octapharma

CLINICAL STUDY PROTOCOL

PROSPECTIVE, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED PHASE III STUDY EVALUATING EFFICACY AND SAFETY OF OCTAGAM 10% IN PATIENTS WITH DERMATOMYOSITIS

(ProDERM Study)

Investigational Product:	Immune Globulin Intravenous, Human 10% (Octagam 10%)
Indication:	Dermatomyositis (DM)
Study Design:	Prospective, parallel group, double-blind, randomized, placebo-controlled, multicenter, phase III study.
Sponsor:	Octapharma Pharmazeutika Produktionsges.m.b.H. Oberlaaer Str. 235, 1100 Vienna, Austria
Study Number:	GAM10-08
EudraCT and IND Number:	EudraCT 2016-002902-37 / IND 16925
Development Phase:	Phase III
Planned Clinical Start:	Quarter 4 2016
Planned Clinical End:	Quarter 4 2019
Date of Protocol:	18-Jun-2019
Version:	12
Coordinating Investigator:	[redacted] Phoenix Neurological Associates 5090 N 40th St, Suite 250 Phoenix, AZ 85018, USA

STUDY OUTLINE

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H., 1100 Vienna, Austria	
Name of Investigational Product: Octagam 10%	**Protocol Identification Code:** GAM10-08 (ProDERM), Version 12
Name of Active Ingredient: Immune Globulin Intravenous, Human 10%	**Date of Protocol:** 18-Jun-2019

Title of Study:

Prospective, Double-blind, Randomized, Placebo-Controlled Phase III Study Evaluating Efficacy and Safety of Octagam 10% in Patients With Dermatomyositis ("ProDERM study")

Indication:

Dermatomyositis (DM).

Number of Study Centre(s):

Approximately 55 selected study sites worldwide.

Objectives:

Primary Objective:

The primary objective of this study is to provide confirmatory data on the beneficial effect of 2.0 g/kg of Octagam 10% given every 4 weeks compared with placebo in subjects with active DM based on the percentage of responders at Week 16.

Secondary Objectives:

The secondary objectives of this study are

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

Study Design:

Prospective, parallel group, double-blind, randomized, placebo-controlled, multicenter Phase III study with a controlled 16-week efficacy period followed by a 24-week open-label extension period.

Number of Subjects:

A minimum of 94 adult subjects of both genders are to be enrolled.

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Subject Selection Criteria:

Inclusion Criteria:

1. Subjects with diagnosis of definite or probable DM according to the Bohan and Peter criteria.
2. Subjects under treatment with corticosteroids and/or maximally 2 immune-suppressants and being on stable therapy for at least 4 weeks (see Section 4.2.1)
   OR
   Subjects with previous failure of response or previous intolerance to corticosteroid and at least 1 additional immunosuppressive drug, and with steroid/immunosuppressive drugs washed out as per Section 4.2.1 (Table 2).
3. Subjects with active disease, assessed and agreed upon by an independent adjudication committee.
4. Manual Muscle Testing-8 (MMT-8) score <142, with at least 2 other abnormal Core Set Measures (CSM) (Visual Analogue Scale [VAS] of patient global activity ≥2 cm, physician's global disease activity ≥2 cm, extra-muscular activity ≥2 cm; at least one muscle enzyme >1.5 times upper limit of normal, Health Assessment Questionnaire ≥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 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 and at least 1 or 5 years, respectively, 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.
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.

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5. Subjects with generalized, severe musculoskeletal conditions other than DM that prevent a sufficient assessment of the subject by the physician.
6. Subjects who have received IgG treatment within the last 6 months before enrolment.
7. Subjects who received blood or plasma-derived products (other than IgG) or plasma exchange within the last 3 months before enrolment.
8. Subjects starting or planning to start a physical therapy–directed exercise regimen during the trial.
9. Cardiac insufficiency (New York Heart Association III/IV), cardiomyopathy, significant cardiac dysrhythmia requiring treatment, unstable or advanced ischemic heart disease.
10. Severe liver disease, with signs of ascites and hepatic encephalopathy.
11. Severe kidney disease (as defined by estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2).
12. Known hepatitis B, hepatitis C or HIV infection.
13. Subjects with a history of TEE such as deep vein thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease (Fontaine IV) ever.
14. Body mass index ≥ 40 kg/m^2.
15. Medical conditions whose symptoms and effects could alter protein catabolism and/or IgG utilization (e.g. protein-losing enteropathies, nephrotic syndrome).
16. Known IgA deficiency with antibodies to IgA.
17. History of hypersensitivity, anaphylaxis or severe systemic response to immunoglobulin, blood or plasma derived products or any component of Octagam 10%.
18. Known blood hyperviscosity, or other hypercoagulable states.
19. Subjects with a history of drug abuse within the past 5 years prior to study enrollment.
20. Subjects unable or unwilling to understand or comply with the study protocol.
21. Participating in another interventional clinical study with investigational treatment within 3 months prior to study enrollment.
22. Women who are breast feeding, pregnant, or planning to become pregnant, or are unwilling to apply an effective birth control method (such as implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence or vasectomized partner) up to four weeks after the last IMP infusion.
23. Subjects who are accommodated in an institution or care facility based on an official directive or court order.

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24. Subjects who are in any way dependent on the Sponsor, Investigator or Study Site.
25. Subjects who received forbidden medication within the washout period as defined in Section 4.2.2 (Table 3).

Test Product, Dose, and Mode of Administration:

Octagam 10% is an IGIV ready for intravenous administration. The product is delivered as ready-to-use solution in glass bottles. Octagam 10% should be stored and transported light-protected at +2°C to +8°C (36°F to 46°F) and must not be frozen.

First Period (Octagam 10% vs. placebo in double-blind design): 2.0 g/kg (20 mL/kg) Octagam 10% or 20 mL/kg placebo given over 2 to 5 days at 4-week intervals (in total 4 infusion cycles).

Extension Period: 2.0 g/kg (20 mL/kg) Octagam 10% given over 2 to 5 days at 4-week intervals (in total 6 infusion cycles). At Week 28, subjects who are stable on 2.0 g/kg Octagam 10% can be switched to 1.0 g/kg (10 mL/kg) Octagam 10%, at the discretion of the investigator.

Duration of Treatment:

The duration of the entire study for each subject will be up to 43 weeks and consists of the following segments: up to 3 weeks for Screening, then 16 weeks of double-blind treatment phase (First Period) followed by 24 weeks of open-label treatment (Extension Period).

Reference Therapy, Dose, Mode of Administration:

Sodium chloride 0.9% w/v solution.

Study Outcome Parameters (Primary and Secondary Endpoints):

Efficacy Endpoints:

Primary

- Proportion of responders in the 2.0 g/kg Octagam 10% and placebo arms at Week 16. A responder is defined as a subject with an increase from baseline (Week 0) of ≥20 points on the Total Improvement Score (TIS) and who has not met "Confirmed Deterioration" criteria at 2 consecutive visits as defined in Section 4.3.1 up to (including) Week 16.

Secondary

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

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- Mean change from end of First Period (Week 16) to end of Extension Period (Week 40) in the modified CDASI.
- Mean change from Baseline (Week 0) to end of First Period (Week 16) and Extension Period (Week 40) in:
  - SF-36v2 Health Survey;
  - Individual 6 CSM used for TIS calculation.
- Mean TIS from Baseline (Week 0) to end of First Period (Week 16) and from Baseline (Week 0) to end of Extension Period (Week 40).
- Time to minimal, moderate and major improvement in TIS.
- Time to confirmed deterioration in the First Period and overall.
- Proportion of subjects in each treatment arm who met confirmed deterioration criteria up to (including) Week 16

Safety Endpoints:

Safety (throughout the entire First and Extension Period):

- Occurrence of all adverse events with particular emphasis on thromboembolic events (TEEs) and hemolytic transfusion reactions (HTRs).
- Occurrence of all adverse drug reactions (ADRs) and suspected ADRs.
- Vital signs (blood pressure, heart rate, body temperature and respiratory rate).
- Physical examination (at Screening and every 12 weeks from Week 4 on).
- Laboratory parameters (hematology, clinical chemistry).

Safety (at Baseline and end of Extension Period):

- Tests for viral safety.
- Pregnancy test, if applicable.

Study Procedures:

Subjects eligible after screening will be randomized 1:1 to receiving up to 4 infusion cycles of either Octagam 10% or placebo every 4 weeks during the First Period lasting 16 weeks. After response assessment at Week 16, all subjects who have not deteriorated at 2 consecutive visits during the First Period will continue to receive 2.0 g/kg (20 mL/kg) of Octagam 10% during the subsequent 6-months Extension Period. At Week 28, the subject may be switched to 1.0 g/kg (10 mL/kg) Octagam 10%, if previously has been stable on the 2.0 g/kg (20 mL/kg) Octagam 10% dose.

In case of confirmed deterioration (i.e. deterioration at 2 consecutive visits) during the First Period, subjects will be switched to the alternate treatment. After response assessment at Week 16 this subgroup of subjects will be unblinded.

