BLA Clinical Review Memorandum

Application Type	Efficacy Supplement
STN	125062/674
CBER Received Date	Sep 14, 2020
PDUFA Goal Date	Jul 15, 2021
Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	
Reviewer Name(s)	Wenyu Sun, MD, MPH Wenyu Sun -S Digitally signed by Wenyu Sun -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Wenyu Sun -S, 0.9.2342.19200300.100.1.1=2002164811 Date: 2021.07.15 08:48:40 -04'00'
Review Completion Date / Stamped Date	July 14, 2021
Supervisory Concurrence	Lei Xu, MD, PhD Lei Xu -S3 Digitally signed by Lei Xu -S3 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lei Xu -S3, 0.9.2342.19200300.100.1.1=2000424164 Date: 2021.07.15 09:11:53 -04'00' Tejashri Purohit-Sheth, MD *Tejashri Purohit-Sheth, M.D.* Tejashri S. Purohitsheth -S Director, DCEPT OTAT/CBER/FDA 2021.07.15 14:06:49 -04'00'
Applicant	OCTAPHARMA
Established Name	Immune Globulin Intravenous, Human 10% S/D
(Proposed) Trade Name	Octagam 10%
Pharmacologic Class	Immune Globulins
Formulation(s), including Adjuvants, etc.	Liquid Solution
Dosage Form(s) and Route(s) of Administration	Intravenous
Dosing Regimen	2 g/kg divided in equal doses given over 2-5 consecutive days every 4 weeks
Indication(s) and Intended Population(s)	Indicated for the treatment of Dermatomyositis in adults
Orphan Designated (Yes/No)	Yes

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GLOSSARY

AE	adverse event
AESI	Adverse Events of Special Interest
ALAT	Alanine Aminotransferase
ANCOVA	analysis of covariance
AR	adverse reaction
ASAT	Aspartate Aminotransferase
BLA	biologics license application
CABG	cardiac bypass graft
CDASI	Cutaneous Dermatomyositis Disease Area and Severity Index
CFR	Code of Federal Regulations
CIDP	chronic inflammatory demyelinating polyneuropathy
CMC	chemistry, manufacturing, and controls
COA	clinical outcome assessment
CR	Complete Response
CSMs	Core Set Measures
CT	computed tomograph
DM	dermatomyositis
DVT	deep vein thrombosis
ECG	electrocardiogram
FAS	Full Analysis Set
eGFR	estimated glomerular filtration rate
GBS	Guillain-Barré syndrome
GDA	global disease activity
HAQ	Health Assessment Questionnaire
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
IgG	immunoglobulin G
IGIV	immunoglobulin intravenous
ITP	immune thrombocytopenic purpura
ITT	intent-to-treat
LDH	Lactate Dehydrogenase
MMN	multifocal motor neuropathy
MMT	Manual Muscle Testing
PAS	Prior Approval Supplement
PD	pharmacodynamics
PeRC	Pediatric Review Committee
PI	package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
SAE	serious adverse event
SAF	Safety Analysis Set
S/D	solvent/detergent
TEE	thromboembolic events
TIS	total improvement score
VAS	Visual Analogue Scale

1. EXECUTIVE SUMMARY

The Applicant, OCTAPHARMA Pharmazeutika Produktionsges.m.b.H. submitted BLA 125062/674, an efficacy supplement, for Immune Globulin Intravenous (Human), Octagam 10% for the treatment of dermatomyositis (DM) in adults.

Octagam 10% is a solvent/detergent (S/D)-treated, sterile preparation of highly purified immunoglobulin G (IgG) derived from large pools of human plasma. Octagam 10% is a solution for infusion to be administered intravenously. It has been licensed for the treatment of chronic immune thrombocytopenic purpura (ITP) in adults since 2014.

