary immunodeficiencies, IGIV is increasingly used for immunomodulating therapy in the treatment of patients with a variety of autoimmune and inflammatory neurological disorders. One placebo-controlled clinical study in 15 subjects with refractory DM employed a dose of 2.0 g/kg IGIV or placebo for 12 weeks. After a 1-month washout phase the subjects crossed over to the alternate therapy.[4] Subjects on IGIV had a significant improvement in muscle strength and neuromuscular symptoms in contrast to subjects on placebo. A total of 12 subjects received IGIV of which 9 subjects had a major improvement to nearly normal function.

Currently, Octapharma is conducting the study ProDERM: "**Pro**gress in **DERM**atomyositis" (study number GAM10-08) to investigate efficacy, safety and tolerability of the IGIV Octagam 10% in DM patients and to confirm the efficacy results, which were observed in the small randomized placebo-controlled cross-over trial [4] and also seen in retrospective studies or case reports, in a much larger setting. Furthermore, ProDERM will systematically investigate the long-term beneficial effect of IGIV in a 6-month open-label extension period. Long-term safety and tolerability of high-dose Octagam 10% (2.0 g/kg) administered for up to 40 weeks will be investigated, since many patients need lifelong treatment. Eventually, Octagam 10% should offer DM patients an additional effective and safe maintenance treatment option that is well tolerated.

The rationale for conducting this study (SubQ-DERM: "Progress with **Subcutaneous** Immunoglobulin in **DERM**atomyositis) is to determine the efficacy of the SCIG *octanorm* administered subcutaneously for 32 weeks compared with placebo in the maintenance treatment of patients with DM who have previously responded to IGIV therapy and to assess treatment outcome, effect on Quality of Life (QoL) measures, compliance and safety of treatment with *octanorm*.

The administration of immunoglobulins via the SC route offers several advantages over IV infusion from a patient's and a physician's perspective. Replacement therapy by rapid SC infusion with a pump was introduced during the late 1980s. Several reports have shown that the SC method is feasible, safe, efficient, cost-effective and highly appreciated by the patients.[5-13]

1.4 Dose Rationale

Findings from the animal experiments performed with *octanorm* (efficacy, safety pharmacology and local tolerance) in different species (mice, rabbits, and dogs) justify the safe use of *octanorm* in humans. No animal pharmacokinetic studies were performed with *octanorm* because pharmacokinetic parameters in animals treated with human immunoglobulin solutions cannot be extrapolated into humans.

There are two major differences in the PK characteristics of IGIV and SCIG: delayed absorption and reduced bioavailability.

Following IV administration, the plasma concentration peaks immediately upon termination of the infusion. After SC administration, the absorption of IgG into the subcutaneous tissue is slower; the IgG must be delivered into the bloodstream by the lymphatic system. Thus, with SCIG, the intravascular IgG concentration increases gradually, peaking at 48–72 hours. In three recent studies comparing IGIV and SCIG in PID patients, the mean peak serum IgG level immediately after IV infusions was 2303 mg/dL.[12, 14, 15] In contrast, the mean peak with SCIG was 1410 mg/dL.[16]

No differences have been reported in the half-life of SCIG and IGIV. With modern IgG preparations, half-lives have generally been reported to be about 30–35 days.[17]

The use of smaller doses of SCIG at more frequent intervals result in stable, higher trough IgG serum concentrations, which remain constant between consecutive SCIG infusions.[18]

Pooled data from 7 studies in which equivalent monthly SC IgG doses were given weekly vs. IGIV every 21–28 days showed that trough serum IgG levels were 10 to 20% higher with weekly SC doses than with the same total monthly IGIV dose. After 6 to 12 weekly infusions, near-steady-state IgG levels were achieved with differences between minimum and peak concentrations of only 5% to 10% of the overall mean.[16, 17]

Thus, on converting from IGIV to SCIG replacement therapy, the equivalent monthly dose of IgG is usually determined in one of two ways:

- 1:1 dosing: The 3 to 4 weekly IGIV dose is split into 3 to 4 equal weekly SCIG infusions.
- Dosing based on the area under the curve. The SCIG dose is calculated from PK data to provide a monthly exposure to IgG equivalent to that with IGIV.

The former is common in Europe, while the latter is a requirement of the US Food and Drug Administration (FDA) for SCIG labeling studies in patients with primary antibody deficiency.[19]

In an open label study in seven female patients (4 with DM, 3 with PM) SCIG was administered at the patients' usual IGIV monthly dose fractioned into equal doses given subcutaneously at weekly intervals. The median follow-up period was 14.4 months. During the treatment period, no relapse of disease occurred. All patients showed a good clinical response and reported good tolerance to the treatment with an improved quality of life.[20]

Therefore, the dose of 0.5 g/kg BW given on a weekly basis proposed for this study a 1:1 equivalent to the IGIV of 2 g/kg BW given every 4 weeks used in the GAM10-08 study, and thus is considered appropriate to determine the efficacy of *octanorm* for the maintenance therapy of patients with DM.

With weekly SCIG administrations, only about 4.4 days elapse between the t_{max} of one dose and the administration of the next dose. Given the half-life of 30 days this means that only about 10 to 20% of the administered IgG is metabolized before the serum level starts to rise again. In contrast, with IGIV dosing intervals of 3–4 weeks (about one half-life), 36 to 48% of the IgG may be metabolized by the time the next dose is due. These differences in the dosing intervals used in most SCIG vs. IGIV regimens result in more stable serum IgG levels with SCIG.[16, 17]

1.5 Benefit-Risk Statement

Despite its well-established safety profile, IGIV often leads to undesired symptoms, ranging from mild systemic adverse reactions, such as flushing, fever, muscle aches, tiredness, headache and dizziness, to severe reactions, manifesting as chest pain, tachycardia, and changes in blood pressure, aseptic meningitis, thrombosis or renal failure.[18]

The slower rate of rise towards the peak and the truncation of its height are believed to be responsible for the much lower incidence of systemic adverse events (AEs) with SCIG. This is consistent with observations that many AEs of IGIV infusions are rate-related, and has been repeatedly confirmed.[21]

On the other hand local reactions at SC injection sites are common. These reactions are rarely severe, and are accepted by most patients. In the meta-analysis by Orange et al. the reporting rate varied from 0.028 to 0.697 per infusion demonstrating that the majority of patients tolerate SCIG well.[19]

Subjects with pre-existing risk factors for thrombotic events (such as advanced age, obesity, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, subjects with acquired or inherited thrombophilic disorders, subjects with prolonged periods of immobilization, severely hypovolemic subjects, subjects with diseases which increase blood viscosity) may be at risk.

Subjects with DM may be at higher risk of developing thromboembolic events (TEEs). Therefore, special emphasis will be given to the occurrence of TEEs such as deep vein thromboses (DVTs) and pulmonary embolism (PE).

Hemolytic transfusion reactions (HTRs) can develop subsequent to IgG therapy. IgG-related hemolysis is associated with passive transfer of anti-A and anti-B hemagglutinins.

When medicinal products prepared from human blood or plasma are given to a subject, the transmission of infectious agents cannot be totally excluded. This applies also to hitherto unknown pathogens. However, specific virus inactivation procedures are implemented in the manufacturing process of *octanorm*, which are described in detail in the Investigator's Brochure.

The safety profile of SCIG is well characterized. For *octanorm*, the same type of adverse reactions may be expected. No new or unknown safety problems are expected to emerge for *octanorm*, which are not already described in the Investigator's Brochure.

As per European Federation of Neurological Societies (EFNS) Guidelines [22], IGIV is recommended as a second-line treatment in combination with prednisone in DM (level B) and treatment option in PM (level C). This is in line with the consensus statement of the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) ad hoc committee on the use of IGIV in the treatment of neuromuscular conditions: Class I evidence exists to support the use of IGIV to treat patients with DM.[23] Over the last years, high-dose IGIV has become an effective and safe therapeutic option for DM and is beneficial as a second-line therapy for DM.[24] The European Dermatology Forum stated in their "Guideline on the use of high-dose intravenous immunoglobulin in dermatology" that, besides Pemphigus vulgaris, DM is the dermatological condition with the highest level of evidence for treatment with IGIV.[25] IGIV is indicated for all severe forms of DM and its use as first-line treatment may be justified in patients with fulminant progressive courses, severe myolysis or paralysis. As a rule, IGIV should be used as a second-line treatment if steroid monotherapy has failed to produce an improvement after 1 month, or if reducing the steroid dose below an acceptable level results in a flare-up of the disease, or if side-effects prevent further steroid medication. The use of IGIV therapy is considered to be an adjuvant treatment with continuation of immunosuppressive therapy with corticosteroids and possibly also other immunosuppressive agents.[25, 26] The German Society for Neurology also recommended in their Guideline[1] to treat patients who do not respond to corticosteroids, azathioprine or methotrexate with IGIV (Class I evidence). Similarly, the Guideline of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology concluded that based on one Class II study, IGIV is possibly effective for the treatment of nonresponsive DM in adults and thus may be considered for the treatment of nonresponsive DM in adults (Level C).[4, 27]

Because of the ease of its application, IGIV has become the treatment of choice as corticosteroid-saving agent or as add-on therapy in severe myositis.[28]

Immunoglobulins administered via the SC route are likely to show the same efficacy as those administered by IV route.

In terms of therapeutic benefits, it can reasonably be assumed that *octanorm* will exhibit the same efficacy, safety and effectiveness as other SCIG brands.

[1] Leitlinien für Diagnostik und Therapie in der Neurologie – Myositissyndrome; www.dgn.org/leitlinien/3011-ll-69-ll-myositis-syndrome

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

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.

2.2 Secondary Objective(s)

The secondary objectives of this study are:

- to assess other efficacy outcomes at the end of study (Week 32 or 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 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint(s)

- Proportion of patients with clinically important deterioration in the treatment period. A patient with clinically important deterioration is defined as a patient with 1) MMT-8 worsening ≥6 points (scale of 150) OR CDASI (Total Activity Score) worsening ≥5 points, AND 2) a Physician's Global Disease Activity VAS worsening ≥2 cm.

3.1.2 Secondary Endpoint(s)

Efficacy:

- Mean change from Baseline (Week 0-defined as end of IGIV therapy) to end of the treatment period (Week 32 or Drop-Out Visit) in:
  - Modified Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI);
  - Six Myositis CSM (MMT-8, Physician's Global Disease Activity, Patient's Global Disease Activity, Extra-Muscular Disease Activity, Muscle enzymes, Health Assessment Questionnaire (HAQ);
  - SF-36v2 Health Survey.
- Mean change in TIS from Baseline (Week 0) to end of treatment period (Week 32 or Drop-Out Visit).
- Time to clinically important deterioration during the treatment period.
- Number and type of deviations from protocol requirements relating to home treatment (dosing, timing).

Safety (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).

Safety:

- Tests for viral safety (at Baseline and end of Treatment Period).
- Pregnancy test, if applicable (at Screening and end of Treatment Period) .

3.2 Overall Study Design and Plan

This study is planned to start in Q3 2018 and to be completed by Q2 2020, resulting in an overall duration of 24 months.

It will be a double-blind, randomized, placebo-controlled, parallel group, multicenter, comparative efficacy and safety study in a minimum of 78 adult subjects of both genders with

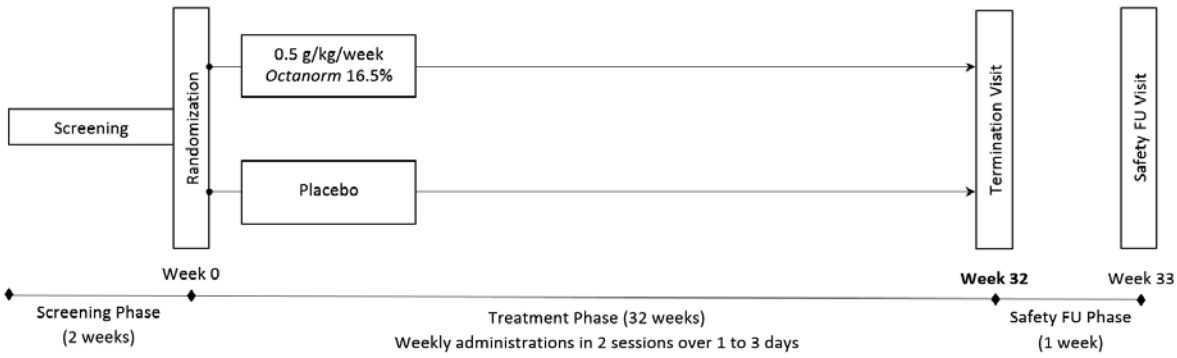
definite or probable DM according to the criteria of Bohan and Peter [29, 30] who have previously responded to IGIV therapy.

As DM is a rare disease, about 45 sites are projected to participate in countries worldwide with emphasis on European countries and North America.