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Subjects originally **randomized to placebo** and switched to 2 g/kg (20 mL/kg) Octagam 10% after confirmed deterioration and who do not further deteriorate during their Octagam 10% treatment will continue and receive 2.0 g/kg (20 mL/kg) Octagam 10% during the 6-months Extension Period. For subjects who will be stable on 2.0 g/kg (20 mL/kg) Octagam 10%, the investigator may decide to switch the subject to 1.0 g/kg (10 mL/kg) Octagam 10%, at Week 28. Subjects originally **randomized to placebo** and switched to Octagam 10% due to confirmed deterioration, who deteriorate also during Octagam 10% treatment at 2 consecutive visits will drop-out after response assessment at Week 16 and will not enter the Extension Period.

Subjects originally **randomized to Octagam 10%** who deteriorate at 2 consecutive visits in the First Period and who were subsequently switched to placebo will drop-out after the response assessment at Week 16 and will not enter the Extension Period.

Subjects dropping out due to confirmed deterioration will in any case be classified as non-responders in the statistical analysis.

Any subject deteriorating in the Extension Period will drop-out, independent of the initially assigned treatment arm.

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

Statistical Analysis Plan:

The primary endpoint measure 'response' will be assessed at Week 16 based on the TIS score; a subject is defined as responder if

(i) the subject has a TIS score of ≥20 points at Week 16 and
(ii) the subject has not met "Confirmed Deterioration" criteria at 2 consecutive visits as defined in Section 4.3.1 up to (including) Week 16

Otherwise the patient will be counted as a non-responder.

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

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

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

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All other endpoints will be analyzed and presented in full detail by means of descriptive statistics and inferential analyses as appropriate, including summary and frequency tables, confidence intervals and graphs.

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.

The evaluation of the primary efficacy endpoint will be based on the intention-to-treat population, i.e. all randomized subjects.

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 Octagam 10% or placebo.

Table 1: *Flowchart of Assessments Performed During the Study*

ASSESSMENTS	Screening	Baseline	First Period				Extension Period						Throughout
	Visit 1 Week -3 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	Visit 10 Week 32	Visit 11 Week 36	Termination visit Week 40 / Drop-out Visit	Unscheduled Visit
Informed consent	X												
Eligibility criteria	X												
Demographic and baseline characteristics	X												
Med. hist./Prior medication	X												
Standard ECG	X												
Pregnancy test	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
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X		X
Body weight[2]	X					X			X				
Safety laboratory[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum IgG[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
Enzymes[2]	X	X	X	X	X	X			X			X	X
Biomarkers blood sample	X					X						X	
Blood sample for additional safety lab[5]		X				X			X			X	
Direct Coombs' test[5]		X				X			X			X	
CSM for TIS determination[2]	X	X	X	X	X	X			X			X	X
CDASI[2]		X	X	X	X	X			X			X	X
SF-36 Health Survey[2]		X				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#	X#	X#		
Adverse event monitoring		Throughout the study											
Concomitant medication		Throughout the study											

[1] Infusion cycles can last between 2 to 5 days, consisting of 2 or more infusion episodes. [2] Before IMP administration;
[3] Before, during and after each infusion episode; [4] At screening and after each infusion cycle; [5] Before and after infusion cycle; *Blinded infusion of either placebo or 2.0 g/kg Octagam 10%
**Unblinded infusions of 2.0 g/kg Octagam 10%; #In case subject is stable on the 2.0 g/kg Octagam 10% dose, they can be switched to 1.0 g/kg Octagam 10%, at the discretion of the investigator

PROTOCOL SIGNATURES

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

[redacted] [redacted] 18.06.2019

International Medical Director Signature Date
on behalf of the Sponsor
Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
1100 Vienna, Austria

[redacted] [redacted] 18 Jun 2019

Clinical Project Manager Signature Date
Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Str. 235
1100 Vienna, Austria

[redacted] [redacted] 18 JUNE 2019

Manager Biometrics Signature Date
Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Str. 235
1100 Vienna, Austria

PROTOCOL SIGNATURES

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

[redacted] [redacted] 6/18/19

Coordinating Investigator Signature Date

Phoenix Neurological Associates
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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
DEHP	Diethylhexylphthalate
DM	Dermatomyositis
DOI	Definition of Improvement
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
GDA	Global Disease Activity
GCP	Good Clinical Practice
HAQ	Health Assessment Questionnaire
HTR	Hemolytic Transfusion Reaction
IAC	Independent Adjudication Committee
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
PVC	Polyvinyl Chloride
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
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
TSH	Thyroid-stimulating hormone
VAS	Visual Analogue Scale
VTE	Venous Thromboembolism

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.

Octagam 5% and Octagam 10% are liquid intravenous polyvalent IGIV preparations, which are prepared from human plasma and mainly contain human normal immunoglobulin G. The molecules are present in their native form, which is essential for their biological activity. Octagam 5% is approved since February 1995 and is currently marketed in 82 countries worldwide, while Octagam 10% got its first license in May 2008 and is now approved in 55 countries worldwide.

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

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. However, there is only 1 placebo-controlled clinical study in 15 subjects with refractory DM published so far, employing 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.

The rationale for conducting this study (ProDERM: "**Pro**gress in **DERM**atomyositis") is to investigate efficacy, safety and tolerability of 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.

1.4 Dose Rationale

In 1989, Imbach and colleagues published a randomized placebo-controlled trial in which IGIV at a dose of 2.0 g/kg has been used for the first time in an immunomodulatory setting in immune thrombocytopenia.[5] Later retrospective and case studies relied mostly to this dosage scheme and the effect of IGIV has never been systematically examined in another randomized placebo-controlled trial since.

Subjects with mild to moderate DM may respond to lower doses of IGIV. Therefore, and following a recommendation of the FDA, subjects may receive the lower 1.0 g/kg Octagam 10% dose from Week 28 on, depending on the investigator's decision and if the higher dose has shown to be effective in the individual subject. An Advisory Board of DM experts in the fields of neurology, rheumatology and immunology confirmed this observation. Reference is also made to a group of investigators in Italy who successfully treat their patients with weekly (subcutaneous) doses of only 0.1-0.2 g/kg, corresponding to a monthly (intravenous) dose of 0.8 g/kg.[31]

1.5 Benefit-Risk Statement

The risks of IGIV administration are well documented. In general, the incidence of adverse events (AEs) associated with IGIV tends to increase with the rate of infusion, and thus the recommended dosage, infusion rates, and monitoring procedures should be adhered to. Subjects that are naïve to IGIV are more at risk than those that are well maintained and on regular therapy.

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). Carruthers and colleagues [33] conducted matched cohort analyses for venous thromboembolism (VTE) (i.e. deep vein thromboses [DVT] or pulmonary embolism [PE]) among individuals with PM (PM cohort) or DM (DM cohort) as compared with individuals without PM or DM (comparison cohorts), using data from the Canadian British Columbia Health Database (PopData BC). This was the first large general population-based study to assess the risk of VTE in PM/DM patients. Risk of VTE was substantially higher in individuals with PM/DM compared to the general population (six and eight times, respectively). According to Chung and colleagues [34] DM and PM patients exhibit even an 11.1-fold increased risk of VTE compared to non-DM/PM patient cohort.
Elderly patients with DM/PM exhibited a multiplicative increased risk of VTE development compared to the control panel, and the DM/PM patients with any comorbidity showed an additive risk of developing VTE.
The risk of VTE may be even higher in the initial years after diagnosis according to Carruthers and colleagues [33], PM patients had the highest risk during the first year of diagnosis and progressively attenuated over time. Similarly, DM patients had the highest risk during the first two years after diagnosis.
Therefore, special emphasis will be given to the occurrence of TEEs such as DVTs and PE.

Hemolytic transfusion reactions (HTRs) can develop subsequent to IGIV therapy. IGIV-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 Octagam 10% which are described in detail in the Investigator's Brochure.

For Octagam 10%, the same type of adverse reactions has been seen as for other IGIV products. No new or unknown safety problems are expected to emerge which are not already described in the Investigator's Brochure.

As per European Federation of Neurological Societies (EFNS) Guidelines[6], 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.[7] 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.[8] 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.[9] 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.[9,10] 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).[4,11]

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.[12]

In terms of efficacy, it can reasonably be assumed that Octagam 10% exhibits the same effectiveness as other IGIV brands.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of this study is to provide confirmatory data on the beneficial effect of 2.0 g/kg of Octagam 10% given every 4 weeks compared with placebo in subjects with active DM based on the percentage of responders at Week 16.

2.2 Secondary Objective(s)

The secondary objectives of this study are:

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

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

- Proportion of responders in the 2.0 g/kg Octagam 10% and placebo arms at Week 16. A responder is defined as a subject with an increase from baseline (Week 0) of

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

≥20 points on the Total Improvement Score (TIS) and who has not met "Confirmed Deterioration" criteria at 2 consecutive visits as defined in Section 4.3.1 up to (including) Week 16.