The safety and efficacy of Octagam 10% in adults with DM was evaluated in a Phase 3 study (Study GAM10-08). The study included two parts: a 16-week, randomized, double-blind, placebo-controlled First Period, and a 6-month, open-label Extension Period. The primary endpoint was the proportion of responders at Week 16 (i.e., end of the First Period). A responder was defined as a subject with an improvement of ≥20 points on the Total Improvement Score (TIS) and who has not met the "confirmed deterioration" criteria, as defined in the protocol, at two consecutive visits up to Week 16.

In the First Period, 95 adults (22-79 years of age) with DM were enrolled and randomized: 47 subjects received 2 g/kg Octagam 10% every 4 weeks for 4 infusion cycles; and 48 subjects received placebo every 4 weeks for 4 infusion cycles. One infusion cycle comprised of all infusions administered over 2-5 days. In the Extension Period, during which all subjects who were eligible to continue, received Octagam 10% 2 g/kg every 4 weeks for a total of 6 infusion cycles. A total of 91 subjects, including 45 subjects in the initial Octagam 10% group and 46 subjects in the placebo group, entered the Extension Period.

At Week 16, the proportion of responders was 78.7% (37/47) in the Octagam 10% group, and 43.8% (21/48) in the placebo group. The difference in responder rate between the two groups was 35% (95% CI: 16.7, 53.2; p=0.0008). The median time to response was 35 days in the Octagam 10% group. In addition, there was a greater proportion of subjects in the Octagam 10% group compared to placebo with at least moderate improvement defined as ≥40 points improvement on the TIS (68.1% versus 22.9%, difference: 45.2%, 95% CI: [27.3%, 63.0%]) and major improvement defined as ≥60 points improvement on the TIS (31.9% versus 8.3%, difference: 23.6%, 95% CI: [8.1%, 39.0%]).

The Octagam 10% group maintained their improvement in TIS (32/45, 71.1%) during the 6-month Extension Period. Among the 46 subjects who switched from placebo to Octagam 10% in the Extension Period, 69.6% (32/46) were classified as responders at the end of the 6-month Extension Period.

Efficacy was further supported by improvement in the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) total activity score, with a mean decrease (improvement) of 9.4 (SD: 10.5) points from baseline to Week 16 in the Octagam 10% group versus 1.2 (SD: 7.0) point in the placebo group.

No subjects died in Study GAM10-08. The following serious adverse reactions were observed: muscle spasms and dyspnea in one subject, loss of consciousness in one subject, and thromboembolic events (TEEs) in five subjects, including deep vein

thrombosis and pulmonary embolism in one subject, cerebrovascular accident in one subject, cerebral infarction in one subject, hypoesthesia in one subject and pulmonary embolism in one subject.

The most common adverse reactions (ARs) reported in >5% of subjects were headache, fever, nausea, vomiting, increased blood pressure, chills, musculoskeletal pain, increased heart rate, dyspnea, and infusions site reactions.

The reviewed safety data do not warrant a Risk Evaluation and Mitigation Strategies (REMS), or a safety postmarketing requirement (PMR) clinical study.

In summary, this reviewer considers that Study GAM10-08, an adequate and well-controlled study with compelling results supported by confirmatory evidence based on additional data from the natural history of the disease, provides substantial evidence of effectiveness of Octagam 10% for the treatment of adults with DM, a serious rare disease with unmet medical needs. Review of the submitted safety data indicates that the risks can be mitigated through routine pharmacovigilance plan and specific adverse reaction follow-up questionnaire for thromboembolic events, medical management, and adequate package insert (PI) without requiring other regulatory measures such as REMS or clinical PMR. The efficacy and safety data in the BLA efficacy supplement support a favorable benefit / risk profile of Octagam 10% for the treatment of DM in adults. Therefore, this reviewer recommends traditional approval of Octagam 10% for the new indication, “treatment of Dermatomyositis in adults.”

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Summary of demographic information for subjects in Study GAM10-08 (safety analysis set, N=95) is shown in Table 1.