Subjects eligible after screening will be randomized 1:1 to receiving up to 32 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 (= 1 infusion cycle for a given weekly administration). An infusion cycle comprises both sessions to be administered on 1 or 2 days, either on the same day or on two consecutive days or with maximum one day in between two sessions.

In case of clinically important deterioration (for definition see Section 4.3.1) during the SC treatment period, subjects will be discontinued from the study, will undergo a termination visit and may optionally receive Octagam 10% as IGIV rescue medication (2g/kg BW one time, provided by the sponsor) or rescue treatment according to standard of care at the site by the treating physician. Octagam 10% or any other commercially available IGIV as optional IGIV rescue medication can be also reimbursed by the sponsor (2g/kg BW one time). IGIV as rescue medication should be administered with infusion rate not higher than 0.04 mL/kg/min (240 mg/kg/h).

Figure 1: Scheme of Study Design



3.3 Discussion of Study Design and Choice of Control Group(s)

3.3.1 Study Design

The study design includes all major scientific, state-of-the-art interventions needed to assess the efficacy, safety and tolerability of therapeutic treatments in DM patients.

octanorm or placebo (see below) will be administered subcutaneously every week (±2 days) using a syringe driver for precise infusion rates. The total dose/volume of a weekly infusion will be calculated on the basis of the body weight. The weekly infusion will be performed in two separate sessions (= 1 infusion cycle for a given weekly administration). An infusion cycle comprises both sessions to be administered on 1 or 2 days, either on the same day or on two consecutive days or with maximum one day in between two sessions.

During the first four weeks (first 4 infusion cycles), all infusions will be administered at the study site. Apart from Visit 3, where at least the first session of an infusion cycle will also be administered at the site, the next two weeks can be performed either at the patient´s home by the mobile healthcare research nurses or at the site (decision to be taken by Investigator and patient based on previous experience). Thereafter, SCIG infusions will be administered at home by mobile healthcare research nurses, apart from Visits 4-9, where at least the first session of an infusion cycle will be administered at the site. Before starting home treatment, a diary will be provided to the patients for documenting AEs and local tissue reactions at injection sites, body temperature around 1 hour after the end of the infusion, and any changes in concomitant drug and non-drug therapies between visits. The date of home treatments, batch numbers, number of vials, volume and speed of infusion, number and location of injection sites will be recorded by the mobile nurses. Based on the Investigator´s decision a home infusion can be replaced with an on-site infusion if considered medically relevant.

In case of clinically important deterioration during the SC treatment period, subjects will be discontinued from the study, will undergo a termination visit, and may optionally receive Octagam 10% as IGIV rescue medication (2g/kg BW one time, provided by the sponsor) or rescue treatment according to standard of care at the site by the treating physician. Octagam 10% or any other commercially available IGIV as optional IGIV rescue medication can be also reimbursed by the sponsor (2g/kg BW one time). IGIV as rescue medication should be administered with infusion rate not higher than 0.04 mL/kg/min (240 mg/kg/h).

3.3.2 Control Group(s)

The efficacy and safety of weekly SCIG infusions in DM have not been studied in well-controlled and adequately powered randomized clinical trials.

Therefore, *octanorm* will be compared with placebo in this trial.

3.3.3 Study Parameters

The study parameters selected in the study are appropriate to verify the clinical efficacy of SCIG in DM.

Patients with "clinically important deterioration" as defined in Section 3.1.1 will be classified as non-responders. The proportion of non-responders will be used as primary endpoint. Clinically important deterioration was defined by the study Steering Committee, consisting of several experts in the field, based on available clinical data and experience. The definition combines established measures of muscle weakness/skin involvement (MMT-8/CDASI) with physician's disease activity assessment. The definition of Oddis et al. 2013 [31] used in other studies including ProDERM was considered too sensitive for well-maintained patients with low disease activity at study entry, and had thus to be adapted.

The CDASI is a clinician-scored single page instrument that separately measures activity and damage in the skin of DM patients for use in clinical practice or clinical/therapeutic studies. The modified CDASI (version 2) is the one in current use. The modified CDASI has 3 activity measures (erythema, scale, and erosion/ulceration) and 2 damage measures (poikiloderma and calcinosis) which are assessed over 15 body areas. In addition, Gottron's papules on the hands are evaluated both for activity and damage. Lastly, the activity of periungual changes and alopecia is assessed.[32]

Core Set Measures of myositis disease activity have been established and validated by the IMACS Group for DM/PM clinical trials.[33-36] Very recently, the CSM have been further developed into conjoint-analysis hybrid response criteria combining 6 CSM to determine clinically meaningful improvement in a Total Improvement Score (TIS).[37]

4 STUDY POPULATION

4.1 Population Base

In total, 78 adult male or female subjects with DM who have responded to treatment with intravenous immunoglobulin, and have been on a stable dose of 2g/kg BW (+/- 10%) for at least 3 months will be enrolled into the study.

4.1.1 Inclusion Criteria

Subjects who meet all of the following criteria are eligible for the study:

1. Subjects with diagnosis of definite or probable DM according to the Bohan and Peter criteria.[29, 30]
2. Subjects who have responded to IGIV treatment as assessed by the treating physician and being on a stable dose for at least 3 months on 2g/kg bodyweight (+/- 10%) prior to study enrolment.
3. For subjects being on other medication(s) for the treatment of DM (immunosuppressants, corticosteroids): a) subject was on such medication(s) at the start of IGIV treatment in the first place, and b) received such medication(s) for at least 3 months prior to study enrolment and at a stable dose for at least 4 weeks prior to study enrolment at the maximally allowed conditions as per Table 2 (see section 4.2.1).
4. MMT-8 score ≥144, with at least 3 other CSM to be normal or near normal as per the following criteria: Visual Analogue Scale [VAS] of patient global disease activity ≤2 cm, physician's global disease activity ≤2 cm, extra-muscular disease activity ≤2 cm; no muscle enzyme >4 times upper limit of normal due to myositis, Health Assessment Questionnaire [HAQ] ≤0.25.
5. Males or females ≥ 18 to <80 years of age.
6. Voluntarily given, fully informed written consent obtained from subject before any study-related procedures are conducted.
7. Subject must be capable and willing to understand and comply with the relevant aspects of the study protocol.

4.1.2 Exclusion Criteria

Subjects who meet any of the following criteria are *not* eligible for the study:

1. Cancer-associated myositis, defined as the diagnosis of myositis within 2 years of the diagnosis of cancer (except basal or squamous cell skin cancer or carcinoma in situ of the cervix that has been excised and cured - at least 1 year for basal or squamous cell skin cancer and 5 years for carcinoma in situ of the cervix must have passed since excision).
2. Evidence of active malignant disease or malignancies diagnosed within the previous 5 years (including hematological malignancies and solid tumors) or breast cancer diagnosed within the previous 10 years. Subjects >5 years (>10 years for breast cancer) of cancer diagnosis who have been treated and are in remission are allowed.
3. Subjects with overlap myositis (except for overlap with Sjögren's syndrome), connective tissue disease associated DM, inclusion body myositis, polymyositis, juvenile dermatomyositis or drug-induced myopathy.

4. Subjects with immune-mediated necrotizing myopathy with absence of typical DM rash.
5. Subjects with generalized, severe musculoskeletal conditions other than DM that prevent a sufficient assessment of the subject by the physician.
6. Subjects who received blood or plasma-derived products (other than IGIV) or plasma exchange within the last 3 months before enrolment.
7. Subjects with administration of permitted concomitant medications exceeding the maximally allowed conditions as per section 4.2.1.
8. Subjects with administration of forbidden concomitant medications within the washout periods as defined in Table 3: see section 4.2.2.
9. Subjects starting or planning to start a physical therapy–directed exercise regimen during the trial. Subjects on stable physical therapy for >4 weeks are allowed but the regimen should remain the same throughout the trial.
10. Cardiac insufficiency (New York Heart Association III/IV), cardiomyopathy, significant cardiac dysrhythmia requiring treatment, unstable or advanced ischemic heart disease.
11. Severe liver disease, with signs of ascites and hepatic encephalopathy.
12. Severe kidney disease (as defined by estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2).
13. Known active or chronic hepatitis B, hepatitis C or HIV infection. Past hepatitis B or C infection that has been cured is allowed.
14. Subjects with a history of deep vein thrombosis within the last year prior to study enrolment or pulmonary embolism ever.
15. Body mass index > 40 kg/m2 and/or body weight > 120 kg.
16. Medical conditions whose symptoms and effects could alter protein catabolism and/or IgG utilization (e.g. protein-losing enteropathies, nephrotic syndrome).
17. Known IgA deficiency with antibodies to IgA.
18. History of hypersensitivity, anaphylaxis or severe systemic response to immuno-globulin, blood or plasma derived products or any component of *octanorm* 16.5% such as polysorbate 80 or to sodium chloride.
19. Known blood hyperviscosity, or other hypercoagulable states.
20. Subjects with a history of drug abuse within the past 5 years prior to study enrolment.
21. Participating in another interventional clinical study with investigational treatment within 3 months prior to study enrolment. Subjects who participated in the Octagam 10% Dermatomyositis Study (GAM10-08) can be included.
22. Women who are breast feeding, pregnant, or planning to become pregnant, or are unwilling to apply an effective birth control method (as per protocol section 7.3.9 b) up to four weeks after the last IMP infusion received.

4.2 Prior and Concomitant Therapy

The following must be recorded in the electronic case report form (eCRF):

- Details of any DM–related medications received within 12 months before screening.
- Details of any other medications received within 3 months before screening.
- Concomitant medications throughout the study.

- Non-drug therapies incl. physiotherapies within 4 months before screening and throughout the study.

4.2.1 Permitted Concomitant Therapy

Previous medications for the treatment of DM (immunosuppressants, corticosteroids) must either be

a) washed-out, i.e. patients can be included into this study only when the following washout periods prior to randomization are considered:

- 3 months for leflunomide, topical application of Tacrolimus;
- 8 weeks for methotrexate, azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil, acthar, hydroxychloroquine, corticosteroids.

or

b) continued if subject received medication at the start of IGIV treatment in the first place and for at least 3 months prior to study enrolment and at a stable dose for at least 4 weeks prior to study enrolment (details see Table 2); however, only one concomitant therapy in addition to corticosteroids is allowed. Topical application of Tacrolimus is allowed in addition to one immunosuppressive drug.

Table 2 specifies which DM-related medications are permitted as concomitant therapy. Only 1 concomitant therapy in addition to corticosteroids is allowed. In addition, the maximal allowed dose which has to remain stable throughout the study is provided.

Throughout the entire treatment period, the dose regimen of concomitant therapies should not be changed to avoid interference with the efficacy endpoint evaluation. However, when safety reasons intervene, concomitant therapies may be changed by the investigator in the interest of the patient.

The routine use of premedication for Ig administrations to alleviate potential side effects is not allowed during the study. However, if a subject experiences 2 consecutive infusion-related AEs that are likely to be prevented by premedication, antipyretics, antihistamines, or antiemetic drugs are allowed before the following infusions of study drug. The dose of premedication should be held stable during the study (except when safety reasons intervene) and its use must be documented.

Local anesthetics to reduce pain associated with needle insertion are allowed.

NSAIDs or opioids are commonly used in DM patients and are therefore allowed. The dose of such medications should be kept stable 2 weeks prior to study enrolment and during the study (except when safety reasons intervene). The use of such medication must be documented.

Topical medication, except topical steroids, is allowed. Such topical medication should be kept stable during the study to avoid interference with the extra-muscular activity, one of the CSM.

However, topical steroids for moderate or severe local injection site reaction treatment are allowed. When possible ultra high potency (very potent) topical steroids should be used with recommended twice-daily treatment duration 3 days, maximum 7 days. The purpose and assignment regimen of treatment should be documented.

The mobile research nurses are not permitted to make any therapy assignments on their own, including premedication; any therapy changes are always to be Investigator´s decisions.

Physical therapy-directed exercise regimen is allowed if started ≥4 weeks prior to study enrolment and kept on a stable schedule, frequency and extent. Any such exercise regimen must be documented.

Table 2: Dose Limitations for Prior/Concomitant DM-Related Medications

Only *one* concomitant therapy in addition to corticosteroids is allowed!*

Drug	Maximally allowed stable dose as concomitant therapy
Immunosuppressive Drugs	
Methotrexate	25 mg/week
Azathioprine	2 mg/kg
Cyclosporine	2 mg/kg
Tacrolimus	0.2 mg/kg
Mycophenolate mofetil	3000 mg daily
Leflunomide	20 mg daily
Acthar	80 IU twice a week
Other	
Hydroxychloroquine	400 mg daily
Corticosteroids	10 mg daily prednisone equivalent

*Note: Topical application of Tacrolimus is allowed in addition to one immunosuppressive drug.