3.1.2 Secondary Endpoints

Efficacy:

- Proportion of TIS responders by improvement category (minimal, moderate, major) at Week 16 and Week 40.
- Mean change from baseline (Week 0) to end of First Period (Week 16) in modified Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI).[29]
- Mean change from end of First Period (Week 16) to end of Extension Period (Week 40) in modified CDASI.
- Mean change from Baseline (Week 0) to end of First Period (Week 16) and Extension Period (Week 40) in:
  - SF-36v2 Health Survey;
  - Individual 6 Core Set Measures (CSM) used for TIS calculation.
- Mean TIS from Baseline (Week 0) to end of First Period (Week 16) and from Baseline (Week 0) to end of Extension Period (Week 40).
- Time to minimal, moderate and major improvement in TIS.
- Time to confirmed deterioration in the First Period and overall.
- Proportion of subjects in each treatment arm who met confirmed deterioration criteria up to (including) Week 16

Safety (throughout the entire First and Extension Period):

- Occurrence of all AEs with particular emphasis on thromboembolic events (TEEs) and hemolytic transfusion reactions (HTRs).
- Occurrence of all adverse drug reactions (ADRs) and suspected ADRs.
- Vital signs (blood pressure, heart rate, body temperature and respiratory rate).
- Physical examination (at Screening and every 12 weeks from Week 4 on).
- Laboratory parameters (hematology, clinical chemistry).

Safety (at Baseline and end of Extension Period):

- Tests for viral safety.
- Pregnancy test, if applicable.

3.2 Overall Study Design and Plan

ProDERM study is planned to start in Q4 2016 and be clinically completed by Q4 2019.

ProDERM study will be a prospective, parallel group, double-blind, randomized, placebo-controlled, multicenter Phase III study in a minimum of 94 adult subjects of both genders with definite or probable DM according to the criteria of Bohan and Peter.[13,14]

As DM is a rare disease, about 55 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 4 infusion cycles of either Octagam 10% or placebo every 4 weeks during the First Period lasting 16 weeks. An infusion cycle comprises all infusion episodes administered over 2 (to 5) days during one

visit. After response assessment at Week 16 (i.e. 4 weeks after start of the previous infusion cycle), all subjects who have not deteriorated at 2 consecutive visits during the First Period will continue to receive 2.0 g/kg (20 mL/kg) of Octagam 10% during the subsequent 6-months Extension Period. For subjects who are stable on the 2.0 g/kg (20 mL/kg) Octagam 10% dose, the investigator may decide to switch them to the 1.0 g/kg (10 mL/kg) Octagam 10% dose, starting at Week 28.

In case of confirmed deterioration (for definition see Section 4.3.1) during the First Period, subjects will be switched to the alternate treatment. After response assessment at Week 16 this subgroup of subjects will be unblinded (see Section 5.6).

Subjects originally **randomized to placebo** who did not deteriorate and thus stayed on placebo until Week 16, will all receive open-label 2.0 g/kg (20 mL/kg) Octagam 10% at Week 16. If they continue to be stable on the Octagam 10% dose, they will have the option to switch to 1.0 g/kg (10 mL/kg) Octagam 10% at Week 28, at the discretion of the investigator.

Subjects originally **randomized to placebo** and switched to Octagam 10% due to confirmed deterioration who do not further deteriorate during their Octagam 10% treatment at 2 consecutive visits will continue and receive 2.0 g/kg (20 mL/kg) Octagam 10% during the 6-months Extension Period.

Subjects originally **randomized to placebo** and switched to Octagam 10% due to deterioration, who deteriorate also during Octagam 10% treatment at 2 consecutive visits will drop-out after response assessment at Week 16 and will not enter the Extension Period.

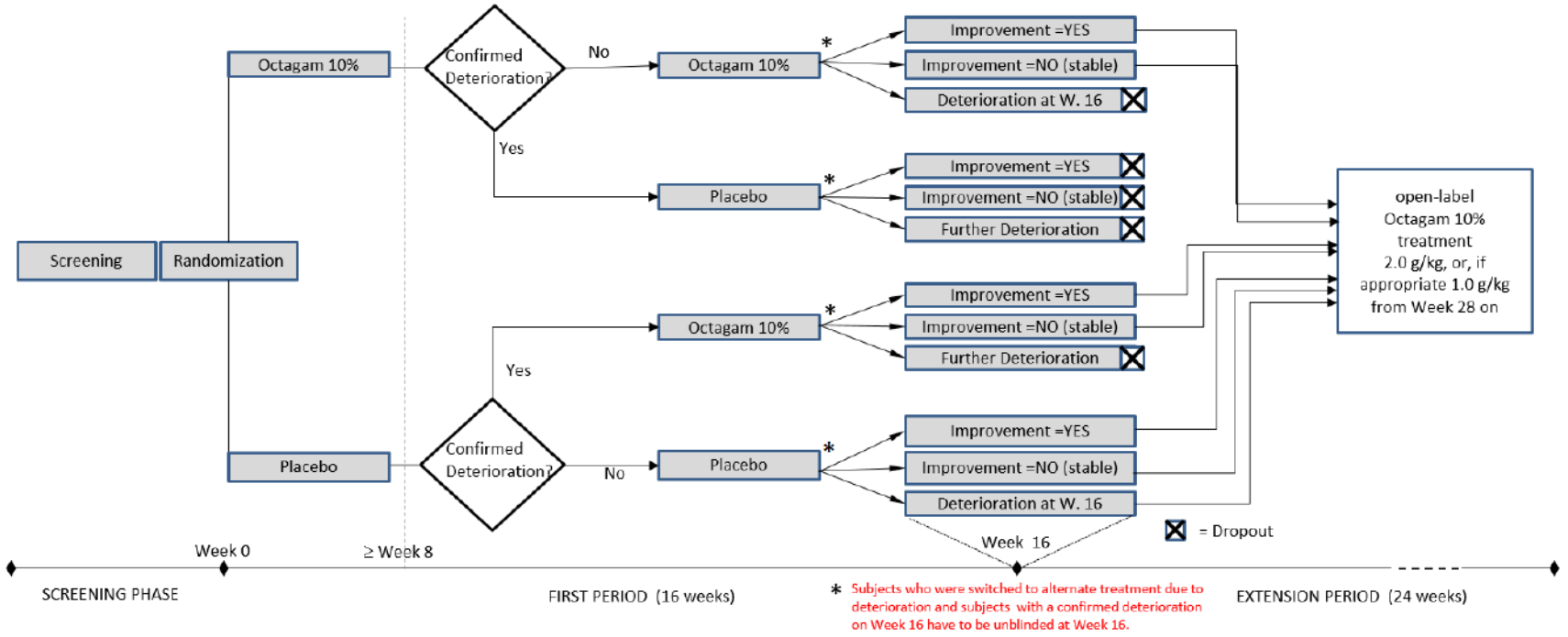
Subjects originally **randomized to Octagam 10%** who deteriorate at 2 consecutive visits in the First Period and who were subsequently switched to placebo will drop-out after the response assessment at Week 16 and will not enter the Extension Period.

Subjects dropping out due to confirmed deterioration at 2 consecutive visits will in any case be classified as non-responders in the statistical analysis.

Any subject deteriorating at 2 consecutive visits in the Extension Period will drop-out, independent of the initially assigned treatment arm and the Octagam 10% dose administered.

Figure 1 depicts the study design.

Figure 1: *Scheme of Study Design*



3.3 Discussion of Study Design and Choice of Control Group

3.3.1 Study Design

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

The total observation period of the study is 40 weeks. For a proper assessment of efficacy, clinical experience has shown that at least 4 treatment cycles are necessary to be documented. This resulted in a duration of 16 weeks for the first (controlled) phase of the study. An active treatment phase of 6 months (24 weeks) is recommended by the International Myositis Assessment and Clinical Studies Group.[32]

In order to minimize the risk for subjects in the **placebo arm**, a conditional switch to active treatment is introduced in the (blinded) First Period: All subjects in the placebo arm who deteriorate at 2 consecutive visits until Week 8 or after Week 8 will be switched to 2.0 g/kg (20 mL/kg) of Octagam 10%. In case of further, confirmed deterioration on the Octagam 10% treatment, subjects will drop-out.

In contrast, subjects in the 2.0 g/kg (20 mL/kg) **Octagam 10% arm** will receive placebo if they deteriorate at 2 consecutive visits until Week 8 or after Week 8. In case of confirmed deterioration after the switch to placebo, subjects will eventually drop-out. Subjects who did not deteriorate after the switch to placebo at 2 consecutive visits will automatically drop out at Week 16. This procedure was introduced to maintain the blinding of treatment.

In the Extension Period of the study, subjects will receive 6 infusion cycles of 2.0 g/kg (20 mL/kg) of Octagam 10% every 4 weeks. If the subject is stable on the 2.0 g/kg (20 mL/kg) dose, the investigator may decide on a case by case basis, if they want to treat the subject with the lower dose of 1.0 g/kg (10 mL/kg) Octagam 10%, starting at Week 28. Thereby, data on long-term efficacy and tolerability will be generated.

The 4-week interval between infusions has been chosen to make results comparable to the old Dalakas study [4] and to stay in line with current clinical practice.

Immunosuppressive agents and corticosteroids are allowed if stable dosages are not exceeded (see Section 4.2.1) in order to comply with the EFNS Guidelines saying that IGIV is recommended as a second-line treatment.[6]

3.3.2 Control Groups

Since the placebo-controlled Dalakas study in 1993 which demonstrated the beneficial effect of IGIV in DM, no confirmatory placebo-controlled study with IGIV has been conducted. Therefore, Octagam 10% will be compared with placebo in the ProDERM trial.