Table 1 Study GAM10-08 Demographics

	Octagam 10% N=47	Placebo N=48	Total N=95
Age [Years]			
Mean (SD)	54.0 (13.8)	51.4 (13.0)	52.7 (13.4)
Median	55.0	51.5	52.0
Min, Max	22.0, 77.0	22.0, 79.0	22.0, 79.0
Gender [N (%)]			
Female	36 (76.6%)	35 (72.9%)	71 (74.7%)
Male	11 (23.4%)	13 (27.1%)	24 (25.3%)
Race [N (%)]			
Asian	1 (2.1%)	1 (2.1%)	2 (2.1%)
Black or African American	2 (4.3%)	3 (6.3%)	5 (5.3%)
White	44 (93.6%)	43 (89.6%)	87 (91.6%)
Other	0 (0.0%)	1 (2.1%)	1 (1.1%)
Region [N (%)]			
US	14 (29.8%)	13 (27.1%)	27 (28.4%)
Non-US	33 (70.2%)	35 (72.9%)	68 (71.6%)
Weight [kg]			
Mean (SD)	74.2 (14.6)	77.5 (12.8)	75.9 (13.8)
Median	74.0	78.0	76.0
Min, Max	45.0, 117.0	52.0, 110.0	45.0, 117.0

Max=maximum; Min=minimum; N=number of patients; SD=standard deviation; US=United States

(Source: Adapted from BLA 125062/674, Summary of Clinical Efficacy, page 4)

Reviewer comment: The demographic characteristics were balanced between the two treatment groups.

1.2 Patient Experience Data

Patient experience data relevant to this submission are summarized in Table 2.

Table 2 Patient Experience Data Relevant to this Application

	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
		Clinical outcome assessment (COA) data, such as		
		☒	Patient reported outcome (PRO)	Section 6.1.7 SF-36 Health Survey
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	Section 6.1.1 Study primary endpoint
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Dermatomyositis (DM), a rare autoimmune disease, is a subtype of idiopathic inflammatory myopathies (IIM), collectively known as myositis. Based on different clinical and histopathological features, IIM can be classified as polymyositis (PM), dermatomyositis, immune-mediated necrotizing myopathy (IMNM), and inclusion body myositis (IBM). The annual incidence of IIM is 2–10 per 1 million and overall prevalence is 50–100 cases/million inhabitants depending on the data origin[1]. The portion of DM among IIM in adults ranges between 26–83%, depending on genetic, geographic, and environmental factors. Dermatomyositis is the predominant form of myositis seen in children (80–85% of cases).

Dermatomyositis is a multisystem disorder with a wide variety of clinical manifestations, including lung, joint, esophageal and cardiac findings; however, its hallmark features

1 Griger Z, et al. Pharmacological management of dermatomyositis. Expert Review of Clinical Pharmacology. 2017; 10(10):1109-1118.

are the characteristic skin rashes and progressive symmetrical proximal muscle weakness. The diagnosis of DM is based on a combination of certain clinical and laboratory features, such as (1) the presence of skeletal muscle weakness; (2) elevated serum levels of muscle enzymes; (3) myopathic triad on electromyography; (4) characteristic histopathological changes on muscle biopsy; and (5) the presence of characteristic skin rashes, including the heliotrope rash or Gottron papules over the joint extensor surfaces.

The causes of DM are still unclear, although an autoimmune process, as well as both genetic and environmental factors have been implicated. Advances in therapy for DM have led to improvement in prognosis and gains in life expectancy in patients with DM. Nevertheless, DM continues to be associated with increased mortality (up to 5% to 48%); in a Finnish study, the overall mortality rate in PM/DM patients was found to be three-fold higher compared with that of the general population.[2]

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Corticosteroids are first-line therapy for the muscle manifestations and are currently the only FDA-approved drugs for DM. Immunosuppressive drugs, such as methotrexate, azathioprine, cyclosporine-A, are commonly used as steroid sparing agents for DM. However, according to the Cochrane Review, high quality randomized and controlled clinical trials are lacking to assess the efficacy and toxicity of these drugs.[3]

Topical agents (topical sunscreens, topical steroids, etc.) have been used as supplementary treatments in patients with DM whose skin involvement is dominant. However, none of these topical agents have been approved for DM in the United States (U.S.).