4.2.2 Forbidden Concomitant Therapy

The following medications or therapies are forbidden during participation in this study:

- Routine premedication to alleviate potential tolerability problems, with the exception of permitted therapy as stated above.
- Corticosteroids at any dose if given as premedication to alleviate potential side effects.
- Drugs in Table 2 at doses higher than stated.
- Other blood or plasma-derived products should only be given for emergency reasons.
- Plasma exchange procedures.
- Live attenuated vaccines such as measles, rubella, mumps and varicella.
- Any experimental drug.

Table 3 lists further medications that are forbidden, but patients can be included into this study when the respective washout period is considered.

Table 3: Forbidden Concomitant Medications

Drug	Washout Period
Monoclonal antibodies (e.g. adalimumab, infliximab, certolizumab, golimumab, abatacept, tocilizumab)	8 weeks
Rituximab	12 months or 6 months plus normal CD19 count
Cyclophosphamide	3 months
Etanercept	4 weeks
Anakinra	2 weeks
Rilanocept	8 weeks
Topical steroids (except for local injection site reaction treatment)	2 weeks

4.2.3 Rescue Medication

Octagam 10% as optional rescue medication for patients with clinically important deterioration during the treatment period will be provided by the sponsor according to local regulation. Octagam 10% or any other commercially available IGIV as optional IGIV rescue medication can be also reimbursed by the sponsor (2g/kg BW one time). IGIV as rescue medication should be administered with infusion rate not higher than 0.04 mL/kg/min (240 mg/kg/h). The use of Octagam 10% or any other IGIV as rescue medication will be recorded.

4.3 Withdrawal and Replacement of Subjects/Patients

4.3.1 Premature Subject/Patient Withdrawal

Subjects have the right to withdraw from the study at any time for any reason, without the need to justify their decision. The Investigator also has the right to withdraw subjects in case of AEs, poor compliance, or other reasons. Since an excessive rate of withdrawals can render the study non-interpretable, any unnecessary withdrawal by investigator's decision should be avoided.

For any withdrawals after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation. If the reason for withdrawal of a subject/patient is an AE, the main specific event or laboratory test will be recorded, and the Investigator will make thorough efforts to clearly document the outcome.

Should a subject decide to withdraw, the Investigator will make the best efforts to complete and report the observations. The Investigator will document the reason(s) for withdrawal of each subject in the eCRF.

Subjects who terminate the study prematurely are drop-outs. The Investigator has to organize the Drop-out visit which is identical to the Termination visit procedures.

Other reasons for premature termination of subjects may be:

1. Withdrawal of subject's consent.
2. Deterioration of DM.
3. Pregnant subjects will be immediately excluded from the study.
4. Investigator's opinion that the subject may be severely harmed if he/she continues trial participation, namely by the treatment and procedures according to the study protocol.
5. Occurrence of a disease which interferes with the study treatment or represents an exclusion criterion.
6. Administration of IgG other than *octanorm*.

"Clinically important deterioration" is defined as follows:

1) MMT-8 worsening ≥6 points (scale of 150) OR CDASI (Total Activity Score) worsening ≥5 points,

AND

2) Physician's Global Disease Activity VAS worsening ≥ 2 cm.

In case of clinically important deterioration during the treatment period, subjects will be discontinued from the study, will undergo a termination visit and may optionally receive Octagam 10% as IGIV rescue medication (2g/kg BW one time, provided by the sponsor) or rescue treatment according to standard of care at the site by the treating physician. Octagam 10% or any other commercially available IGIV as optional IGIV rescue medication can be also reimbursed by the sponsor (2g/kg BW one time). IGIV as rescue medication should be administered with infusion rate not higher than 0.04 mL/kg/min (240 mg/kg/h).

4.3.2 Subject/Patient 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 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.

4.4 Assignment of Subjects/Patients to Treatment Groups

The registration of subjects as screened/randomized will be managed via an interactive response technology (IRT) system.

The screening ID will be a 5-digit number with the first digit being the study number ("2"), the next 2 digits identifying the center (01, 02, …) and the last 2 digits the sequence number assigned by the IRT (01, 02, …) for each site continuously. Leading zeros will be used for center and subject numbers below 10. The second subject screened at center 4 will be identified as e.g. 20402.

The Investigator will enter the screening ID into the confidential subject identification list.

If the subject qualifies, randomization will be done centrally through the IRT. The fact that a subject has been randomized will be reported immediately and automatically by the system to

the Investigator, the contract research organization (CRO) and the sponsor. The result of randomization, i.e. the treatment group assignment, will however only be accessible to study personnel not involved in the conduct or analysis of the trial. The unblinded hospital pharmacist or designee will be informed through the system about the vials to be dispensed for a patient. The responsible monitor(s) will be informed of new subjects enrolled automatically by the IRT system via email.

The subject will be identified by the previously assigned screening ID throughout the trial. Under no circumstances are subjects who enroll in the study permitted to re-enroll.

4.5 Relevant Protocol Deviations

Deviations from the protocol should be avoided. A complete list of all minor and major deviations will be compiled and provided for preparation of the clinical study report.

Examples of relevant protocol deviations that will be addressed are:

- Subjects who entered the study even though they did not satisfy the entry criteria.
- Subjects who developed withdrawal criteria during the study (see Section 4.3.1).
- Subjects who received the wrong treatment or incorrect dose (also see Section 5.4).
- Subjects who received an excluded concomitant treatment or a change in the permitted DM-related therapies.
- Subjects who had no CSM or CDASI at Week 32 or Drop-Out Visit.

In case of any major protocol deviation, the Investigator and Octapharma will decide on the further participation of the subject/patient in this study after having discussed all relevant aspects.

4.6 Subsequent Therapy

All subjects who leave the study – be it prematurely or per protocol – will continue with the DM–related treatment they had before study participation, or with another standard of care at the discretion of the investigator.

5 INVESTIGATIONAL MEDICINAL PRODUCT(S)

5.1 Characterisation of Investigational Product(s)

Name of Medicinal Product: *octanorm*

Active ingredient of *octanorm*: Human normal immunoglobulin

The biochemical characteristics of the product are displayed in Table 4.

Table 4: Biochemical Characteristics of *octanorm*

Parameter	
Total protein (of which ≥96% or ≥95% is human IgG, depending on regulatory requirements)	150 – 180 mg per mL
Maltose	70 – 90 mg per mL
Octoxynol	≤5 µg per mL
TNBP	≤1 µg per mL
IgA	≤0.6 mg per mL
Polysorbate 80	25 – 60 µg per mL
pH	5.0 – 5.8
Osmolality	310 – 380 mosmol/kg
Polymers + Aggregates	≤5% of the total chromatogram area
Monomers + Dimers	≥90% of the total chromatogram area
Fragments	≤5% of the total chromatogram area
Sodium	≤30 mMol/L

octanorm is a sterile solution of human normal immunoglobulin containing 16.5% (165 mg/mL) protein. Each batch (lot) of *octanorm* is prepared from at least 3,500 donations of human fresh frozen plasma. Effective viral reduction is obtained via a combination of 3 validated manufacturing steps: cold-ethanol fractionation, solvent/detergent treatment with TNBP and Octoxynol, and pH 4 treatment. The manufacture of *octanorm* is based on the *Octagam* manufacturing process including an additional adsorption step onto commercially available and widely used chromatography column for the removal of coagulation factor XI. The process is identical up to the step of diafiltration. After this step the product solution is concentrated to a target concentration of 200 g/L. Polysorbate 80 and maltose are added during final formulation to final concentrations of 25-60 µg/mL and 70-90 mg/mL, respectively.

The efficacy of the virus inactivation / removal procedures has been extensively validated according to relevant international guidelines. Further information can be found in the Investigators' Brochure.

For placebo, 0.9% sodium chloride solution will be used.

5.2 Packaging and Labelling

Each vial will be labelled as given in the following master labels:

US Master Label – Open label octanorm:

Caution: New Drug-Limited by Federal (or United States) law to investigational use

Study: **SCGAM-02**

Octanorm 16.5% Unit size: _____ **mL**

1 mL contains 165 mg protein of which ≥ 96% is human normal immunoglobulin.
Solution for subcutaneous injection.
To be stored at +2°C (36°F) to +8°C (46°F) and protected from light. Must not be frozen.
Must be inspected visually for particulate matter and discoloration prior to administration.
Do not use non-homogenous solutions or those that have a deposit.
To be warmed up to room or body temperature before use.
Dosage: please refer to the handling instruction provided.
Keep out of reach of children.

Patient no.: _____ Infusion Cycle: _____

Batch no.: _____ Infusion Session: _____

Expiration date: _____

Sponsor: OCTAPHARMA Pharmazeutika Produktionsges.m.b.H., Oberlaaer Str. 235, 1100 Vienna, Austria, Tel: [redacted]

EU Master Label – Open label octanorm:

FOR CLINICAL TRIAL USE ONLY

Study: **SCGAM-02**

Octanorm 16.5% Unit size: _____ **mL**

1 mL contains 165 mg protein of which ≥ 95% is human normal immunoglobulin.
Solution for subcutaneous injection.
To be stored at +2°C to +8°C and protected from light. Must not be frozen.
Must be inspected visually for particulate matter and discoloration prior to administration.
Do not use non-homogenous solutions or those that have a deposit.
To be warmed up to room or body temperature before use.
Dosage: please refer to the handling instruction provided.
Keep out of reach of children.

Patient no.: _____ Infusion Cycle: _____

Batch no.: _____ Infusion Session: _____

Expiration date: _____

Investigator:

Sponsor: OCTAPHARMA Pharmazeutika Produktionsges.m.b.H., Oberlaaer Str. 235, 1100 Vienna, Austria, Tel: [redacted]

US Master Label – Open label placebo:

Caution: New Drug-Limited by Federal (or United States) law to investigational use
Study: **SCGAM-02**
Sodium Chloride 0.9% w/v solution Unit size: _____ **mL**
Sterile solution for subcutaneous injection
1000 mL of solution contain
Sodium chloride 9.00 g
Electrolyte concentrations mmol per 1000 mL (approx):
Sodium 154 mmol
Chloride 154 mmol
Do not store above +25°C (+77°F) *[depending on product purchased]*. Do not freeze.
Only to be used if solution is clear and container undamaged.
Dosage: please refer to the handling instruction provided.
Patient no.: _____ Infusion Cycle: _____
Batch no.: _____ Infusion Session: _____
Expiration date: _____
Sponsor: OCTAPHARMA Pharmazeutika Produktionsges.m.b.H., Oberlaaer Str. 235, 1100 Vienna, Austria, Tel: [redacted]

EU Master Label – Open label placebo:

FOR CLINICAL TRIAL USE ONLY
Study: **SCGAM-02**
Sodium Chloride 0.9% w/v solution Unit size: _____ **mL**
Sterile solution for subcutaneous injection
1000 mL of solution contain
Sodium chloride 9.00 g
Electrolyte concentrations mmol per 1000 mL (approx):
Sodium 154 mmol
Chloride 154 mmol
Do not store above +25°C *[depending on product purchased]*. Do not freeze.
Only to be used if solution is clear and container undamaged.
Dosage: please refer to the handling instruction provided.
Patient no.: _____ Infusion Cycle: _____
Batch no.: _____ Infusion Session: _____
Expiration date: _____
Investigator: _____
Sponsor: OCTAPHARMA Pharmazeutika Produktionsges.m.b.H., Oberlaaer Str. 235, 1100 Vienna, Austria, Tel: [redacted]

Final labelling will comply with the national requirements of each country where the study is to be conducted. Blinded labels for syringes will be provided.

5.3 Conditions for Storage and Use

octanorm 16.5% must be stored and transported light-protected at 2 °C to +8 °C (36 °F to 46 °F) and must not be frozen. *octanorm* 16.5% must not be used after its expiration date.

Sodium chloride 0.9% solution should be stored and transported according to its product information. Conditions will be stated on the IMP label.

The authorised personnel at the site will ensure that the IMP is stored in appropriate conditions with restricted access and in compliance with national regulations.

5.4 Dose and Dosing Schedule

octanorm 16.5% is available in vials with different volumes of solution 12 mL (2 grams) or 48 mL (8 grams). Vials of different volume should be combined in order to reach the required volume of amount of IgG.

Subjects are randomly assigned to *octanorm 16.5%* 0.5 g/kg/week or to placebo (0.9% sodium chloride solution).

If a subject is randomized to receive placebo (0.9% sodium chloride solution), the same volume with the same infusion rate as would have been applied in case the subject would have been randomized to 0.5 g/kg *octanorm 16.5%* will be used.