3.3.3 Study Parameters

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

Core Set Measures of myositis disease activity have been established and validated by the IMACS Group for DM/PM clinical trials.[15-18] 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).[19,30] ProDERM will employ the TIS in its final version for the definition of improvement (DOI) used as the primary endpoint. The final TIS used for this protocol was submitted for publication by Prof. Aggarwal who was a member of an Advisory Board who helped developing this protocol.

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. 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.[18] Therefore, it is justified to use the response criterion based on the TIS changes as primary endpoint.

4 STUDY POPULATION

4.1 Population Base

In total, 94 adult male or female subjects with acute DM 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.[13,14]
2. Subjects under treatment with corticosteroids and/or maximally 2 immune-suppressants and being on stable therapy for at least 4 weeks (see Section 4.2.1)
   OR
   Subjects with previous failure of response or previous intolerance to corticosteroid and at least 1 additional immunosuppressive drug, and with steroid/immunosuppressive drugs washed out as per Section 4.2.1 (Table 2).
3. Subjects with active disease, assessed and agreed upon by an independent adjudication committee (see Section 8.6).
4. MMT-8 score <142, with at least 2 other abnormal CSM (Visual Analogue Scale [VAS] of patient global activity ≥2 cm, physician's global disease activity ≥2 cm, extra-muscular activity ≥2 cm; at least one muscle enzyme >1.5 times upper limit of normal, 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 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 and at least 1 or 5 years, respectively, 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.
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 have received IgG treatment within the last 6 months before enrolment.
7. Subjects who received blood or plasma-derived products (other than IgG) or plasma exchange within the last 3 months before enrolment.
8. Subjects starting or planning to start a physical therapy–directed exercise regimen during the trial.
9. Cardiac insufficiency (New York Heart Association III/IV), cardiomyopathy, significant cardiac dysrhythmia requiring treatment, unstable or advanced ischemic heart disease.
10. Severe liver disease, with signs of ascites and hepatic encephalopathy.
11. Severe kidney disease (as defined by estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2).
12. Known hepatitis B, hepatitis C or HIV infection.
13. Subjects with a history of TEE such as deep vein thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease (Fontaine IV) ever.
14. Body mass index ≥ 40 kg/m^2.
15. Medical conditions whose symptoms and effects could alter protein catabolism and/or IgG utilization (e.g. protein-losing enteropathies, nephrotic syndrome).
16. Known IgA deficiency with antibodies to IgA.
17. History of hypersensitivity, anaphylaxis or severe systemic response to immunoglobulin, blood or plasma derived products or any component of Octagam 10%.
18. Known blood hyperviscosity, or other hypercoagulable states.
19. Subjects with a history of drug abuse within the past 5 years prior to study enrollment.
20. Subjects unable or unwilling to understand or comply with the study protocol.
21. Participating in another interventional clinical study with investigational treatment within 3 months prior to study enrollment.
22. Women who are breast feeding, pregnant, or planning to become pregnant, or are unwilling to apply an effective birth control method (such as implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence or vasectomized partner) up to four weeks after the last IMP infusion received.

23. Subjects who are accommodated in an institution or care facility based on an official directive or court order.
24. Subjects who are in any way dependent on the Sponsor, Investigator or Study Site.
25. Subjects who received forbidden medication within the washout period as defined in Section 4.2.2 (Table 3: Forbidden Concomitant Medications).

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 previous DM-related treatment failure or intolerance, including medication, maximum dose reached, and reason for discontinuation (insufficient therapeutic effect or intolerable side effect).
- 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 or biologicals) must either be

a) washed-out (details see Table 2)

or

b) continued if subject received medication for at least 3 months prior to study enrollment and at a stable dose for at least 4 weeks prior to study enrollment (details see Table 2).

Table 2 specifies which **DM–treatment-related medications** are permitted as concomitant therapy. In addition, the maximally allowed dose which has to remain stable during the First Period is given. If treatment for DM is to be stopped prior to study enrollment, the required washout periods, the period which needs to elapse from discontinuing, can be retrieved from the table.

During the First Period of the study, the dose regime of concomitant therapies should not be changed. During the Extension Period of the study, therapies may be tapered off.

TEE prophylaxis, if deemed necessary by the investigator, is allowed as a precautionary measure and should follow standard of care. Its use must be documented.

The routine use of **premedication** to alleviate potential side effects should be avoided. However, if a subject experiences 2 consecutive infusion-related AEs that are likely to be prevented by premedication, then antipyretics, antihistamines, mild analgesics (acetaminophen/paracetamol or acetylsalicylic acid) or antiemetic drugs are allowed before the following infusions of study drug. The dose of premedication should be held stable during the First Period and its use must be documented.

NSAIDs or opioids are commonly used in DM patients and are therefore allowed. The dose of such medications should be held stable 2 weeks prior to study enrollment and during the First Period. The use of such medication must be documented.

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

Physical therapy-directed exercise regimen is allowed if started ≥4 weeks prior to randomization and entry into the double-blind treatment period at Visit 2 and kept on a stable schedule, frequency and extent. Any such exercise regimen must be documented.

Table 2: *Washout Periods or Dose Limitations for Prior/Concomitant DM-related Medications to be fulfilled prior to randomization*

Drug	Washout Period (prior to randomization)	Maximally allowed stable dose as concomitant therapy
Immunosuppressive Drugs		
Methotrexate	8 weeks	25 mg/week
Azathioprine	8 weeks	2 mg/kg
Cyclosporine	8 weeks	2 mg/kg
Tacrolimus	8 weeks	0.2 mg/kg
Mycophenolate mofetil	8 weeks	3000 mg daily
Leflunomide	3 months	20 mg daily
Other		
Hydroxychloroquine	8 weeks	400 mg daily
Corticosteroids	8 weeks	20 mg daily prednisone equivalent

4.2.2 Forbidden Concomitant Therapy

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

- Corticosteroids at any dose if given as **premedication** to alleviate potential side effects following Octagam 10% treatment.
- Corticosteroids at doses higher than 20 mg/day prednisone equivalent.
- Other blood or plasma-derived products. Note that subjects will be withdrawn from the study if IgG preparations other than Octagam 10% are administered.
- 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** (prior to randomization)
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
Immunoglobulin G	6 months
Etanercept	4 weeks
Anakinra	2 weeks
Rilanocept	8 weeks
Topical steroids	2 weeks

4.3 Withdrawal and Replacement of Subjects

4.3.1 Premature Subject 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 from the study in case of AEs, poor compliance, or other reasons. Since an excessive rate of withdrawal can render the study non-interpretable, the unnecessary withdrawal of subjects must be avoided.

For any discontinuation after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation in the eCRF. If the reason for withdrawal of a subject is an AE, the main specific event or laboratory test will be recorded in the eCRF, 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.

At Week 16, certain subjects have to drop-out, especially in case of (further) confirmed deterioration after the switch to the alternate treatment option. Please see Figure 1 for details.

Other reasons for premature termination of subjects may be:

1. Withdrawal of subject's consent.
2. Deterioration of DM (during Extension Period).
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 IGIV other than Octagam 10%.

"Confirmed deterioration" is essentially defined as follows according to Oddis et al. 2013 with a slight adaptation as agreed with the study's Steering Committee (excluding enzymes, which will not immediately be available for the evaluation of deterioration):[20]

- Physician's Global Disease Activity VAS worsening ≥ 2 cm and MMT-8 worsening ≥20% on 2 consecutive visits,

or

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

or

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

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

4.3.2 Subject Replacement Policy

Not applicable. Withdrawals will not be replaced.

4.4 Assignment of Subjects 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 ("8"), 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. 80402.

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 IRT will ensure balance of allocation by means of a stratified block design, thus, equally distributing subjects with different disease course (mild, moderate or severe defined as a Physician's Global Disease Activity (GDA) value of 0-3 [mild], 4-6 [moderate], 7-10 [major]). 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 reported to the hospital pharmacist or designee by a dedicated email that no other trial personnel will have access to.

The subject will be identified by the previously assigned screening ID throughout the trial. No additional subject or randomization number will be used.

No randomization results will be transmitted to the sponsor to comply with the double-blind character of this study. The responsible monitor(s) will be informed of new subjects enrolled automatically by the IRT system via email.

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. If deviations occur, the Investigator should promptly inform the Monitor and the implication of the deviation must be assessed and discussed. Any deviation must be documented, stating the reason and date and the action taken. The documentation must be kept in the Investigator's trial file and the Sponsor's trial master file. A complete list of all minor and major deviations is to be compiled and regularly updated by the Project Manager 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.
- Subjects who had no CSM at Week 16.

In case of any major protocol deviation, the Investigator and Sponsor will decide on the further participation of the subject 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 as per the discretion of the investigator.

5 INVESTIGATIONAL MEDICINAL PRODUCT(S)

5.1 Characterization of Investigational Product(s)

Octagam is a 10% IGIV ready for intravenous administration. Octagam 10% is produced from a pool of at least 1000 donations of human fresh frozen plasma per batch. The large donor pool ensures that the product contains a broad range of antibodies directed against pathogens and foreign antigens, which is far more diverse than that of plasma from an individual donor. Donor plasma sampling, the manufacturing of the product and the measures to ensure the product's viral safety are subject to strict regulations laid down by regulatory authorities. Octapharma exclusively uses plasma which has been tested by nucleic acid testing techniques.