2.3 Safety and Efficacy of Pharmacologically Related Products

Immune globulin intravenous (IGIV) has been increasingly used in the treatment of patients with a variety of autoimmune and inflammatory neurological disorders, including DM. However, only one placebo-controlled clinical study that enrolled 15 subjects with refractory DM has been published so far. The study randomized the subjects to receive either IGIV at the dose of 2.0 g/kg or placebo for 12 weeks. After a 1-month washout phase the subjects crossed over to the alternate therapy. A total of 12 subjects received IGIV of whom 9 subjects with severe disabilities had a major improvement to nearly normal function[4]. Of 11 placebo-treated subjects, none had major improvement, 3 had mild improvement, 3 had no change in their condition, and 5 had worsening of their condition. None of the commercially available immune globulin products have been FDA-approved for DM.

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2 Marie I. Morbidity and mortality in adult polymyositis and dermatomyositis. Current Rheumatology Reports. 2012; 14:275-285.
3 Gordon PA, et al. Drugs that suppress or modify the immune system for dermatomyositis and polymyositis (Review). Cochrane Database of Systematic Reviews 2012, Issue 8. 4 Dalakas MC, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. N Engl J Med. 1993;329(27):1993–2000.
4 Dalakas MC, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. N Engl J Med. 1993;329(27):1993–2000.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

The first marketing authorization for Octagam 10% was obtained in Europe in 2008 for the indications of primary immunodeficiency (PID), secondary immune deficiency (SID), immune thrombocytopenic purpura (ITP), Kawasaki disease, and Guillain Barré Syndrome (GBS). In 2019, Octagam 10% was approved for the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) in Europe. In the U.S., Octagam 10% was approved for the treatment of ITP in adults in 2014. Up to July 2020, Octagam 10% was approved in 57 countries worldwide.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

- The studies were conducted under IND 16925.
- Octagam 10% for the treatment of DM granted Orphan Drug designations: 4/19/2017
- BLA Efficacy supplement submission: 9/14/2020
- PDUFA due date: 7/16/2021

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated for a complete clinical review.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The Applicant states that the Phase 3 trial was carried out in accordance with the ICH (International Conference on Harmonization) Good Clinical Practice (GCP) guidelines. The study was conducted after obtaining the written informed consent of subjects.

3.3 Financial Disclosures

The Applicant adequately disclosed financial arrangements with all clinical investigators through Form 3454. No issues were identified that raised concerns regarding potential for bias in conduct of the study.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Octagam 10%, is a solvent/detergent (S/D)-treated, sterile preparation of purified immunoglobulin G (IgG) derived from large pools of human plasma.

This preparation contains approximately 100 mg of protein per mL (10%) of which not less than 96% is normal human immunoglobulin G. Octagam 10% contains not more than 3% aggregates, not less than 94% monomers and dimers and not more than 3% fragments. On average, the product contains 106 µg/mL of IgA and even lower amounts of IgM.

All units of human plasma used in the manufacture of Octagam 10% are provided by FDA-approved blood establishments, and are tested by FDA-licensed serological tests for HBsAg, antibodies to HCV and HIV and Nucleic Acid Test (NAT) for HCV and HIV-1 and found to be non-reactive (negative).

4.2 Assay Validation

Octapharma proposes the use of a (b) (4) assay (b) (4) (b) (4) (b) (4) will submit a Prior Approval Supplement (PAS) with the fully validated assay and set a final specification. See CMC Review memo for more details.