Body weight is to be measured prior to the first IMP administration and reported to the IRT as it is needed for the calculation of the required IMP dose. Body weight is also to be measured at Visit 5 Week 12, and Visit 8 Week 24. These weight measurements are to be reported to the IRT and will be used by IRT for IMP dose adjustment.

octanorm or placebo has to be administered subcutaneously every week (±2 days).

A minimum interval of 4 days must be kept in between two consecutive subcutaneous infusion cycles.

5.5 Preparation and Method of Administration

Vials of *octanorm* or placebo must be allowed to warm to room or body temperature prior to infusion. Thereafter, *octanorm* or placebo should be infused subcutaneously using a syringe driver for precise infusion rates and standard infusion materials provided to the patients by the site. The correct amount of solution taken from 12 or 48 mL vials of *octanorm* or placebo containers will be infused with the aid of a syringe driver.

The content of the vials/containers will have to be transferred into the syringes suitable for the syringe driver selected.

octanorm or placebo must not be mixed with other medicinal products. An aseptic technique must be used throughout the procedure.

Each vial of *octanorm* must be examined visually by unblinded site personnel and if administered at home by the unblinded home healthcare nurse for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. Solutions that are cloudy or have a deposit must not be used. The same procedures should also be performed for 0.9% sodium chloride solution.

The mobile healthcare research nurses will be instructed in the use of the following:

- syringe driver,
- infusion techniques,
- aseptic technique,
- document completion and

- measures to be taken in case of severe AEs.

Patients will be instructed in keeping of a patient diary and measures to be taken in case of severe AEs. During the first four weeks (first 4 infusion cycles), all infusions will be administered at the study site. Apart from Visit 3, where at least the first session of an infusion cycle will also be administered at the site, the next two weeks can be performed either at the patient´s home by the mobile healthcare research nurses or at the site (decision to be taken by Investigator and patient based on previous experience). Thereafter, SCIG infusions will be administered at home by mobile healthcare research nurses, apart from Visits 4-9, where at least the first session of an infusion cycle will be administered at the site. Based on the Investigator´s decision a home infusion can be replaced with an on-site infusion if considered medically relevant. Investigator´s decision should be documented in this case in patient´s source documents.

Patients must be monitored at the study site for one hour after the infusion of *octanorm* or placebo.

octanorm or placebo (see below) has to be administered subcutaneously every week (±2 days) using a syringe driver for precise infusion rates. The total dose/volume of a weekly infusion will be calculated on the basis of the body weight. The weekly infusion will be performed in two separate sessions (= 1 infusion cycle for a given weekly administration). An infusion cycle comprises both sessions to be administered on 1 or 2 days, either on the same day or on two consecutive days or with maximum one day in between two sessions.

Infusion sites: Up to 6 injection sites and up to 2 syringe drivers can be used simultaneously in one session. In case the allowed flow rate cannot be reached with the 2 syringe drivers because of currently approved/available syringe drivers in the particular country – up to 4 syringe drivers can be used, although the number of simultaneous injection sites remains maximum 6. Up to 12 injection sites can be used consecutively during a single session. Injection sites should be at least 2 inches (approx. 5 cm) apart. The actual sites of injection should be changed with each administration.

Volume per injection site: In the first two weeks (infusion cycles 1-2), 20 mL per injection site should not be exceeded. In the next two weeks (infusion cycles 3-4), max. 25 mL per injection site are permitted. In infusion cycles 5 – 12, this may gradually be increased to 35 mL/site. Starting with infusion cycle 13 and when the previous volumes were well tolerated, increases of ≤ 10 mL/site per infusion cycle can be made up to a maximum of 60 mL/site.

Infusion rate: The initial flow rate in the first two weeks is 20 mL per hour per site. For subsequent infusions, the flow rate may gradually be increased to a maximum of 30 mL/hr/site as tolerated. The maximum flow rate for all sites combined should not exceed a total of 180 mL per hour.

5.6 Blinding, Emergency Envelopes, and Breaking the Study Blind

To maintain blinding, the unblinded pharmacist or designee will receive and prepare IMP. IMP will be prepared and infused in a manner that will blind the Investigator and other blinded personnel to the study treatment. Unblinded personnel must not communicate to the Investigator or other blinded site personnel which product was assigned to the subject. The total dose and required volume will be calculated on the basis of the bodyweight. Subjects randomized to receive placebo will receive the same volume as if the subject would have been

randomized to 0.5 g/kg *octanorm* 16.5%. IMP preparation during home treatments will be performed by unblinded mobile research nurses.

The subject and blinded study personnel will remain blinded with respect to study treatment throughout the entire 32 week treatment period.

To further assure the double-blind character of this study, the Investigator or designee who applies and provides the medication to the subject will not be involved in any evaluations other than drawing blood samples or checking for vital signs, i.e. will not be involved in any subject ratings (e.g. CSM, CDASI).

The Investigators will be provided with an unblinding procedure to disclose the actual treatment of a particular subject in case of medical emergency; this can be a sealed envelope or its electronic equivalence.

Blinding should only be broken under the following circumstances:

- Occurrence of serious and presumably related AEs but only if the Investigator needs to know the assigned treatment for a proper clinical management of the subject.
- If unblinding is required by the local regulatory authorities.

Whenever possible, the Investigator should notify the Sponsor prior to unblinding. However, the decision and the responsibility to break the blind in emergency situations resides solely with the investigator. In the event of medical emergency to keep subject safety, the investigator will be able to unblind a patient immediately without needing to contact any third party.

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.

5.7 Treatment Compliance

5.7.1 Drug Dispensing and Accountability

Any IMP provided to the site will be accounted for. This includes IMP received at the site and IMP dispensed to patients.

octanorm or placebo will be delivered to the participating sites by the Sponsor or designee.

A Drug Inventory and Dispensing Log will be kept current by the pharmacist or designee, detailing the dates and quantities of IMP received and dispensed to each subject/patient and the remaining quantity. The inventory and dispensing log will be available to the unblinded monitor to verify drug accountability during the study.

Unused IMP can be destroyed at the study site or returned to the Sponsor for destruction. Destruction can be initiated only after accountability has been verified and fully reconciled by the unblinded monitor and after the Sponsor has granted written approval of destruction. Empty or partially used vials should be destroyed at the study site or at the pharmacy following local policies.

5.7.2 Assessment of Treatment Compliance

Patients will receive all subcutaneous infusions either at the study site by authorized study personnel or by mobile healthcare research nurses at home.

Throughout the study, mobile healthcare research nurses will be asked to document the dates of home treatment, batch numbers, number of vials, volume and speed of infusion, number and location of injection site(s). Infusion details for infusions administered at the study site will be documented at the study site.

6 STUDY CONDUCT

Subjects have to be informed about the study details and have to give their written informed consent. A full written informed consent must be available before the start of any screening activities.

The flowchart of assessments by study visit is shown in Table 1.

Prior to treatment initiation, subjects will have to be screened for eligibility (inclusion and exclusion criteria).

If feasible, screening should be completed within 2 weeks. However, screening results should be available as soon as possible. Based on the screening results, the subjects' eligibility for the study is determined. The Baseline Visit is to be performed 4 weeks (+/- 4 days) after the last pre-study IGIV treatment.

For Screening failures, the reason for screen failure and demographic information will be entered into the eCRF.

6.1 Observations by Visit

6.1.1 Screening Visit (Visit 1; duration up to 14 days, i.e. Week -2 to 0)

The following assessments will be performed during the Screening Visit:

- Obtaining voluntarily given, written (signed and dated) informed consent.
- Demographic and baseline characteristics.
- Medical history and prior/concomitant therapy.
- Physical examination.
- Vital signs (including body weight and height).
- Standard ECG.
- Blood samples for safety laboratory (hematology and clinical chemistry).
- Blood samples for enzymes.
- Blood sample for biomarkers of disease activity.
- Pregnancy test (in WOCBP).
- CSM.
- Wells probability score for deep vein thrombosis (DVT).
- Wells probability score for pulmonary embolism (PE).
- Inclusion and exclusion criteria.
- Visit registration in IRT.

<u>For patients from Study GAM10-08:</u>

- SCGAM-02 Informed consent to be provided to patient before GAM10-08 Week 40 visit.

6.1.2 Visit 2 (Week 0; Baseline)

Subjects who are eligible will visit the study site and enter the treatment period after randomization.

Visit 2 should take place within 2 weeks after the Screening Visit. The Baseline Visit is to be performed 4 weeks (+/- 4 days) after the last pre-study IGIV treatment.

All eligible subjects will receive their first infusion session of either 0.5 g/kg *octanorm 16.5%* or placebo as per randomization. The following assessments will be performed:

Before infusion:

- Randomization and enrolment.
- SF-36v2.
- Physical examination.
- Vital signs and body weight.
- Blood sample for safety laboratory (hematology and clinical chemistry).
- Blood sample for additional safety lab parameters (serum haptoglobin and plasma-free hemoglobin)
- Direct Coombs' test (if positive, the antibodies responsible for the positive Coombs' test will be eluted to investigate their specificity (anti-A, anti-B or anti-D)).
- Urinalysis.
- Blood sample for serum IgG.
- Blood samples for enzymes.
- Blood sample for viral markers.
- Blood sample for D-dimers.
- CSM.
- CDASI.
- Visit registration in IRT.

During and after the infusion session:

- Administration/Infusion of IMP.
- Vital signs at least once during and 1 hour (+/- 10 min) after the end of the infusion session.

At least 1 hour after the infusion session:

- Wells probability score for DVT. If score is likely for DVT (≥2 points), perform Doppler scan and take blood sample for D-dimers.
- Wells probability score for PE.
- Assessment of local injection site reactions.

In addition, AEs will be monitored and concomitant therapy will be documented.

The second session of the infusion cycle will be administered either on the same day or on two consecutive days or with maximum one day in between two sessions.

During the first four weeks (first 4 infusion cycles), all infusion sessions will be administered at the study site.

For patients from Study GAM10-08:

- GAM10-08 Week 40 Termination Visit will be SCGAM-02 Baseline Visit. GAM10-08 Week 40 test results will be used for SCGAM-02 Baseline Visit evaluations and subjects who are eligible will be randomized and will receive their first SCGAM-02 infusion at the day of the GAM10-08 Week 40 Termination Visit.

6.1.3 Visit 3 (Week 4)

At least the first session of the infusion cycle needs to be administered at the site. The following assessments will be performed:

Before the infusion session:

- Patient diary check.
- Physical examination.
- Vital signs.
- Blood sample for safety laboratory (hematology and clinical chemistry). If hemoglobin is found to have decreased by ≥ 2 g/dL from baseline, the additional safety laboratory parameters (serum haptoglobin, plasma-free hemoglobin) and Direct Coombs' test will be performed as well.
- Blood sample for serum IgG.
- Blood samples for enzymes.
- CSM.
- CDASI.
- Visit registration in IRT.

During and after the infusion session:

- Administration/Infusion of IMP.
- Vital signs at least once during and 1 hour (+/- 10 min) after the end of the infusion session.

At least 1 hour after the infusion session:

- Wells probability score for DVT. If score is likely for DVT (≥2 points), perform Doppler scan and take blood sample for D-dimers.
- Wells probability score for PE.
- Assessment of local injection site reactions.

In addition, AEs will be monitored and concomitant therapy will be documented.

Apart from this visit, the fifth and sixth infusion cycle can be performed either at the patient´s home by the mobile healthcare research nurses or at the site (decision to be taken by Investigator and patient based on previous experience). Thereafter, SCIG infusions will be administered at home by mobile healthcare research nurses, apart from Visits 4-9, where at least the first session of an infusion cycle will be administered at the site. Based on the

Investigator´s decision a home infusion can be replaced with an on-site infusion if considered medically relevant.

Home visits:

To ensure blinding of the patient, SCIG infusions at home will always be administered by mobile healthcare research nurses who are obliged to keep patients blinded during home infusions.

The following assessments will be performed by research nurse:

Before the infusion session:

- Patient diary check for completeness
- Review of adverse events and concomitant medication changes. All new AEs and concomitant medication changes are to be documented by patient in the patient´s diary.
- Contact Investigator to discuss patient´s safety or IMP administration, if necessary

Preparation and administration of IMP

After the infusion session:

- Notify site staff about completed infusion session
- Schedule the next home visit

Patient has to take temperature 1 hour after the end of the infusion

6.1.4 Visit 4 (Week 8)

At least the first session of the infusion cycle will be administered at the site. The following assessments will be performed:

Before the infusion session:

- Patient diary check.
- Physical examination.
- Vital signs.
- Blood sample for safety laboratory (hematology and clinical chemistry). If hemoglobin is found to have decreased by ≥ 2 g/dL from baseline, the additional safety laboratory parameters (serum haptoglobin, plasma-free hemoglobin) and Direct Coombs' test will be performed as well.
- Blood sample for serum IgG.
- Blood samples for enzymes.
- CSM.
- CDASI.
- Visit registration in IRT.