During the manufacturing process of Octagam 10%, significant viral reduction is obtained via a combination of 3 validated manufacturing steps: cold-ethanol fractionation, solvent/detergent treatment with tri-n-butyl phosphate (TNBP) and Octoxynol (Triton X-100), and pH 4 treatment. The efficacy of the virus inactivation procedures has been

extensively validated according to relevant international guidelines. The composition with the most important ingredients and the biochemical characteristics are summarized in the Investigators' Brochure.

For placebo, sodium chloride 0.9% w/v solution for intravenous infusion will be used.

5.2 Packaging and Labeling

Octagam 10% is delivered as ready-to-use solution in glass bottles.

Each Octagam 10% bottle will be labeled as follows:

US Master Label – Octagam 10%:

Caution: New Drug-Limited by Federal (or United States) law to investigational use
Study: **GAM10-08**
Octagam 10% Unit size: _____ **mL**
1 mL contains: 100 mg protein of which ≥ 96% is human normal immunoglobulin.
Infusion solution for intravenous administration.
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: refer to Clinical Study Protocol, section 5.4
Patient no.: |__|__|__|__|__| Visit no.: |____| Infusion Day: |____|
Sponsor: OCTAPHARMA PPG, Oberlaaer Str. 235, 1100 Vienna, Austria, Tel: [redacted]
Batch no.: _____ Expiration date: _____

EU Master Label – Octagam 10%:

FOR CLINICAL TRIAL USE ONLY Study: **GAM10-08**
Octagam 10% Unit size: _____ **mL**
1 mL contains: 100 mg protein of which ≥ 95% is human normal immunoglobulin.
Infusion solution for intravenous administration.
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: refer to Clinical Study Protocol, section 5.4
Patient no.: |__|__|__|__|__| Visit no.: |____| Infusion Day: |____|
Investigator: _____
Sponsor: OCTAPHARMA PPG, Oberlaaer Str. 235, 1100 Vienna, Austria, Tel: [redacted]
Batch no.: _____ Expiration date: _____

Sodium chloride 0.9% w/v solution for intravenous infusion, licensed for the US and EU market, will be purchased centrally and provided to the local pharmacies. Each bottle will be labeled as follows:

US Master Label – Sodium Chloride 0.9% w/v solution:

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

Study: **GAM10-08**

Sodium Chloride 0.9% w/v solution Unit size: _____ **mL**

Sterile solution for intravenous infusion

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]*

Only to be used if solution is clear and container undamaged

Dosage: refer to Clinical Study Protocol, section 5.4

Sponsor: OCTAPHARMA PPG, Oberlaaer Str. 235, 1100 Vienna, Austria, Tel: +[redacted]

Batch no.: _____ Expiration date: _____

EU Master Label – Sodium Chloride 0.9% w/v solution:

FOR CLINICAL TRIAL USE ONLY Study: **GAM10-08**

Sodium Chloride 0.9% w/v solution Unit size: _____ **mL**

Sterile solution for intravenous infusion

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]*

Only to be used if solution is clear and container undamaged

Dosage: refer to Clinical Study Protocol, section 5.4

Investigator: _____

Sponsor: OCTAPHARMA PPG, Oberlaaer Str. 235, 1100 Vienna, Austria, Tel: +[redacted]

Batch no.: _____ Expiration date: _____

Final labeling will be in compliance with the national requirements of each country where the study will be conducted.

After transfer and pooling into Polyvinyl Chloride (PVC)-free, Diethylhexylphthalate (DEHP)-free and latex–free, infusion bags, the medication (Octagam 10% or sodium

chloride 0.9% w/v solution) will be blinded with an over pouch and re-labeled (both, the infusion bag and the over pouch). The following labels will be used for sending the medication from the pharmacy to the ward:

US Master Label – Blinded label for infusion bags and over pouch:

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

Study: **GAM10-08**

Octagam 10% OR Sodium Chloride 0.9% w/v solution Unit size: _____ **mL**

1 mL contains either 100 mg protein of which ≥ 96% is human normal immunoglobulin **OR** sodium chloride 0.9% w/v solution.

Infusion solution for intravenous administration.

Patient no.: |__|__|__|__|__| Visit no.: |____| Infusion Day: |____|

Investigator: _____

Date and time of preparation: _____

If not infused immediately, to be stored at +2°C (36°F) to +8°C (46°F) until
Expiration date and time: _____

Must not be frozen.

To be warmed up to room or body temperature before use.

Sponsor: OCTAPHARMA PPG, Oberlaaer Str. 235, 1100 Vienna, Austria, Tel: +[redacted]

EU Master Label – Blinded label for infusion bags and over pouch:

FOR CLINICAL TRIAL USE ONLY Study: **GAM10-08**

Octagam 10% OR Sodium Chloride 0.9% w/v solution Unit size: _____ **mL**

1 mL contains either 100 mg protein of which ≥ 95% is human normal immunoglobulin **OR** sodium chloride 0.9% w/v solution.

Infusion solution for intravenous administration.

Patient no.: |__|__|__|__|__| Visit no: |____| Infusion Day: |____|

Investigator: _____

Date and time of preparation: _____

If not infused immediately, to be stored at +2°C to +8°C until
Expiration date and time: _____

Must not be frozen.

To be warmed up to room or body temperature before use.

Sponsor: OCTAPHARMA PPG, Oberlaaer Str. 235, 1100 Vienna, Austria, Tel: +[redacted]

Final labeling will be in compliance with the national requirements of each country where the study is to be conducted.

5.3 Conditions for Storage and Use

Octagam 10% should be stored and transported light-protected at +2°C to +8°C (36°F to 46°F) and must not be frozen. Octagam 10% must not be used after its expiration date.

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

Storage conditions for pooled IMP are described in Section 5.5.

The authorized personnel at the individual pharmacies 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

Octagam 10% is available in glass bottles with different volumes of human immunoglobulin. Glass bottles of different volume should be combined in order to reach the required amount of IgG.

No product should be discarded; therefore, the amount to be administered will be rounded up or down to the value closest to the smallest vial size available. The range of such a rounded difference must not exceed ±2.5 g in total.

If a subject is randomized to receive placebo (0.9% w/v isotonic 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 2.0 g/kg Octagam 10% will be used. Therefore, they will receive a dose of 20 mL/kg 0.9% w/v isotonic sodium chloride solution given over 2 to 5 days.

Body weight is to be measured at certain visits prior to IMP administration and reported to the pharmacist or designee as it is needed for the preparation of the following study medication dosages.

All subjects should be clinically assessed for being adequately hydrated prior to IMP administration. TEE prophylaxis should be considered for subjects with risk factors for TEE or subjects in the early phase of diagnosis as a precautionary measure. Please refer to Section 4.2.1.

The initial infusion rate for each infusion episode will be 0.01 mL/kg/min (60 mg/kg/h) for the first 30 minutes; if tolerated, advanced to 0.02 mL/kg/min (120 mg/kg/h) for the next 30 minutes; if tolerated, advanced to 0.04 mL/kg/min (240 mg/kg/h) for the remainder of the infusion.. The interval of 30 minutes may be prolonged as per discretion of the investigator.

In patients at risk for thromboembolic adverse reactions and acute renal failure (such as advanced age, hypertension, history of thrombotic episodes not excluded by exclusion criterion number 13, patients with prolonged periods of immobilization, concomitant nephrotoxic medication, diabetes mellitus, overweight, hypovolemia), IMP should be administered at the minimum rate of infusion practicable.

During the First Period (16 weeks), subjects will receive double-blinded treatment at 4-week intervals (Week 0, 4, 8 and 12; i.e. 4 infusion cycles) of either 2.0 g/kg BW (20 mL/kg BW) Octagam 10% or 20 mL/kg BW 0.9% w/v isotonic sodium chloride solution as placebo. Infusions should be given on two consecutive days. At the discretion of the investigators each infusion cycle can be prolonged up to five days. Total dose for an infusion cycle will be given in equally divided doses on each infusion episode. If a patient will be infused over

two days, each infusion episode will take up to about 5.5hours dependent on the infusion rate. If infusion will be given over more than 2 days, the time for each infusion episode will be proportionately shorter. At each infusion episode the infusion will be given continuously.

In the Extension Period, subjects will receive 6 infusion cycles of 2.0 g/kg (20 mL/kg BW) Octagam 10% given over 2 to 5 consecutive days at 4-week intervals (Week 16, 20, 24, 28, 32 and 36). Total dose for an infusion cycle will be given in equally divided doses on each infusion episode. If a patient will be infused over two days, each infusion episode which will be given continuously will take up to about 5.5 hours, dependent on the infusion rate. At each infusion episode the infusion will be given continuously. Optionally, the subject may receive Octagam 10% in a dose of 1.0 g/kg BW (10 mL/kg BW) at the discretion of the investigator and if the subject remained stable on the higher dose.

If AEs occur during the infusion, the rate is to be reduced to half the rate at which the event occurred or the infusion is to be interrupted until symptoms subside. The infusion may then be resumed at a rate tolerated by the subject.