4.3 Nonclinical Pharmacology/Toxicology

No additional nonclinical data were submitted in the BLA supplement.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action of immunoglobulins in the treatment of DM has not been fully elucidated.

4.4.2 Human Pharmacodynamics (PD)

Not applicable.

4.4.3 Human Pharmacokinetics (PK)

Pharmacokinetic studies with Octagam 10% have not been performed in patients with *chronic* ITP nor in patients with Dermatomyositis.

Reviewer Comment: PK studies were performed for Octagam 5% in subjects with PID, and the PK parameters were within the known range of other IGIV products. Octagam 10% is expected to have comparable PK characteristics to Octagam 5% based on in vitro comparability between 5% and 10% solution.

4.5 Statistical

See FDA Biostatistical Review memo. The statistical reviewer concluded that the efficacy results of Study GAM10-08 provided sufficient statistical evidence to support the indication of Octagam 10% for treatment of dermatomyositis in adults.

4.6 Pharmacovigilance

See Epidemiology Review memo. Continued routine pharmacovigilance and specific adverse reaction follow-up questionnaire for thromboembolic events are recommended.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This application is supported by a single Phase 3 study, for both efficacy and safety for the indication of DM.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The clinical review focused the final study report, protocol, summary of clinical efficacy, summary of clinical safety, clinical overview, risk management plan, statistical analysis plan, data listings, and data sets of Study GAM10-08, and the revised PI.

5.3 Table of Studies/Clinical Trials

Table 3 List of Study

Study ID	No. of Study Centers, Location(s), Study Period	Design	# Subjects by Arm	Study Drug, Route and Dose	Study Objective	Gender M/F Mean Age	Primary Endpoints
GAM10-08	17 sites in the United States, 5 in Russia, 3 in Ukraine, 3 in Hungary, 2 in Germany, 2 in Poland, 1 in Canada, 1 in Czech Republic, 1 in the Netherlands, 1 in Romania Feb 2017 – Nov 2019	Phase 3, Prospective, double-blind, randomized, placebo-controlled, multicenter	95 adults with DM were enrolled in the following groups: N=47 in the Octagam 10% arm N=48 in the placebo arm	Octagam 10% Human normal immunoglobulin solution for IV infusion, Up to 4 infusion cycles of either 2.0 g/kg Octagam 10% or placebo (20 mL/kg) every 4 weeks (Weeks 0, 4, 8 and 12) during the First Period. After the response assessment, 2.0 g/kg (20 mL/kg) of Octagam 10% at 4-week intervals during 6- month Extension Period.	Efficacy, Safety	N=95 24 M / 71 F Mean Age: 52.7 years (22 – 79 years)	Efficacy: Proportion of responders at Week 16 compared to baseline, responder = subject with improvement of ≥20 points on Total Improvement Score and who had not met 'confirmed deterioration' criteria at 2 consecutive visits up to and including Week 16

Source: Adapted from BLA 125062/674, Summary of Clinical Efficacy, Appendix Table 2.7.3.6, Page 10.

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

No Advisory Committee Meeting was held because review of information submitted in the BLA supplement did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

5.4.2 External Consults/Collaborations

There were no external consultants or collaborators involved in this BLA review.

5.5 Literature Reviewed (if applicable)

During review of the BLA supplement, this reviewer consulted FDA regulatory guidance documents, as well as academic literature, for background and context regarding the targeted disease and the mechanism of action of the product. The literature consulted is provided in References.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study GAM 10-08