During and after the infusion session:

- Administration/Infusion of IMP.
- Vital signs at least once during and 1 hour (+/- 10 min) after the end of the infusion session.

At least 1 hour after the infusion session:

- Wells probability score for DVT. If score is likely for DVT (≥2 points), perform Doppler scan and take blood sample for D-dimers.
- Wells probability score for PE.
- Assessment of local injection site reactions.

In addition, AEs will be monitored and concomitant therapy will be documented.

6.1.5 Visit 5 (Week 12)

At least the first session of the infusion cycle will be administered at the site. The following assessments will be performed:

Before the infusion session:

- Patient diary check.
- Physical examination.
- Vital signs (including body weight).
- Blood sample for safety laboratory (hematology and clinical chemistry).
- Blood sample for additional safety lab parameters (serum haptoglobin, plasma-free hemoglobin).
- Direct Coombs' test (if positive, the antibodies responsible for the positive Coombs' test will be eluted to investigate their specificity (anti-A, anti-B or anti-D)).
- Urinalysis.
- Blood sample for serum IgG.
- Blood samples for enzymes.
- Blood sample for biomarkers of disease activity.
- CSM.
- CDASI.
- Visit registration in IRT.

During and after the infusion session:

- Administration/Infusion of IMP.
- Vital signs at least once during and 1 hour (+/- 10 min) after the end of the infusion session.

At least 1 hour after the infusion session:

- Wells probability score for DVT. If score is likely for DVT (≥2 points), perform Doppler scan and take blood sample for D-dimers.
- Wells probability score for PE.
- Assessment of local injection site reactions.

In addition, AEs will be monitored and concomitant therapy will be documented.

6.1.6 Visit 6 (Week 16)

At least the first session of the infusion cycle will be administered at the site. The following assessments will be performed:

Before the infusion session:

- Patient diary check.
- Physical examination.
- Vital signs.
- Blood sample for safety laboratory (hematology and clinical chemistry). If hemoglobin is found to have decreased by ≥ 2 g/dL from baseline, the additional safety laboratory parameters (serum haptoglobin, plasma-free hemoglobin) and Direct Coombs' test will be performed as well.
- Blood sample for serum IgG.
- Blood samples for enzymes.
- CSM.
- CDASI.
- Visit registration in IRT.

During and after the infusion session:

- Administration/Infusion of IMP.
- Vital signs at least once during and 1 hour (+/- 10 min) after the end of the infusion session.

At least 1 hour after the infusion session:

- Wells probability score for DVT. If score is likely for DVT (≥2 points), perform Doppler scan and take blood sample for D-dimers.
- Wells probability score for PE.
- Assessment of local injection site reactions.

In addition, AEs will be monitored and concomitant therapy will be documented.

6.1.7 Visit 7 (Week 20)

At least the first session of the infusion cycle will be administered at the site. The following assessments will be performed:

Before the infusion session:

- Patient diary check.
- Physical examination.
- Vital signs.
- Blood sample for safety laboratory (hematology and clinical chemistry). If hemoglobin is found to have decreased by ≥ 2 g/dL from baseline, the additional safety laboratory parameters (serum haptoglobin, plasma-free hemoglobin) and Direct Coombs' test will be performed as well.
- Blood sample for serum IgG.
- Blood samples for enzymes.

- CSM.
- CDASI.
- Visit registration in IRT.

During and after the infusion session:

- Administration/Infusion of IMP.
- Vital signs at least once during and 1 hour (+/- 10 min) after the end of the infusion session.

At least 1 hour after the infusion session:

- Wells probability score for DVT. If score is likely for DVT (≥2 points), perform Doppler scan and take blood sample for D-dimers.
- Wells probability score for PE.
- Assessment of local injection site reactions.

In addition, AEs will be monitored and concomitant therapy will be documented.

6.1.8 Visit 8 (Week 24)

At least the first session of the infusion cycle will be administered at the site. The following assessments will be performed:

Before the infusion session:

- Patient diary check.
- Physical examination.
- Vital signs (including body weight).
- Blood sample for safety laboratory (hematology and clinical chemistry).
- Blood sample for additional safety lab parameters (serum haptoglobin, plasma-free hemoglobin).
- Direct Coombs' test (if positive, the antibodies responsible for the positive Coombs' test will be eluted to investigate their specificity (anti-A, anti-B or anti-D)).
- Urinalysis.
- Blood sample for serum IgG.
- Blood samples for enzymes.
- Blood sample for biomarkers of disease activity.
- CSM.
- CDASI.
- Visit registration in IRT.

During and after the infusion session:

- Administration/Infusion of IMP.
- Vital signs at least once during and 1 hour (+/- 10 min) after the end of the infusion session.

At least 1 hour after the infusion session:

- Wells probability score for DVT. If score is likely for DVT (≥2 points), perform Doppler scan and take blood sample for D-dimers.
- Wells probability score for PE.
- Assessment of local injection site reactions.

In addition, AEs will be monitored and concomitant therapy will be documented.

6.1.9 Visit 9 (Week 28)

At least the first session of the infusion cycle will be administered at the site. The following assessments will be performed:

Before the infusion session:

- Patient diary check.
- Physical examination.
- Vital signs.
- Blood sample for safety laboratory (hematology and clinical chemistry). If hemoglobin is found to have decreased by ≥ 2 g/dL from baseline, the additional safety laboratory parameters (serum haptoglobin, plasma-free hemoglobin) and Direct Coombs' test will be performed as well.
- Blood sample for serum IgG.
- Blood samples for enzymes.
- CSM.
- CDASI.
- Visit registration in IRT.

During and after the infusion session:

- Administration/Infusion of IMP.
- Vital signs at least once during and 1 hour (+/- 10 min) after the end of the infusion session.

At least 1 hour after the infusion session:

- Wells probability score for DVT. If score is likely for DVT (≥2 points), perform Doppler scan and take blood sample for D-dimers.
- Wells probability score for PE.
- Assessment of local injection site reactions.

In addition, AEs will be monitored and concomitant therapy will be documented.

6.1.10 Termination Visit (Week 32 or Drop-out Visit)

The Termination Visit is performed at Week 32.

The following assessments will be performed:

- SF-36v2.
- Patient diary check.

- Physical examination.
- Vital signs and body weight.
- Blood sample for safety laboratory (hematology and clinical chemistry).
- Blood sample for additional safety lab parameters (serum haptoglobin, plasma-free hemoglobin).
- Direct Coombs' test (if positive, the antibodies responsible for the positive Coombs' test will be eluted to investigate their specificity (anti-A, anti-B or anti-D)).
- Urinalysis.
- Blood sample for serum IgG.
- Blood samples for enzymes.
- Blood sample for viral markers.
- Blood sample for biomarkers of disease activity.
- CSM.
- CDASI.
- Wells probability score for DVT. If score is likely for DVT (≥2 points), perform Doppler scan and take blood sample for D-dimers.
- Wells probability score for PE.
- Monitoring of AEs.
- Assessment of local injection site reactions.
- Documentation of concomitant therapy.
- Pregnancy test (in WOCBP).
- Visit registration in IRT.

6.1.11 Week 33 Safety Follow-up

The Safety Follow-up visit is performed at week 33 (1-2 weeks after the last IMP administration). At minimum, all patients should be assessed for:

- Vital signs.
- Wells probability score for DVT. If score is likely for DVT (≥2 points), perform Doppler scan and take blood sample for D-dimers.
- Wells probability score for PE.
- Adverse Events.
- Concomitant therapy.

Other safety and/or efficacy laboratory assessments, and physical exam should be repeated only if found abnormal at the termination visit.

After the final examination, the clinical study is considered completed for the subject/patient. No further study-related assessments will be performed, unless safety concerns (e.g., ongoing AEs) require follow-up.

The Investigator will follow up on each AE until it has resolved or until the medical condition of the subject has stabilized. Any relevant follow-up information will be reported to the Sponsor.

6.1.12 Time Windows Used in this Study, including Tolerances

In this study, the following time windows and tolerances apply:

Table 5: Time Windows Used in This Study

Time Point	Time stated	Tolerance
Interval between visits	4 weeks	± 4 days
Interval between infusion cycles	1 week	± 2 days
Interval between infusion sessions	Same day or on two consecutive days or with maximum one day in between two sessions	1 – 54 hours
Vital signs	before IMP administration at the site	≤ 60 minutes
	1 hour after the infusion session	± 10 minutes
Direct Coombs' test	before IMP administration at the site	≤ 4 hours
Wells probability score for DVT	after IMP administration at the site	≥ 60 minutes
Wells probability score for PE	after IMP administration at the site	≥ 60 minutes

6.2 Duration of the Study

6.2.1 Planned Duration for an Individual Subject/Patient

The duration of the entire study for each subject will be up to 35 weeks and consists of the following segments: up to 2 weeks for Screening, then 32 weeks of double-blind treatment period, followed by a 1 week safety follow-up period.

For patients from GAM10-08 study, GAM10-08 Week 40 Termination Visit will be SCGAM-02 Baseline Visit.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed when all subjects have completed the planned observation period/Final Examination Visit.

The study as a whole should be completed within about 24 months. The estimated clinical start of the study (enrolment of first subject) is Q3 2018 with the estimated clinical end in Q2 2020.

The clinical end of the study is defined as the last visit of the last subject participating in the study.

The clock start date for results publication is the date of database lock of the clinical study database when all data cleaning activities have been completed.

6.2.3 Premature Termination of the Study

Both the Investigator and the Sponsor reserve the right to terminate the study at any time. In this event, any necessary 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 patients' interests.

Regulatory authorities and IECs/IRBs should be informed in accordance with national regulations.

Early termination of the study as a whole or by centre may apply for the following reasons:

6.2.3.1 Early Termination of the Entire Clinical Study

At any time, the study as a whole will be terminated prematurely if:

- New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk-assessment.
- If more than 3 TEEs (i.e. ischemic stroke, transient ischemic attack, cerebral infarction, cerebrovascular accident, cerebral thrombosis, embolic infarctions, [acute] myocardial infarction, deep vein thrombosis, pulmonary embolism, venous thrombosis excluding thrombophlebitis or infusion site thrombosis) are observed during the treatment period of the study, fulfilling the following criteria:
    - assessed as probably or possibly related to *octanorm* 16.5% treatment by Investigator and/or Sponsor;
    - confirmed by the Independent Data Monitoring Committee (IDMC);

  AND

  if ≤2 TEEs (as defined above) are observed during the treatment period of the study, fulfilling the following criteria:
    - assessed as probably or possibly related to placebo treatment by Investigator and/or Sponsor;
    - confirmed by the IDMC.

  NOTE: Causality assessments of suspected TEEs have to be made in a blinded manner by all involved parties (Investigator, Sponsor, IDMC). After individual causality assessment, the IDMC is entitled to unblind cases in order to monitor the stopping rule.

- If more than 4 clinically significant (definition see Section 7.3.2.1) hemolytic transfusion reactions (HTRs) are observed during the treatment period of the study, fulfilling the following criteria:
    - assessed as probably or possibly related to *octanorm* 16.5% treatment by Investigator and/or Sponsor;
    - confirmed by the IDMC.

  AND

  if less than 3 clinically significant HTRs are observed during the treatment period of the study, fulfilling the following criteria:
    - assessed as probably or possibly related to placebo treatment by Investigator and/or Sponsor;
    - confirmed by the IDMC.

  NOTE: Causality assessments of suspected HTRs have to be made in a blinded manner by all involved parties (Investigator, Sponsor, IDMC). After individual causality assessment, the IDMC is entitled to unblind cases in order to monitor the stopping rule.
- Any other reason rendering the continuation of the study impossible for the Sponsor.

6.2.3.2 Early Termination at an Individual Study Centre

At any time, the study can be terminated at an individual centre if:

- The centre cannot comply with the requirements of the protocol.
- The centre cannot comply with GCP standards.
- The centre's first patient is not recruited by 20 weeks after initiation of the centre.
- The required recruitment rate is not met.

Should the study be prematurely terminated, all study materials (IMPs, etc.) must be returned to the Sponsor.

7 ASSESSMENTS AND METHODS

7.1 Demographic and Baseline Information

The following information will be recorded during the Screening Visit:

7.1.1 Demographic and Baseline Characteristics

The demographic and baseline characteristics are sex, age, race, ethnic origin, height, weight, and Body Mass Index (BMI).

7.1.2 Medical History and Prior/Concomitant Medications

The medical history will be obtained by interviewing the subject/patient. Records of past diseases and treatments (e.g., hospital discharge letters) will be obtained for the study files, if available. Based on the available data patients will also be classified according to The European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for adult and juvenile idiopathic inflammatory myopathies (IIMs).

Prior and concomitant medications as well as physical therapy-directed exercise regimen will be obtained by interview.