5.5 Preparation and Method of Administration

During the **First Period** it is recommended that the calculated IMP vials/bottles are pooled in PVC-free, DEHP-free and latex–free infusion bags by the hospital pharmacist or designee.

Each bottle of Octagam 10% must be examined visually by the pharmacist or designee for particulate matter and discoloration prior to pooling. Non-homogenous solutions or those that have a deposit must not be pooled. The same procedures should be performed also for sodium chloride 0.9% w/v solution.

The preparation should be performed under aseptic conditions preferably using a sterile bench, as described in the manual handed out to the hospital pharmacist or designee. IMP administration must be started within 3 to 4 hours after preparation.

The Octagam 10% must be allowed to warm to room or body temperature prior to IMP administration. The same holds true for sodium chloride 0.9% w/v solution for subjects in the placebo arm of the first period.

Subjects must be monitored before infusion and carefully observed for any symptoms at least once throughout the infusion period and at least 1 hour thereafter.

In the **Extension Period**, Octagam 10% vials may also be administered without pooling.

Note that Octagam 10% must not be mixed with other medicinal products or saline. For other IV products a separate IV line must be used.

The special warnings and precautions for use (see Investigator's Brochure) of Octagam 10% must be respected.

5.6 Blinding, Emergency Envelopes, and Breaking the Study Blind

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.

To maintain blinding in the first period, infusions will be given in blinded infusion bags (corresponding to a volume of 0.4 to 1.0 g/kg (4 to 10 mL/kg) Octagam 10% or sodium chloride 0.9% w/v solution at each of the 2 to 5 consecutive infusion days). Thus, the old

label will be discarded together with the vial/bottle, and a new label will be fixed onto an opaque over pouch by the hospital pharmacist or designee. The over pouch (normally used for light protection) will be put over the infusion bag to maintain blinding. The new labels will be identical for both, Octagam 10% and sodium chloride 0.9% w/v solution, so that the content of the bags is only known to the unblinded hospital pharmacist or designee. An example of this label can be found in Section 5.2.

The hospital pharmacist or designee will send the infusion bag(s) per subject (potentially already fixed to the opaque infusion line) to the ward.

To further assure the double-blind character of this study, the Investigator or designee who applies the medication to the subject will not be involved in any other 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 subject will be blinded with respect to study treatment throughout the entire First Period. Treatment given during First Period will also not be disclosed in the Extension Period. Because of the opaque (non-transparent) infusion line and over pouches, the subject will not be able to see the medication he/she is treated with.

Blinding will only be broken under the following circumstances:

- Occurrence of serious and presumably related AEs but only if the Investigator wants to know the assigned treatment for a proper clinical management of the subject.
- At Week 16 for subjects who were switched to the alternate treatment group due to deterioration or when deterioration is confirmed at Week 16 (see Figure 1 for details).
- If unblinding is required by the local regulatory authorities.

Whenever possible, the Investigator should notify the Sponsor prior to unblinding.

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 pharmacy, IMP dispensed to subjects, and IMP returned unused/partially used by the subject.

Octagam 10% will be delivered to the participating pharmacists by the Sponsor or designee.

A Drug Inventory and Dispensing Log will be kept current by the pharmacist, detailing the dates and quantities of IMP received and dispensed to each subject 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 pharmacy 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 bottles should be destroyed at the study site or at the pharmacy following local policies.

5.7.2 Assessment of Treatment Compliance

All subjects will be infused at the study site under the surveillance of authorized study personnel. Infusion details will be documented at the study site while the batch number(s) on the drug accountability form will be kept by the pharmacist or designee, which will be checked regularly by the unblinded monitor.

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

If feasible, screening should be completed within 3 weeks. However, screening results should be available as soon as possible. Based on the screening results, the subjects' eligibility for the study is determined.

Screening failures will be entered into the eCRF.

6.1 Observations by Visit

6.1.1 Screening Visit (Visit 1; duration up to 21 days, i.e. Week -3 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 sample for serum IgG.
- Blood samples for enzymes.
- Blood sample for viral markers.
- Blood sample for biomarkers of disease activity.
- Blood sample for D-dimers.
- Pregnancy test.
- CSM.
- Wells probability score for deep vein thrombosis (DVT).
- Wells probability score for pulmonary embolism (PE).

- Inclusion and exclusion criteria.

6.1.2 Visit 2 (Week 0; Baseline of First Period)

Subjects who are eligible will visit the study site and enter the controlled phase (First Period) after randomization.

Visit 2 should take place within 3 weeks after the Screening Visit.

All eligible subjects will receive their first infusion of either 2.0 g/kg (20 mL/kg) Octagam 10% or placebo as per randomization. The following assessments will be performed:

Before infusion cycle:

- Randomization and enrollment into the double-blind treatment period.
- SF-36v2.
- Vital signs.
- Blood sample for safety laboratory (hematology and clinical chemistry).
- Blood sample for additional safety lab parameters "Panel 1" (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)).
- Blood sample for serum IgG.
- Blood samples for enzymes.
- CSM.
- CDASI.

Before, during and after each infusion episode:

- Administration/Infusion of IMP (2.0 g/kg [20 mL/kg] Octagam 10% or placebo given in infusion episodes over 2 to 5 consecutive days).
- Vital signs before, at least once during and at least 1 hour after each infusion episode.

At least 1 hour after the infusion cycle:

- Blood sample for additional safety lab parameters "Panel 2" (serum haptoglobin, hemoglobin, plasma-free hemoglobin, LDH).
- 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)).
- 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.

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

6.1.3 Visit 3 (Week 4; First Period)

The following assessments will be performed:

Before infusion cycle:

- Physical examination.

- Vital signs.
- Blood sample for safety laboratory (hematology and clinical chemistry).
- Blood sample for serum IgG.
- Blood samples for enzymes.
- CSM.
- CDASI.

Before, during and after each infusion episode:

- Administration/Infusion of IMP (2.0 g/kg [20 mL/kg] Octagam 10% or placebo given in infusion episodes over 2 to 5 consecutive days).
- Vital signs before, at least once during and at least 1 hour after each infusion episode.

At least 1 hour after the infusion cycle:

- 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.

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

6.1.4 Visits 4 and 5 (Week 8 and 12; First Period)

The following assessments will be performed:

Before infusion cycle:

- Vital signs.
- Blood sample for safety laboratory (hematology and clinical chemistry).
- Blood sample for serum IgG.
- Blood samples for enzymes.
- CSM.
- CDASI.

Before, during and after each infusion episode:

- Administration/Infusion of IMP (2.0 g/kg [20 mL/kg] Octagam 10% or placebo given in infusion episodes over 2 to 5 consecutive days, or alternate IMP for subjects who deteriorated at 2 consecutive visits).
- Vital signs before, at least once during and at least 1 hour after each infusion episode.

At least 1 hour after the infusion cycle:

- 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.

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

6.1.5 Visit 6 (Week 16; End of First Period, Start of Extension Period)[2]

The following assessments will be performed:

Before infusion cycle:

- 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 "Panel 1" (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)).
- Blood sample for serum IgG.
- Blood samples for enzymes.
- Blood sample for biomarkers of disease activity.
- CSM.
- CDASI.

Before, during and after each infusion episode:

- Administration/Infusion of IMP (2.0 g/kg [20 mL/kg] Octagam 10% given in infusion episodes over 2 to 5 consecutive days).
- Vital signs before, at least once during and at least 1 hour after each infusion episode.

At least 1 hour after the infusion cycle:

- Blood sample for additional safety lab parameters "Panel 2" (serum haptoglobin, hemoglobin, plasma-free hemoglobin, LDH).
- 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)).
- 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.

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

6.1.6 Visits 7 and 8 (Week 20 and 24; Extension Period)

The following assessments will be performed:

Before infusion cycle:

- Vital signs.
- Blood samples for safety laboratory (hematology and clinical chemistry).
- Blood sample for serum IgG.

[2] 4 weeks after the last infusion

Before, during and after each infusion episode:

- Administration/Infusion of IMP (2.0 g/kg [20 mL/kg] Octagam 10% given in infusion episodes over 2 to 5 consecutive days).
- Vital signs before, at least once during and at least 1 hour after each infusion episode.

At least 1 hour after the infusion cycle:

- 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.

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

6.1.7 Visit 9 (Week 28)

The following assessments will be performed:

Before infusion cycle:

- Physical examination.
- Vital signs and body weight.
- Blood sample for safety laboratory (hematology and clinical chemistry).
- Blood sample for additional safety lab parameters "Panel 1" (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)).
- Blood sample for serum IgG.
- Blood samples for enzymes.
- CSM.
- CDASI.

Before, during and after each infusion episode:

- Administration/Infusion of IMP (2.0 g/kg [20 mL/kg] Octagam 10% given in infusion episodes over 2 to 5 consecutive days). At the discretion of the investigator and, if the subject is stable on 2.0 g/kg (20 mL/kg) Octagam 10%, the subject may receive 1.0 g/kg (10 mL/kg) Octagam 10%.
- Vital signs before, at least once during and at least 1 hour after each infusion episode.

At least 1 hour after the infusion cycle:

- Blood sample for additional safety lab parameters "Panel 2" (serum haptoglobin, hemoglobin, plasma-free hemoglobin, LDH).
- 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)).
- 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.