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

6.1.1 Objectives

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

The secondary objectives were

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

6.1.2 Design Overview

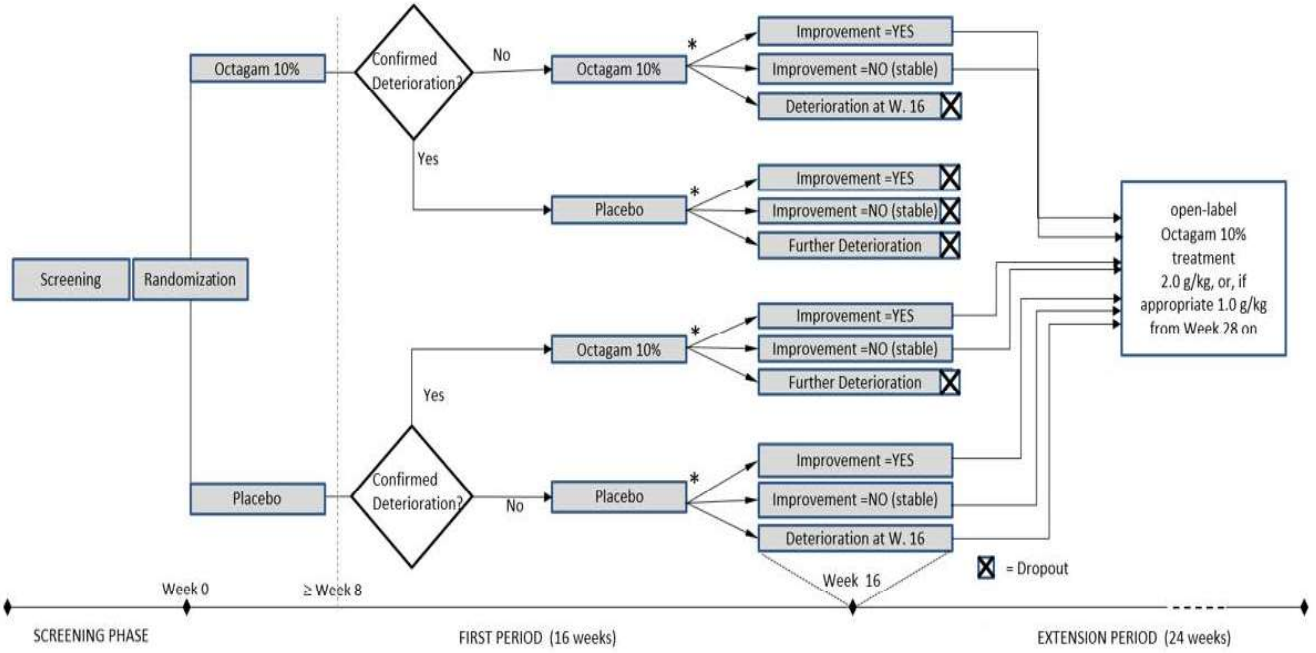
Study GAM 10-08 was a prospective, double-blind, randomized, placebo-controlled, multicenter Phase 3 study. After screening, eligible subjects were randomized 1:1 to receive up to four infusion cycles of either 2.0 g/kg Octagam 10% or placebo every 4 weeks during the 16-week First Period. An infusion cycle comprised of all infusions administered over 2 - 5 days. Subjects who had confirmed deterioration at 2 consecutive visits in the First Period crossed over to the alternate treatment for Week 8 and/or Week 12.

After the response assessment at Week 16, the following groups continued to receive 2.0 g/kg Octagam 10% during the subsequent 6-month (24-week), open-label Extension Period.

- Subjects randomized to Octagam 10% without confirmed deterioration during the First period including Week 16.
- Subjects randomized to placebo without confirmed deterioration during the First Period prior to Week 16; the status at Week 16 was irrelevant for the decision to continue.
- Subjects randomized to placebo who had confirmed deterioration and switched to Octagam 10% and showed no further deterioration at Week 16.

A dose reduction to 1.0 g/kg was possible from Week 28 for subjects who were stable. Figure 1 below depicts the study design.

Figure 1: Scheme of Study Design



* Subjects who were switched to alternate treatment due to deterioration and subjects with a confirmed deterioration at Week 16 had to be unblinded at Week 16.
(Source: Original from BLA 125062/674, Clinical Study Report, Figure 1, Scheme of Study Design, page 24)

6.1.3 Population

In total, 95 adult male or female subjects with DM were enrolled and randomized with 47 to the Octagam 10% group and 48 to the placebo group.