For patients from GAM10-08 study: Information on medical history and on prior and concomitant therapy can be taken from GAM10-08 study records.

7.2 Efficacy Assessments

CSM assessments should always be performed by the same investigator or designee. The same applies to the assessment of CDASI. Training for CSM and CDASI will be done by third parties.

6 CSM of myositis disease activity have been established for clinical trials in subjects with DM and PM:

- Physician's Global Disease Activity (part of MDAAT; 10 cm VAS assessing global disease activity from "No evidence of disease activity" to "Extremely active or severe disease activity"; Disease Activity being defined as potentially reversible pathology or physiology resulting from the myositis).
- Patient's Global Disease Activity (10cm VAS assessing the overall activity of the patient's disease today from "No evidence of disease activity" to "Extremely active or severe disease activity", Disease Activity being active inflammation in the patient's muscles, skin, joints, intestines, heart, lungs or other parts of the body, which can improve when treated with medicines).
- Manual Muscle Testing (MMT-8; a set of 8 designated muscles tested bilaterally [potential score 0 – 150]).
- Health Assessment Questionnaire (HAQ; a generic rather than a disease-specific instrument; comprised of 8 sections: dressing, arising, eating, walking, hygiene, reach, grip, and activities. There are 2 or 3 questions for each section. Scoring within each section is from 0 [without any difficulty] to 3 [unable to do]. For each section the score given to that section is the worst score within the section. The 8 scores of the 8 sections are summed and divided by 8).[38, 39]

- Enzymes (aldolase, creatine kinase, alanine aminotransferase [ALAT], aspartate aminotransferase [ASAT], lactate dehydrogenase [LDH]).
- Extra-muscular activity (part of MDAAT; a combined tool that captures the physician's assessment of disease activity of various organ systems using [1] a scale from 0 = "Not present in the last 4 weeks" to 4 = "New - in the last 4 weeks [compared to the previous 4 weeks]" and [2] a VAS).

The CDASI is a clinician-scored single page instrument that separately measures activity and damage in the skin of DM patients for use in clinical practice or clinical/therapeutic studies. The modified CDASI (version 2) is the one in current use. The modified CDASI has 3 activity measures (erythema, scale, and erosion/ulceration) and 2 damage measures (poikiloderma and calcinosis) which are assessed over 15 body areas. In addition, Gottron's papules on the hands are evaluated both for activity and damage. Lastly, the activity of periungual changes and alopecia is assessed.[32]

7.2.1 Assessments for Primary Efficacy Endpoint(s)

"Clinically important deterioration" is defined as follows: 1) MMT-8 worsening ≥6 points (scale of 150) OR CDASI (Total Activity Score) worsening ≥5 points, AND 2) Physician's Global Disease Activity VAS worsening ≥2 cm.

7.2.2 Assessments for Secondary Efficacy Endpoint(s)

The CSM were validated by the International Myositis Assessment and Clinical Studies Group (IMACS). However, conjoint analysis was introduced to develop a definition of improvement derived from the 6 CSM to calculate the TIS. The TIS is a scale from 0 to 100 that allows for the discrimination between minimal, moderate and major responders depending on their improvement in the combined 6 CSM: ≥20 to 39 points being minimal improvement, ≥40 to 59 points being moderate improvement, and ≥60 points being major improvement.[37] It does not discriminate stable from worsening patients.

The Quality of Life questionnaire SF-36 is described in Section 7.4.3.

7.3 Safety Assessments

7.3.1 Assessments for Safety Endpoints

Any of the following drug safety information shall be collected:

- Adverse events (AEs) and serious adverse events (SAEs) temporally associated with the administration of IMP, comparator, or placebo (for definitions and reporting requirements, see Sections 7.3.2, through Section 7.3.5)
- Pregnancies, drug overdose, interaction, medication error, and post-study SAEs (see Section 7.3.9)

7.3.2 Adverse Events (AEs)

7.3.2.1 Definitions

- **Adverse event (AE):** An AE is any untoward medical occurrence in a study subject/patient receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.
- **Adverse drug reaction (ADR):** An ADR is any noxious and unintended response to an IMP related to any dose. The phrase 'response to an IMP' means that a causal relationship between the IMP and an AE carries at least a reasonable possibility, i.e., the relationship cannot be ruled out.
- **Other significant AEs:** Any marked laboratory abnormalities or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction, or significant additional concomitant therapy.
- **Withdrawal due to AE/ADR:** AE/ADR leading to discontinuation of treatment with IMP. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the subject/patient is stable. All follow-up information collected will be made available to the Sponsor.

7.3.2.2 Collection of AEs

The condition of the subject/patient will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard non-leading question such as "How have you been since the last visit/during the previous study period?" AEs should be registered starting from the first dose of IMP (start of first injection).

In addition, the Investigator will check the subject/patient diaries (if applicable) for any documented event.

Local injection site reactions are to be assessed by both patients and investigators.

Patients have to grade the overall perception of local reactions in their diaries at 24 hours (±3 hours) post-infusion session using a 4-point rating scale: 0=none, 1=mild, 2=moderate, 3=severe.

Investigators have to evaluate local reactions at approximately 1 hour post-infusion session at every study site visit, using the same 4-point rating scale: 0=none, 1=mild, 2=moderate, 3=severe.

Local infusion site reactions will be noted on the adverse event pages in the CRF.

Any AE or ADR occurring during the study will be noted in detail on the appropriate pages of the eCRF. If the subject reports several signs or symptoms representing a single syndrome or diagnosis, the diagnosis should be recorded in the eCRF. The Investigator will grade the severity of all AEs or ADRs (mild, moderate, or severe), the seriousness (non-serious or serious), and the causality as defined in Sections 7.3.2.3, 7.3.2.4, and 7.3.3. The Sponsor is responsible for assessing the expectedness of each ADR (expected or unexpected) as defined in Section 7.3.2.5.

In the event of clinically significant abnormal laboratory findings, the tests will be confirmed and the patient followed up until the laboratory values have returned to normal and/or an adequate explanation for the abnormality has become available.

Diseases, signs and symptoms, and/or laboratory abnormalities already present before the first administration of IMP will not be considered AEs unless an exacerbation in intensity or frequency (worsening) occurs.

The Investigator will provide detailed information about any abnormalities and about the nature of and reasons for any action taken as well as any other observations or comments that may be useful for the interpretation and understanding of an AE or ADR.

7.3.2.3 Severity of AEs

The intensity/severity of AEs will be graded as follows:

- **Mild:** an AE, usually transient, which causes discomfort but does not interfere with the subject's/patient's routine activities
- **Moderate:** an AE which is sufficiently discomforting to interfere with the subject's/patient's routine activities
- **Severe:** an AE which is incapacitating and prevents the pursuit of the subject's/patient's routine activities

The grading of an AE is up to the medical judgement of the Investigator and will be decided on a case-by-case basis.

7.3.2.4 Causality of AEs

The relationship of AEs to the administered IMP will be assessed by the Investigator:

- **Probable:** reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the subject's/patient's clinical state.
- **Possible:** reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.
- **Unlikely:** reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the subject's/patient's clinical state or by environmental factors or other therapies administered.
- **Not related (unrelated):** events for which sufficient information exists to conclude that the aetiology is unrelated to the IMP.
- **Unclassified:** reports which for one reason or another are not yet assessable, e.g., because of outstanding information (can only be a temporary assessment).

7.3.2.5 Classification of ADRs by Expectedness

ADRs will be classified by the Sponsor as either expected or unexpected:

- **Expected:** an ADR that is listed in the current edition of the Investigator's Brochure or other reference safety information.
- **Unexpected:** an ADR that is not listed in the current edition of the Investigator's Brochure or other reference safety information, or that differs because of greater severity or greater specificity.

7.3.2.6 Outcome of AEs

The outcome of all reported AEs has to be documented as follows:

1. Recovered, resolved
2. Recovering, resolving
3. Not recovered, not resolved
4. Recovered, resolved with sequelae
5. Fatal
6. Unknown

NOTE: A subject's/patient's **death** per se is not an event, but an outcome. The event which resulted in the subject's/patient's death must be fully documented and reported, even in case the death occurs within 4 weeks after IMP treatment end and regardless of whether or not it is considered treatment-related.

7.3.2.7 Action(s) taken

AEs requiring action or therapy must be treated with recognised standards of medical care to protect the health and wellbeing of the subject/patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment in an emergency situation.

The action taken by the Investigator must be documented:

a) General actions taken in the event of an AE

- None
- Medication (other than IMP) or other (e.g., physical) therapy started
- Test performed
- Other (to be specified)

b) IMP-related actions taken in the event of an AE

- None
- Product withdrawn
- Dose reduced
- Dose increased

The Investigator will follow up on each AE until it has resolved or until the medical condition of the subject/patient has stabilised. Any relevant follow-up information will be reported to the Sponsor.

7.3.3 Serious Adverse Events (SAEs)

A **serious AE (SAE)** is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (see below),
- requires hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is another important medical event.

NOTE: The term 'life-threatening' refers to an event in which the subject/patient was, in the view of the reporting Investigator, at immediate risk of death at the time of the event; it does not refer to an event which may hypothetically have caused death had it been more severe.

In deciding whether an AE/ADR is serious, medical judgment should be exercised. Thus, important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject/patient or may require intervention to prevent one of the other outcomes listed in the definitions above should also be considered serious.

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent should be reported as SAE. A suspected virus transmission means that virus antigen has been detected in the patient. A passive transmission of antibodies alone does not constitute a suspected virus transmission.

7.3.4 SAE Reporting Timelines

All SAEs, whether or not they are suspected to be related to study treatment, are to be reported immediately by telephone, fax, or email to the Clinical Project Manager or designee.

The contact details will be communicated at the study initiation visit.

In addition, within 24 hours after recognition of the event, an Octapharma Serious Adverse Event Report must be completed and submitted to:

Ex- US & Canada:

E-mail: [redacted]

Fax: [redacted]

US & Canada:

E-mail: [redacted]

Fax: [redacted]

24 hours emergency telephone number:

Europe: [redacted]

USA: [redacted]

Waivers the from SAE Reporting Requirement

Waivers from the SAE reporting requirement include:

- hospitalizations due to infusions on consecutive days (e.g. for subjects with long travel hours);
- surgeries that are elective or were planned before study entry;
- prolongation of existing hospitalizations for economic or social, but not medical, reasons.

Such hospitalizations, surgeries, or prolongation of hospitalizations should not be considered SAEs.

7.3.5 Adverse Events of Special Interest (AESI)

The following AEs are defined as AESI:

- thromboembolic events (TEEs);
- hemolytic transfusion reactions (HTRs).

For these AESI, the general definitions and procedures that are described elsewhere in Section 7.3 apply as well, and they must be reported as SAEs. Premature termination criteria related to AESI are defined in Section 6.2.3.1. The IDMC will review all AESI in real time through an electronic system to be set up by the sponsor.

7.3.5.1 Thromboembolic Events (TEEs)

There is clinical evidence of an association between IgG administration and TEEs such as ischemic stroke, transient ischemic attack, cerebral infarction, cerebrovascular accident, cerebral thrombosis, embolic infarctions, [acute] myocardial infarction, deep vein thrombosis (DVT), pulmonary embolism (PE), venous thrombosis.

TEEs will be monitored as follows:

- Wells criteria for assessment of probability for possible DVTs at each visit [40] modified according to NICE Clinical Guideline 144, 2012]:

Present		**Score**
☐	Active cancer (treatment ongoing, within 6 months, or palliative)	+1
☐	Paralysis, paresis or recent plaster immobilization of the lower extremities	+1
☐	Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anesthesia	+1
☐	Localized tenderness along the distribution of the deep venous system	+1
☐	Entire leg swollen	+1
☐	Calf swelling at least 3 cm larger than asymptomatic side	+1
☐	Pitting edema confined to the symptomatic leg	+1
☐	Collateral superficial veins (non-varicose)	+1
☐	Previously documented DVT*	+1
☐	An alternative diagnosis is at least as likely as DVT	-2
Clinical Probability Simplified Score	DVT likely ≥2 points DVT unlikely ≤1 point	

*Note: This is also an exclusion criterion.

- If the Well's DVT probability score is ≥2, then a Doppler screening for DVT will have to be completed (recommended: Doppler using color duplex sonography) and a blood sample will have to be taken for D-dimers.

- Wells criteria for assessment of probability for possible PE at each visit [41]; modified according to NICE Clinical Guideline 144, 2012]:

Present		Score
☐	Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
☐	An alternative diagnosis is less likely than PE	3
☐	Heart rate > 100 beats per minute	1.5
☐	Immobilization for more than 3 days or surgery in the previous 4 weeks	1.5
☐	Previous DVT/PE	1.5
☐	Hemoptysis	1
☐	Malignancy (on treatment, treated in the last 6 months, or palliative)	1
Clinical Probability Simplified Score	PE likely >4 points PE unlikely ≤4 point	

*Note: This is also an exclusion criterion.