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

6.1.8 Visits 10, 11 (Week 32 and 36; Extension Period)

The following assessments will be performed:

Before infusion cycle:

- Vital signs.
- Blood samples for safety laboratory (hematology and clinical chemistry).
- Blood sample for serum IgG.

Before, during and after each infusion episode:

- Administration/Infusion of IMP (2.0 g/kg [20 mL/kg] Octagam 10% given in infusion episodes over 2 to 5 consecutive days). At the discretion of the investigator and, if the subject is stable on 2.0 g/kg (20 mL/kg) Octagam 10%, the subject may receive 1.0 g/kg (10 mL/kg) Octagam 10%.
- Vital signs before, at least once during and at least 1 hour after each infusion episode.

At least 1 hour after the infusion cycle:

- 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.

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

6.1.9 Unscheduled Visit

If an unscheduled visit becomes necessary, e.g. after disease deterioration between 2 regular visits, the same procedures as described in Section 6.1.3 for Visit 3 (without IMP infusion) should be performed.

Wells probability scores for DVT and PE should also be performed. If the Wells score is likely (≥2 points) for DVT, a Doppler scan should be performed and a blood sample should be taken for assessment of D-dimers.

6.1.10 End-of-Study (Final Examination) Visit 12 (Week 40; Extension Period) or Drop-out Visit

The final examination is performed 4 weeks after the last IMP administration.

The following investigations will be performed:

- SF-36v2.
- Physical examination.
- Blood sample for safety laboratory (hematology and clinical chemistry).
- Blood sample for additional safety lab parameters "Panel 1" (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)).
- Blood sample for serum IgG.
- Blood samples for enzymes.

- Blood sample for viral markers.
- Blood sample for biomarkers of disease activity.
- CSM.
- CDASI.
- Monitoring of AEs.
- Documentation of concomitant medication.
- Pregnancy test.

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

6.1.11 Time Windows Used in this Study, Including Tolerances

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

Table 4: *Time Windows Used in this Study*

Time Point	Time stated	Tolerance
Interval between visits / infusion cycles	4 weeks	± 4 days
Interval between infusion episodes	1 day (next day)	15 – 30 hours
Vital signs	before IMP administration of infusion episode	≤ 60 minutes
	after each IMP administration	≥ 60 minutes
Direct Coombs' test	before first IMP administration of infusion cycle	≤ 4 hours
	after last IMP administration of infusion cycle	≥ 60 minutes
Wells probability score for DVT	after IMP administration of last infusion episode of a cycle	≥ 60 minutes
Wells probability score for PE	after IMP administration of last infusion episode of a cycle	≥ 60 minutes

6.1.12 Clinical Terms Used in this Study

Table 5: *Clinical Terms Used in this Study*

Term	
Clinical Start of Study	Screening of First Subject
Enrollment	Randomization and entry into the double-blind treatment period
Washout period	Period which needs to elapse from discontinuing previous DM related medication until randomization
Clinical End of Study	Last Visit of the Last Subject

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Subject

The duration of the entire study for each subject will be up to 43 weeks and consists of the following segments: up to 3 weeks for Screening, then 16 weeks of double-blind treatment phase (First Period) followed by 24 weeks of open-label treatment (Extension Period).

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 36 months. The estimated clinical start of the study is Q4 2016 with the estimated clinical end in Q4 2019.

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 subjects' 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 first (controlled) period of the study, fulfilling the following criterion:
  - associated with Octagam 10% treatment;

  AND

  if less than half of the number of TEEs reported as associated with Octagam 10% are observed during the first (controlled) period of the study, fulfilling the following criterion:
  - associated with placebo treatment.

  .
- For TEEs observed on or after the cut-off date of 04-Jul-2018 (since introduction of reduced maximum infusion rate of 0.04 mL/kg/min) TEE rates (per 100 patient-months) will be calculated as follows:
  - Ro = 100* Number of TEEs observed on or after the cut-off date in patients last treated with Octagam / Total person-months of patients on Octagam since the cut-off date
  - Rp = 100* Number of TEEs in patients last treated with Placebo / Total person-months of patients on Placebo. Rp is based on the whole study period, no cut-off is applied)

  These rates will be calculated on basis of the actual last treatment.
  The study as a whole will be terminated
  - if Ro exceeds Rp by more than 1.0

  AND
  - at least 4 TEEs have been observed in the Octagam group after the cut-off date of 04-Jul-2018.

  TEEs with a likely temporal and cause-effect relationship which occur in a single subject within a short clinical time period should be counted as a single AESI, including for the

calculations performed for stopping rules: For example a DVT which subsequently embolized to cause a PE or a transient ischemic attack (TIA) followed in short order by a cerebrovascular accident (CVA).

Medical judgement will be applied to determine if these represent separate discrete events or if they represent expressions of a single AESI based on the relatedness of the underlying pathophysiology. The IDMC will confirm if they are clinically and pathophysiologically manifestations of a single process.

However, all TEEs will be captured separately in the clinical data base.

- If more than 4 clinically significant (definition see Section 7.3.2.1) hemolytic transfusion reactions (HTRs) are observed during the first (controlled) period of the study, fulfilling the following criteria:
  - assessed as probably or possibly related to Octagam 10% treatment by Investigator and/or Sponsor;
  - confirmed by the IDMC.

  AND

  if less than 3 clinically significant HTRs are observed during the first (controlled) 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 Independent Data Monitoring Committee (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 subject 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, ethnic origin, height, weight, and Body Mass Index.

7.1.2 Medical History and Prior/Concomitant Medications

The relevant medical history will be obtained by interviewing the subject. Records of past diseases and treatments (e.g., hospital discharge letters) will be obtained for the study files, if available.

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

7.2 Efficacy Assessments

All participating centers will be trained in the DOI assessed by the TIS based on its 6 CSM. CSM assessments should always be performed by the same investigator or designee. Training will be done by a third party.

7.2.1 Assessments for Primary Efficacy Endpoint(s)

The TIS is a score derived from the evaluation of the results from 6 CSM of myositis disease activity 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).[27,28]

- 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).

These 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.[19,30] It does not discriminate stable from worsening patients.

7.2.2 Assessments for Secondary Efficacy Endpoint(s)

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.[29]

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:

- AEs and SAEs (for definitions and reporting requirements, see Section 7.3.2 thru Section 7.3.5).
- ADRs and suspected ADRs (for definition see Section 7.3.2.1).
- 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 receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable 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.
- **Suspected ADR:** Suspected ADR is an AE that fulfills at least one of the following criteria:
    - AE starts during the infusion cycle or within 72 hours after the end of the last infusion episode of the respective infusion cycle/visit.
    - The incidence of the preferred term in the Octagam 10% arm is greater than in the placebo arm.
    - The investigator's assessment is missing or indeterminate.
- **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 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 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?"

Any AE or ADR which occurs 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 other than those related to the basic disease, the tests will be confirmed and the subject 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 routine activities
- **Moderate:** an AE which is sufficiently discomforting to interfere with the subject's routine activities
- **Severe:** an AE which is incapacitating and prevents the pursuit of the subject's routine activities

The grading of an AE is up to the medical judgment 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 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 clinical state or by environmental factors or other therapies administered.
- **Not related (unrelated):** events for which sufficient information exists to conclude that the etiology 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 **death** per se is not an event, but an outcome. The event which resulted in the subject'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 recognized standards of medical care to protect the health and well-being of the subject. 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 has stabilized. 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 hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is another important medical event (including TEEs as defined in section 7.3.5.1).

NOTE: The term 'life-threatening' refers to an event in which the subject 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 hospitalization but may jeopardize the subject 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 subject. 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 from the 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. TEEs must be reported as SAE as described in Section 7.3.3. Premature termination criteria related to AESI are defined in Section 6.2.3.1.

7.3.5.1 Thromboembolic Events (TEEs)

There is clinical evidence of an association between IGIV 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 ([25] 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 ([26]; 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 IGIV therapy. IGIV-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).
- Additional safety lab parameters (hemoglobin, serum haptoglobin, plasma-free hemoglobin, LDH).

Intravascular hemolysis will be suspected if all of the following criteria are fulfilled (modified acc. to FDA Guidance for Industry 2008[3]):

- 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.

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

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

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, thyroid-stimulating hormone (TSH).

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

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)

Additional safety laboratory parameters:
Panel 1: serum haptoglobin and plasma-free hemoglobin.
Panel 2: serum haptoglobin, hemoglobin, plasma-free hemoglobin, LDH.

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.

Blood 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 sampling and shipment procedures will be provided to each study site.

7.3.6.2 Local Laboratory

The following laboratory tests will be done in some countries 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.

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 Screening and at the Termination Visit.

Viral marker samples will be analyzed at a central laboratory.

Full blood sample must be taken and centrifuged, aliquoted, 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 analyzed by serology tests or nucleic acid testing for HIV, hepatitis B and hepatitis C virus. In case of any change of a subject'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.

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

The vital signs obtained at the time points specified in Section 6.1 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 each infusion, and at least 1 hour after end of infusion. Hemodynamic changes may occur during IGIV infusion and minor changes in pulse and blood pressure are frequent. For this reason, only changes in vital signs considered clinically significant by the Investigator are to be reported as AEs. Fever will be defined as a body temperature >38°C, and has to be documented as an AE.