Inclusion Criteria
Subjects who met all of the following criteria were eligible for the study:
1. Subjects with a 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, OR Patients 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 Table 2 in the study protocol,
3. Subjects with active disease, assessed and agreed upon by the Independent Adjudication Committee,
4. Manual Muscle Testing-8 (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 (GDA) ≥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 were conducted,

7. Subject had to be capable to understand and comply with the relevant aspects of the study protocol.

Reviewer Comment: Bohan and Peter Criteria have been used to diagnose DM and are acceptable to define the study population. It is acceptable to include both definite and probable DM as either of these categories would be treated similarly in a clinical setting. The proposed minimum disease activity requirements seem reasonable as they should allow for at least 20 points improvement on the TIS to be demonstrated.

Exclusion Criteria

Subjects who met any of the following criteria were 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 had been excised and cured and at least 1 or 5 years, respectively, had 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 would have prevented a sufficient assessment of the patient by the physician,
6. Subjects who had received IgG treatment within the 6 months before enrolment,
7. Subjects who had received blood or plasma-derived products (other than IgG) or plasma exchange within the 3 months before enrolment,
8. Subjects starting or who were 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 any history of TEE such as deep vein thrombosis (DVT), pulmonary embolism, myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease (Fontaine IV),
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 5 years prior to study enrolment.
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 enrolment,
22. Women who were breast feeding, pregnant, or planning to become pregnant, or were unwilling to apply an effective birth control method (such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomized partner) up to four weeks after the last investigational medicinal product (IMP) infusion received,
23. Subjects who were accommodated in an institution or care facility based on an official directive or court order,
24. Subjects who were 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 9.4.7.2.

Reviewer Comment: It is acceptable to exclude subjects with cancer-associated myositis, overlap myositis, connective tissue disease-associated DM, inclusion body myositis, polymyositis, or drug-induced myopathy in order to minimize confounders for the efficacy assessment.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Octagam 10% is a 10% immunoglobulin intravenous (IGIV) ready for intravenous administration. Placebo is sodium chloride 0.9% solution for intravenous infusion.

First Period: Subjects received up to 4 infusion cycles of either 2.0 g/kg Octagam 10% or placebo (20 mL/kg) every 4 weeks (Weeks 0, 4, 8 and 12).

Extension Period: Subjects received up to 6 infusion cycles of 2.0 g/kg (20 mL/kg) of Octagam 10% every 4 weeks (Weeks 16, 20, 24, 28, 32 and 36).

For subjects who were stable on the 2.0 g/kg (20 mL/kg) Octagam 10% dose, the investigator could decide to switch them to the 1.0 g/kg (10 mL/kg) Octagam 10% dose, starting at Week 28.

6.1.5 Directions for Use

Infusions were to be given on 2 consecutive days. At the discretion of the investigators each infusion cycle could be prolonged to up to 5 days. The total dose for an infusion cycle was given in equally divided doses on each infusion episode.

The initial infusion rate for each infusion episode was 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 could be prolonged as per discretion of the investigator. If adverse events (AEs) occurred during the infusion, the rate was to be reduced to half of the rate at which the AE occurred, or the infusion was to be interrupted until symptoms subsided. The infusion could then be resumed at a rate tolerated by the subject.

In subjects at risk for TEEs and acute renal failure (such as advanced age, hypertension, history of thrombotic episodes not excluded by exclusion criterion 13, prolonged periods of immobilization, concomitant nephrotoxic medication, diabetes mellitus, overweight or hypovolemia), the infusion was to be administered at the rate of 0.01 mL/kg/min.