Therapeutic measures managing suspected TEEs shall be initiated according to local clinical practice (e.g. anticoagulation).

7.3.5.2 Hemolytic Transfusion Reactions (HTRs)

HTRs can develop subsequent to immunoglobulin therapy. Immunoglobulin-related hemolysis is associated with passive transfer of anti-A and anti-B hemagglutinins.

HTRs will be monitored as follows at pre-defined visits (see Flowchart of Study Events):

- Direct Coombs' test. If a positive result is obtained, the antibodies responsible for the positive test result will be eluted to investigate their specificity (anti-A, anti-B or anti-D).
- Other safety lab parameters: hemoglobin, serum haptoglobin, plasma-free hemoglobin, LDH.
- Urinalysis parameters.

Intravascular hemolysis will be suspected if all of the following criteria are fulfilled (modified acc. to FDA Guidance for Industry 2008[2]):

- a positive direct Coombs' test result;
- a drop in hemoglobin of 2 g/dL or greater;
- a drop in serum haptoglobin to below the lower limit of normal;
- a rise in serum LDH from baseline.

In case of a patient's positive direct Coombs test the investigator has to check if the above mentioned criteria are fulfilled. The results of these additional tests and any clinical signs or symptoms potentially related to hemolysis will be documented in the patient's medical record.

[2] Guidance for Industry. Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency. 2008

Therapeutic measures managing suspected HTRs shall be initiated according to local clinical practice.

7.3.6 Laboratory Tests

The following laboratory parameters will be investigated during the study at the time points specified in Section 6.1.

7.3.6.1 Central Laboratory

The following laboratory tests will be done at a central laboratory:

Clinical chemistry: Na+ (sodium), K+ (potassium), glucose, ALAT, ASAT, LDH, total bilirubin, BUN (blood urea nitrogen) or urea, creatinine, albumin.

Hematology: hematocrit, hemoglobin, complete blood count with differential (red blood cell counts, white blood cell counts [neutrophils, eosinophils, basophils, lymphocytes, monocytes], platelets).

Additional safety laboratory parameters:
serum haptoglobin and plasma-free hemoglobin.

Direct Coombs' test: if positive, the antibodies responsible for the positive Coombs' test will be eluted to investigate their specificity (anti-A, anti-B or anti-D).

D-dimers.

Serum IgG.

Enzymes: aldolase, creatine kinase and, if clinical chemistry will be performed by a local laboratory, ALAT, ASAT and LHD. For the CSM only values measured in the central laboratory will be used.

Viral markers: details see Section 7.3.7.

Pregnancy test: in blood if not performed locally.

Urinalysis: protein, glucose, pH, nitrite, ketones, leukocytes, hemoglobin, bilirubin, urobilinogen, and urine hemosiderin.

Blood and urine sampling will take place according to the time points given in Section 6.1. The methods used for each parameter and the normal ranges of each determination will be provided in the Clinical Study Report. A lab manual detailing blood and urine sampling and shipment procedures will be provided to each study site.

7.3.6.2 Local Laboratory

The following laboratory tests will in some countries be done by the local laboratories of each study site:

- Hematology: hematocrit, hemoglobin, complete blood count with differential (red blood cell counts, white blood cell counts (neutrophils, eosinophils, basophils, lymphocytes, monocytes), platelets.
- Chemistry: Na+ (sodium), K+ (potassium), glucose, ALAT, ASAT, LDH, total bilirubin, BUN (blood urea nitrogen) or urea, creatinine, albumin.
- Pregnancy test: either in urine or in blood.

- Urinalysis: protein, glucose, pH, nitrite, ketones, leukocytes, hemoglobin, bilirubin, urobilinogen, and urine hemosiderin.

The methods of determination and normal ranges for each parameter will be provided in the clinical study report.

7.3.7 Viral Safety Tests

Viral marker samples will be taken before the first IMP infusion at Baseline and at the Termination Visit.

Viral marker samples will be analysed at a central laboratory.

Full blood sample must be taken and centrifuged, aliquoted in storage tubes, and the storage tubes must be frozen at ≤–70°C. Further details will be provided in the lab manual.

At sites where a freezer of –70°C or below is not available, samples can be stored at or below –20°C. In such cases, shipment to the central laboratory should be performed shortly, but not later than 2 months after the day of collection.

Samples will be analysed by serology tests or nucleic acid testing for HIV, hepatitis B and hepatitis C virus. In case of any change of a patient's viral status between baseline and follow-up and a suspected seroconversion, the viral tests will be repeated by the laboratory. In case the result is confirmed, additional testing will be performed as necessary to rule out or confirm suspected transmission of an infectious agent.

Retention samples of all blood draws for virus safety will be kept at ≤–70°C at the central laboratory for possible future testing.

7.3.8 Vital Signs and Physical Examination

To evaluate short-term tolerance, vital signs will be monitored. The vital signs obtained at the time points specified in Section 6.1 at each on-site infusion are blood pressure, body temperature, pulse rate, and respiratory rate. Measurements will be carried out before the start of each infusion, at least once during and 1 hour (+/- 10 min) after end of each infusion session.

At the home infusions, patients will measure their body temperature around 1 hour after the end of the infusion session.

Physical examinations will be performed at the visits specified in Section 6.1. Body weight will be measured at baseline, at weeks 12 and 24 prior to IMP administration and at the Termination visit.

7.3.9 Other Relevant Safety Information

a) Post-study related safety reports

Any SAE which occurs up to 4 weeks after the last IMP administration should be reported by the Investigator to the Sponsor in case the Investigator becomes aware of it. Proactive monitoring for post-study SAEs is not required.

In case a post-study SAE is identified, the Investigator should complete an SAE form and also state the relation to the clinical study in the report.

Deaths occurring within 4 weeks after the last IMP administration should also be reported, regardless of whether or not they are considered treatment-related.

b) Pregnancies

Clinical experience with immunoglobulins suggests that no harmful effects are to be expected on the course of pregnancy, or on the fetus and the neonate, or on fertility.

However, every effort will be made to avoid a pregnancy during the use of an IMP up to four weeks after last IMP infusion. However, contraception for male subjects and partners of women included in the trial are not compulsory.

WOCBP using an acceptable effective contraceptive method during the study will be enrolled.

Pregnancy test (serum or urine) will be completed at Screening and Termination Visit.

WOCBP is defined as fertile woman, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Acceptable effective contraceptive measures include the following:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide

Pregnancies occurring during the study (foetal exposure to the IMP) need to be reported.

In case of pregnancy during the study, the Investigator should complete the Pregnancy Notification Form and send or fax it to the Clinical Project Manager or designee (see Section 7.3.4).

Follow-up information on the outcome of both mother and foetus will be requested by a Sponsor representative.

Overdose, interaction, and medication error

The following safety relevant information should be reported as AE or, if the reaction fulfills one of the criteria for seriousness, as SAE.

c) Drug overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than the known therapeutic dose that is of clinical relevance. The reaction must be clearly identified as an overdose.

d) Drug interaction

A drug interaction is a situation in which a substance or medicinal product affects the activity of an IMP, i.e., increases or decreases its effects, or produces an effect that none of the products would exhibit on its own. The reaction must be clearly identified as a drug interaction.

e) Medication error

A medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, or instructions for use/labelling. The reaction must be clearly identified as a medication error.

7.4 Other Assessments

7.4.1 Drug Concentration Measurements

The trough level IgG concentrations will be measured at each visit prior to IMP administration in order to potentially correlate the IgG levels with the disease activity and responder classification.

7.4.2 Blood Sample for Biomarkers of Disease Activity

A biorepository blood sample will be taken in order to investigate potential biomarkers of disease activity (e.g. myositis-specific antibodies, cytokine, chemokine or monoclonal antibody changes).

It is not intended to conduct genetic testing on the biorepository blood samples in the future.

7.4.3 Quality of Life Assessment

The generic SF-36v2 Health Survey will be used for assessing quality of life (www.sf-36.org/; www.qualitymetric.com). The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. The SF-36 is the most widely evaluated generic patient assessed health outcome measure being used in more than 200 diseases and conditions. It has been validated in multiple diseases and languages and has been used successfully in more than 600 randomized clinical trials reported in over 240 scientific and medical journals. The SF-36 has been proven responsive in 44 disease conditions and is accepted by the FDA as proof of benefit for improved functioning and other patient-reported outcomes. Its newer version, the SF-36v2, is available in 170 language translations.

The SF-36v2 has mental (4) and physical (4) component subscales.

7.5 Appropriateness of Measurements

The measurements selected in this study are appropriate to verify the clinical efficacy of SCIG in DM. The study design includes all major scientific, state-of-the-art interventions with respect to assessment of the efficacy, safety and tolerability of SCIG administration in DM patients.

Despite significant morbidity and mortality associated with DM/PM, there are currently no therapies approved for these syndromes by the US or European regulatory authorities, FDA and EMA, based on adequate randomized controlled trials. However, with the advancement in novel therapeutics that target various biological pathways implicated in the pathogenesis of DM/PM, there is a need for well-designed clinical trials using validated and universally accepted outcome measures.[42] Recent clinical trials completed in adult DM/PM and juvenile DM have utilized varying response criteria, again highlighting the need for both data- and consensus-driven criteria to be used uniformly in future studies.[43-45]

Patients with "clinically important deterioration" as defined in Section 3.1.1 will be classified as non-responders, and used as primary endpoint. Clinically important deterioration was defined by the study Steering Committee, consisting of several experts in the field, based on available clinical data and experience. The definition combines established measures of muscle weakness/skin involvement (MMT-8/CDASI) with physician's disease activity assessment. The definition of Oddis et al. 2013 [31] used in other studies including ProDERM was considered too sensitive for well-maintained patients with low disease activity at study entry, and had thus to be adapted.

The CDASI is a clinician-scored single page instrument that separately measures activity and damage in the skin of DM patients for use in clinical practice or clinical/therapeutic studies. The modified CDASI (version 2) is the one in current use. The modified CDASI has 3 activity measures (erythema, scale, and erosion/ulceration) and 2 damage measures (poikiloderma and calcinosis) which are assessed over 15 body areas. In addition, Gottron's papules on the hands are evaluated both for activity and damage. Lastly, the activity of periungual changes and alopecia is assessed.[32]

CSM of myositis disease activity for DM/PM clinical trials have been established and validated by the IMACS Group.[33-35] Very recently, these IMACS CSM have been further developed into conjoint-analysis hybrid response criteria combining 6 CSM to determine clinically meaningful improvement in the Total Improvement Score (TIS).[37] A big advantage of these hybrid response criteria over the previous IMACS response criteria is that inclusion criteria for clinical trials will not require a minimal severity in any CSM, because all levels of improvement in each CSM contribute more or less to the response (the previous IMACS preliminary response criteria required a baseline deficit of at least 20% in each CSM in the clinical trial inclusion criteria to enable reaching the threshold of ≥20% improvement in CSM after treatment).[36]

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records, allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (e.g., case histories or subject/patient files for each subject/patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each subject enrolled, the Investigator will indicate in the source record(s) that the subject/patient participates in this study.

All data entered in the CRF must be supported by source data in the subject/patient records.

The Investigator will permit study-related monitoring, audit(s), IEC/IRB review(s), and regulatory inspection(s), by providing direct access to the source data/records.

The Investigator may authorise site staff (e.g., sub-investigators, nurses) to enter study data into the CRF. This must be documented in the Delegation of Authority Log signed by the Investigator.

8.1.2 Electronic Case Report Forms

For each patient enrolled, an electronic CRF (eCRF) will be completed within the Electronic Data Capture (EDC) system and approved by the Investigator or an authorised sub-investigator.

Study site staff (e.g., research nurse) will be responsible for entering patient data into the validated EDC system. All site personnel will be trained on the EDC system and study specific eCRFs prior to receiving access to the live database for data entry.

The site is also provided with the approved eCRF Completion Guidelines which will assist in data entry and data issues/questions. The site will be notified once the database is active to begin data entry. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or change eCRF data must be listed in the Delegation of Authority Log.

8.1.3 Changes to Case Report Form (CRF) Data

Monitors will perform source data verification (SDV) as defined for the study.

If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated programmatically within the EDC system, and 'manual' queries will be generated by either a monitor or Data Management.

Discrepancies and queries can only be corrected by the Investigator(s) or other authorised site personnel. An audit trail documents all changes to the data over the entire study period. If the reason for a change is not obvious, a comment must be supplied in the query's response, stating the reason for the change, prior to closing. The study monitor should provide guidance

to Investigator(s) and the Investigator(s)' designated representatives on making such corrections.

Once queries have been resolved by the site staff, the responses are assessed by Data Management. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks are performed and programs are run throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the Investigator prior to database lock.