Physical examinations will be performed at the visits specified in Section 6.1. Both height and weight will be measured at screening. In addition, body weight will be measured at certain visits prior to IMP administration and reported back to the pharmacist or designee as it is needed for the preparation of the next study medication dosage by the unblinded pharmacist or designee 4 weeks later.

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.

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. Pregnancies occurring during the study (fetal 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 fetus 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 fulfils 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/labeling. 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 ProDERM in the First Period are appropriate to verify the clinical efficacy of IGIV in DM. The study design of ProDERM includes all major scientific, state-of-the-art interventions with respect to assessment of the efficacy, safety and tolerability of IGIV administration in DM patients.

While Dalakas et al. 1993 stated that most of the IGIV responders did so after the second course of IGIV, an Advisory Board of DM experts in the fields of neurology, rheumatology and immunology recommended to extend the placebo-controlled First Period to 4 courses of either IGIV or placebo (last infusion at Week 12) and to evaluate the primary endpoint at Week 16 (4 weeks [±4 days] after the last infusion). In order to assess the long-term efficacy of IGIV maintenance therapy subjects will receive further 6 courses of Octagam 10% during the open-label Extension Period (unless they have to drop out, see Section 4.3.1). To keep the blinding, subjects worsening in both treatment arms will be switched to the alternate treatment.

The comparability with the Dalakas trial results will be limited due to the different primary endpoint selected. 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.[21] 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.[22-24]

CSM of myositis disease activity for DM/PM clinical trials have been established and validated by the IMACS Group.[15-17] 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).[19,30] ProDERM will employ the TIS in its final version (submitted for publication by Prof. Aggarwal who was member of a highly experienced Advisory Board that helped developing this protocol) for the DOI used as primary endpoint. 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).[18] Therefore, it is justified to use the response criterion based on the TIS changes as primary endpoint.

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 files for each subject 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 participates in this study.

All data entered in the eCRF must be supported by source data in the subject 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 authorize site staff (e.g., sub-investigators, nurses) to enter study data into the eCRF. This must be documented in the Delegation of Authority Log signed by the Investigator.

8.1.2 Electronic Case Report Forms

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

Study site staff (e.g., research nurse) will be responsible for entering subject 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 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 authorized 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 resolutions 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 eCRFs 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 authorized 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 identification code list, which provides the unique link between named source records and eCRF 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 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 confidentiality is protected in accordance with applicable regulations.

8.6 Committees

8.6.1 Independent Adjudication Committee

An Independent Adjudication Committee (IAC) will be established by the Sponsor. The IAC will be composed of 4 permanent members who shall have – as a group – experience in the fields of neurology, rheumatology and/or dermatology. The members of the IAC must not actively recruit subjects.

The responsibility of the IAC will be to review individual case histories and to assess disease activity as requested by inclusion criterion no. 3.

An IAC charter will be developed before study start to serve as the central reference document for the IAC process and its participants. The charter will define, at a minimum, the purpose of the IAC, member requirements and qualifications, event definitions, adjudication rules and voting scheme that will document how events will be adjudicated and how final IAC decision will be reached.

8.6.2 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 fields of immunology, rheumatology, and dermatology, and of 1 unblinded statistician. The members of the IDMC must not actively recruit subjects.

The IDMC will have the following responsibilities:

- to review relevant safety data periodically;
- to review TEEs in a timely fashion and monitor the stopping rules as defined in Section 6.2.3.1;
- 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.

8.6.3 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 parameters for the evaluation of the primary endpoint, i.e. the proportions of responders in the Octagam 10% and the placebo group at the end of the 16-week efficacy period (First Period).

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

A stratified analysis using Cochran-Mantel-Haenszel test will finally be applied as primary analysis, to account for the stratification of the randomization (see Section 9.2.2).

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

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

9.2 Statistical Analysis

A formal SAP describing all details of the analyses to be performed will be finalized by the study statistician and approved by the Sponsor prior to the start of the statistical analysis.

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

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

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

9.2.1 Populations for Analysis

The following populations will be considered for the statistical analysis:

The safety analysis set (SAF) consists of all subjects who received at least part of 1 infusion of Octagam 10% or placebo.

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

The per-protocol set 1 (PP1) consists of all subjects of the FAS excluding those with significant protocol deviations that occurred before the Week 16 assessments, and which may have an impact on the analysis of the primary endpoint. This is the set of subjects for whom the primary endpoint can be evaluated as planned; it also includes subjects who deteriorated at 2 consecutive visits (see Section 4.3.1) up to (including) Week 16 and that are therefore counted as non-responders, and also subjects that were withdrawn from the study for any AEs or insufficient response before Week 16. Protocol deviations in the open-label extension period are irrelevant for the definition of this population.

The per-protocol set 2 (PP2) consists of all subjects of the FAS who received at least part of 1 infusion of Octagam 10%, excluding those with significant protocol deviations which may have an impact on the evaluation of the treatment effects of Octagam 10%. This set of subjects is defined to allow the assessment of Octagam 10% throughout the study and will not be used for comparisons with the placebo group.

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

- Violations of the study entry criteria.
- Withdrawal criteria that developed during the study (see Section 4.3.1).
- Wrong treatment or incorrect dose.
- Prohibited concomitant medication (e.g., IGIV other than Octagam 10%).

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

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

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

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

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

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

9.2.2 Efficacy Analysis Plan

The primary endpoint measure 'response' will be assessed at Week 16 based on the TIS score; a subject is defined as responder if

(iii) the subject has a TIS score of ≥20 points at Week 16 and
(iv) the subject has not met "Confirmed Deterioration" criteria at 2 consecutive visits as defined in Section 4.3.1 up to (including) Week 16.

Otherwise the subject will be counted as non-responder. Thus subjects who discontinued from the study prior to Week 16 will also be considered as non-responders.

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

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

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

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

For TIS response at Week 16 by improvement category, the proportion of subjects with at least moderate improvement and the proportion of subjects with major improvement will be

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

All mean changes to be evaluated as secondary endpoints (listed in section 3.1.2) will be presented by a full set of descriptive parameters: number of subjects with non-missing values, mean, standard deviation, median, minimum and maximum, 1st and 3rd quartile, 95% CI. Moreover, for all continuous secondary endpoints, an analysis of covariance (ANCOVA) will be used to analyze changes from baseline to Week 16. For patients who are switched to the alternate treatment before Week 16, the last value prior to switch will be carried forward to Week 16 and used to calculate change from baseline to Week 16. The model will include treatment and global disease activity as a fixed factor. Center will be included as random factor. The baseline value of the variable to be analyzed will be included as a covariate. Least square means will be derived and presented together with 95%-confidence intervals by treatment group. Moreover, two-sided 95% confidence intervals will be derived for the overall difference in least square means between Octagam and placebo treatment. As sensitivity analysis, a modified ANCOVA model will be used, where the changes from baseline to Week 16 are calculated based on Week 16 values, even if a patient is switched to the alternate treatment before Week 16. To incorporate the switch into the model, the variable crossover (yes/no) which indicates if there was a switch to the alternate treatment will be included as additional factor into the ANCOVA model, as well as the treatment-by-cross-over interaction term.

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

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

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

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

Further details on the statistical presentations will be given in the SAP.

9.2.3 Safety Analysis Plan

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

9.2.4 Handling of Missing Data

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

For missing weight measurements the last available body weight will be used for all calculations related to dosing (last observation carried forward, LOCF); however, in individual subject data listings missing data will not be replaced by imputed values.

9.3 Randomization, Stratification, and Code Release

All subjects qualified to participate in the study at Visit 2 will be randomized to 1 of the 2 treatment arms by an electronic IRT tool and thereby enrolled into the double-blind treatment period. The randomization will apply a randomization ratio of 1:1 with respect to 2.0 g/kg of Octagam 10% vs. placebo by means of a stratified block design, using the seriousness of disease before enrollment (mild, moderate or severe defined as a Physician's Global Disease Activity value of 0-3 [mild], 4-6 [moderate], 7-10 [major]) as strata and a fixed block size. This will ensure the desired overall randomization ratio and avoid random differences between the treatment groups with respect to the seriousness of DM prior to enrollment into the ProDERM study.

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

The result of randomization, i.e. the treatment group assignment of individual subjects will only be reported to the hospital pharmacist or designee by a defined manner that no other trial personnel will have access to.

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.

9.4 Interim Analysis

No interim analysis is planned.

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 IEC/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 information and informed consent form, any other materials provided to the subjects, 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 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 is enrolled in the study.

10.3 Subject Information and Informed Consent

The Investigator will obtain freely given written consent from each subject 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 decision to participate. The informed consent form must be signed, with name and date and time noted by the subject, before the subject is exposed to any study-related procedure, including screening tests for eligibility.

The Investigator will explain that the subjects 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 enrolled.

Each subject 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.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Coordinating Investigator 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, the objective/design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of subjects treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Subject Data

The Investigator will ensure that the subject's confidentiality is preserved. On eCRFs or any other documents submitted to the Sponsor, the subjects will not be identified by their names, but by a unique subject 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 routine monitoring visit shall take place shortly after the inclusion of the first subject. 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, analyze, 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 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 Coordinating 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 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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