8.2 Information to Investigators

An Investigator's Brochure (IB) will be handed out to the Investigator before the start of the study. The IB contains all information in the Sponsor's possession necessary for the Investigator to be fully and accurately informed about the safety of the IMP under evaluation and the respective benefit-risk ratio.

The IB will be updated by the Sponsor at regular intervals and whenever relevant new information concerning the IMP becomes available.

The Investigator will be informed about the methods for rating relevant study outcomes and for completing CRFs to reduce discrepancies between participating Investigator and study sites.

The Investigator will be kept informed of important data that relate to the safe use of the IMP as the study proceeds.

8.3 Responsibilities

The Principal Investigator is accountable for the conduct of the clinical study. Responsibilities may be delegated to appropriately qualified persons.

A Delegation of Authority Log will be filled in and signed by the Principal Investigator. In accordance with this authority log, study site staff (e.g., sub-investigators, nurses) is authorised to perform tasks relating to the study.

Monitoring will either be done by the Sponsor or by a subcontractor (to be appointed later).

All parties involved in the study are responsible to comply with local and international obligations, regulatory requirements and duties in accordance with local laws, GCP and Good Laboratory Practice guidelines, SOPs and other applicable regulations.

8.4 Investigator's Site File

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (e.g., copies of the protocol, study approval letters, all original informed consent forms, site copies of all CRFs, drug dispensing and accountability logs, correspondence pertaining to the study, etc.) should be filed accurately and kept by the Investigator for the maximum period of time required by local regulations.

The Investigator is responsible for maintaining a confidential subject/patient identification code list, which provides the unique link between named source records and CRF data for the Sponsor. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.5 Provision of Additional Information

On request, the Investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records, ensuring that the subject's/patient's confidentiality is maintained. This is particularly important when errors in data transcription are encountered. In case of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the subject's/patient's confidentiality is protected in accordance with applicable regulations.

8.6 Committees

8.6.1 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established by the Sponsor. The IDMC will be composed of 3 experts in the field of immunology, rheumatology, and dermatology and of 1 unblinded statistician. The members of the IDMC must not actively recruit subjects/patients.

The IDMC will have the following responsibilities:

- to review all AESI in real time and monitor the stopping rules for TEEs and HTRs;
- to review relevant safety data periodically;
- to give advice on the continuation, modification, or termination of the study.

A Charter will be prepared before study start and will define in detail the composition, responsibilities, and procedures of the IDMC.

8.6.2 Steering Committee

A Steering Committee will be appointed by the Sponsor. This committee will be composed of investigators, other experts in myositis not otherwise involved into this study and representatives of the Sponsor.

The Steering Committee will be responsible, among others, for the scientific integrity of the study, maintaining the quality of study conduct, scientific quality of any protocol amendments and the final study report, and providing input to or co-authoring publications. The Steering Committee will also be responsible for any decision with regard to the biorepository blood samples as defined in Section 7.4.2.

The Steering Committee will be kept blinded until the blind is officially broken.

9 STATISTICAL METHODS AND SAMPLE SIZE

The statistical analysis will be delegated under an agreement of transfer of responsibilities to an external CRO. All Octapharma procedures and policies have to be met by this CRO. Discrepancies or exceptions are to be approved by the Sponsor's Manager of Biometrics.

9.1 Determination of Sample Size

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 safety reason or lack of efficacy will also be analysed as patients with clinically important deterioration.

The following assumptions for the true proportion of patients to be analysed 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 randomised 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 to be 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 enrol a minimum of 78 patients, randomized to the two treatments groups in a balanced 1:1 ratio.

9.2 Statistical Test Procedure

To test the null hypothesis H_0 against the alternative hypothesis H_A a two-sided Pearson Chi-square Test for Proportion Difference will be performed at a significance level of 5% to compare the placebo group against the high dose group.

If a subject is prematurely withdrawn from the study, or misses data required for the evaluation of the primary endpoint, this subject will be analysed as a treatment failure, i.e. as having a clinically important deterioration.

9.3 Statistical Analysis Plan

A formal statistical analysis plan (SAP) describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to the start of the statistical analysis. A detailed list of all tables, figures and graphs, and the analysis

populations used for each analysis will be appended to the SAP when all feedback from authorities will be available.

9.4 General Principles of Statistical Analysis

In accordance with the design and objectives of this study, the statistical analysis will include the test of the statistical hypothesis of the study and a summary and detailed description of all data collected during the investigation. Descriptive methods and graphs will be used to present study results for each treatment group. Continuous variables will in general be described by number of valid (evaluable) cases, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum. Categorical variables will be described by number of cases, frequency and percentage. If appropriate, continuous variables may be categorized and additionally treated as ordinal variables.

The level of significance is set at 0.05 (5%) for the study.

If considered relevant, tests for statistical significance besides the test of the study hypothesis will be presented for important parameters, but shall be interpreted in a descriptive-exploratory way only. No adjustment of level of significance for these tests will be performed.

Where appropriate, 95% confidence intervals for means and proportions will be computed.

The statistical analysis will focus on the comparison between subcutaneous immunoglobulin *octanorm* and placebo on basis of the study endpoints assessed in the 32-week treatment period.

9.5 Populations for Analysis

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 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 therapy
- Subjects who had no CSM or CDASI at Week 32.

Protocol deviations during the safety follow up are irrelevant for the definition of this population.

9.6 Analysis of Patient Disposition

The description of patient disposition will be based on the all patients enrolled set.

The number of patients enrolled, randomized and treated will be depicted. A listing will be provided of all patients who discontinued the study, including their reason for discontinuation.

The reasons for the assignment of the patients to the different analysis populations are presented and a listing will be produced showing the belonging of each patient enrolled into the study to the analysis populations.

9.7 Efficacy Analysis Plan

9.7.1 Analysis of the Primary Efficacy Endpoint Proportion of Patients with Clinically Important Deterioration

Evaluation of primary efficacy endpoint will be made with the FAS population and the PP population. The FAS analysis is considered the actual primary study outcome, whereas 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.

If a subject is prematurely withdrawn from the study, or misses data required for the evaluation of the primary endpoint, this subject will be analysed as treatment failure, i.e. as having a clinically important deterioration. This conservative approach was chosen to obviate discussions about possible relatedness between failure to complete the study and the underlying disease, study procedures, or adverse medical conditions on the individual patient level. 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 a EU Member State request, and the primary efficacy endpoint will also be analysed on basis of their individual evaluation of treatment stops. 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 primary efficacy outcome will also be presented for the subgroups defined by age, sex, race and geographical region (North America / Europe).

The H_0 hypothesis will be tested as described in Section 9.2. 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.

9.7.2 Analysis of the Secondary Efficacy Endpoints

Evaluation of secondary efficacy endpoints will be made with the FAS population. In case essential differences would be found between the FAS and PP population for the primary efficacy endpoint, the analysis of the secondary endpoints will be performed for the PP population too.

All secondary efficacy endpoints will be analysed and presented in full detail by means of descriptive statistics, including summary and frequency tables, confidence intervals and graphs as will be detailed in the SAP and its appendices.

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.

9.8 Analysis of Compliance of Administered Treatment

The following parameters will be listed and summarized per patient 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.

9.9 Safety Analysis Plan

Evaluation of safety will be made with the SAF population. Patients will be analysed by actual treatment group.

If present, adverse events in patients who are not included in the SAF population will be listed.

The safety analysis will comprise descriptive statistics, tabulations and listings of all adverse events, safety laboratory results, viral markers, vital signs, physical examination findings, and any other relevant safety information as detailed in Section 7.3.

Adverse events will be coded according to the MedDRA system and described according to their preferred term and the system organ class. Statistical analysis will not take in account MedDRA low level terms but will start at preferred term level. Information pertaining to adverse events noted during the study will be listed by patient, detailing verbatim given by the investigator, preferred term, system organ class, date of onset, date of resolution, outcome, seriousness, criteria of seriousness, and relationship to study treatment. The onset of adverse events will also be shown relative (in number of days) to the day of first infusion of study treatment. All serious adverse events will be described in detail in the study report, based on CIOMS-listings and CRF-data.

In addition to an analysis of all adverse events, adverse events with a causal relation to the study treatment, that is adverse reactions, will be analysed separately.

9.10 Handling of Missing Data

For missing data with respect to the primary endpoint evaluation, please refer to Section 9.7.1.

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 caused by subjects who dropped out of the study or for other reasons will not be replaced by any methods of imputation. Instead, frequency of missing values will be presented.

9.11 Deviations from the Previously Described Statistical Plan

Any deviations from the previously described statistical plan will be described and justified in a protocol amendment and/or in the final study report.

9.12 Randomisation, Stratification, and Code Release

All subjects qualified to participate in the study at baseline will be block randomized to one of the two treatment arms by an electronic IRT tool. The randomization will apply a randomization ratio of 1:1 with respect to *octanorm* 0.5 g/kg/week and placebo.

The block randomization method is used to ensure a balance in sample size across groups over time. The block size will be determined by the statisticians responsible for randomization and will only be known to the statisticians themselves and the programmer of the IRT system. Varying block sizes may be used to facilitate balanced enrolment.

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 study site personnel or to the sponsor or any CRO personnel responsible for the conduct of the study or the analysis of data.

Blinding will only be broken in circumstances described in 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.

9.13 Interim Analysis (if Applicable)

No interim analysis is planned.

9.14 Centre effects

As there are 45 centres planned, and the number of subjects per centre is small, centre effects will not be taken into account.

9.15 Coding

The following coding dictionaries will be used:

- Medical history and adverse events will be coded with the Medical Dictionary for Regulatory Activities (MedDRA, according to the version specified in the Data Management Plan).
- Prior and Concomitant 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.

10 ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical/Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP guidelines, and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (e.g., CRO) as required by national law and in accordance with FDA/Regulatory Authority regulations.

10.2 Approval of Study Documents

The study protocol, a sample of the subject/patient information and informed consent form, any other materials provided to the subjects/patients, and further requested information will be submitted by the Sponsor or the Investigator to the appropriate IEC/IRB and the Regulatory Authority. The study must be approved by the IEC/IRB and the Regulatory Authority before any IMP may be shipped to the study sites and any subject/patient is exposed to a study-related procedure.

The Sponsor, the Investigator, and any third party (e.g., CRO) involved in obtaining approval must inform each other in writing that all ethical and legal requirements have been met before the first subject/patient is enrolled in the study.

10.3 Subject/Patient Information and Informed Consent

The Investigator will obtain freely given written consent from each subject/patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study which is relevant to the subject's/patient's decision to participate. The informed consent form must be signed, with name and date and time noted by the subject/patient, before the subject/patient is exposed to any study-related procedure, including screening tests for eligibility.

The Investigator will explain that the subjects/patients are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify. The Investigator will complete the informed consent section of the eCRF for each subject/patient enrolled.

Each subject/patient will be informed that his/her medical (source) records may be reviewed by the study monitor, a quality assurance auditor, or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations. Each subject/patient will be informed, in compliance with local regulations, that his/her name and address will be provided to third parties including mobile research nurses and, if applicable, medication couriers for the purpose of home treatment, and that these parties are bound by confidentiality obligations.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Investigator (Co-ordinating Investigator in multi-centre studies) and the Sponsor prior to its implementation. Any such amendments will be submitted to the any competent IEC/IRB and/or competent authority responsible as required by applicable regulations.

IEC/IRB approval will, at a minimum, be requested for any change to this protocol which could affect the safety of the subjects/patients, the objective/design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of subjects/patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Subject/Patient Data

The Investigator will ensure that the subject's/patient's confidentiality is preserved. On CRFs or any other documents submitted to the Sponsor, the subjects/patients will not be identified by their names, but by a unique subject/patient identifier. Documents not intended for submission to the Sponsor, i.e., the confidential subject identification code list, original consent forms, and source records, will be maintained by the Investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries compared to source data. The Investigator will co-operate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take place shortly after the inclusion of the first subject/patient. Thereafter, monitoring frequency will depend on study progress.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify, and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the eCRFs, including all laboratory results.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IEC/IRB/regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the subjects/patients have been adequately protected, and that all data relevant for the assessment of safety and efficacy of the IMP have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines and the Sponsor's SOPs) will be prepared by the Sponsor after completion of the study. The Co-ordinating Investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study may be published or presented at scientific meetings.

If this is envisaged by an Investigator, the Investigator agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor prior to submission to an editorial board or scientific review committee. This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multi-centre studies only in their entirety and not as individual centre data. Authorship will be determined by mutual agreement.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a subject/patient in association with the IMP or participation in the study, the Sponsor will contract insurance in accordance with local regulations.

The Investigator is responsible for dispensing the IMP according to this protocol and for its secure storage and safe handling throughout the study.

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