6.1.6 Sites and Centers

Subjects were enrolled at 36 study sites, including 17 sites in the United States, 5 sites in Russia, 3 sites each in Ukraine and Hungary, 2 sites each in Germany and Poland, and 1 site each in Canada, Czech Republic, the Netherlands, and Romania.

6.1.7 Surveillance/Monitoring

Table 4 shows the timing of efficacy and safety assessments as scheduled per protocol.

Table 4 Schedule of Assessments

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

(Source: Original from sBLA 125062/674, Report Clinical Study, Table 2, page 25)

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint:
Proportion of responders in the 2.0 g/kg Octagam 10% and placebo groups at Week 16 compared to baseline. A responder was defined as a subject with an improvement of ≥20 points on the Total Improvement Score (TIS) and who had not met 'confirmed deterioration' criteria at 2 consecutive visits up to and including Week 16.

The TIS is a score derived from the following six Core Set Measures (CSMs) of myositis disease activity established for clinical trials in subjects with DM:

- Physician's Global Disease Activity (part of Myositis Disease Activity Assessment Tool (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).
- Enzymes (aldolase, creatine kinase, Alanine Aminotransferase (ALAT), Aspartate Aminotransferase (ASAT), Lactate Dehydrogenase (LDH)).
- Extra-muscular activity (part of MDAAT; a combined tool that captures the physician's assessment of disease activity of various organ systems using (1) a scale from 0 = "Not present in the last 4 weeks" to 4 = "New - in the last 4 weeks (compared to the previous 4 weeks)" and (2) a VAS).

The TIS, with a range of 0 to 100, was calculated as the sum of sub-scores of changes in the six CSMs as shown in Table 5. The level of improvement was based on the comparison of the current CSMs to the baseline (Week 0) values. A TIS of 20 to 39 points is defined as minimal improvement. A TIS of 40 to 59 points is defined as moderate improvement. A TIS of ≥60 points is defined as major improvement.

Table 5 Total Improvement Score as a Sum of Scores of Improvements in the Six Core Set Measures

Core set measure	Level of improvement	Level score
Physician Global Activity	Worsening to 5% improvement >5% to 15% improvement >15% to 25% improvement >25% to 40% improvement >40% improvement	0 7.5 15 17.5 20
Patient Global Activity	Worsening to 5% improvement >5% to 15% improvement >15% to 25% improvement >25% to 40% improvement >40% improvement	0 2.5 5 7.5 10
Manual Muscle Testing (MMT)	Worsening to 2% improvement >2% to 10% improvement >10% to 20% improvement >20% to 30% improvement >30% improvement	0 10 20 27.5 32.5
Health Assessment Questionnaire (HAQ)	Worsening to 5% improvement >5% to 15% improvement >15% to 25% improvement >25% to 40% improvement >40% improvement	0 5 7.5 7.5 10
Enzyme (most abnormal)*	Worsening to 5% improvement >5% to 15% improvement >15% to 25% improvement >25% to 40% improvement >40% improvement	0 2.5 5 7.5 7.5
Extra Muscular Activity	Worsening to 5% improvement >5% to 15% improvement >15% to 25% improvement >25% to 40% improvement >40% improvement	0 7.5 12.5 15 20

Reviewer Comment: Use of the TIS as the primary endpoint in the study is deemed reasonable in the absence of a widely accepted endpoint for myositis clinical trials. The CSMs on which the TIS is based have been validated and accepted for use by the academic community. DM is a rare disease with unmet medical need. Thus, requiring formal validation of the TIS levels of improvement before use in clinical trials may be unduly burdensome. In addition, although other endpoints have been used in myositis clinical trials, none have been determined to be clearly superior to the TIS.

Confirmed Deterioration is defined as follows:

- Physician's Global Disease Activity (GDA) VAS worsening ≥ 2cm and MMT-8 worsening ≥ 20% on 2 consecutive visits, OR
- global extra-muscular activity worsening ≥ 2cm on the MDAAT VAS on 2 consecutive visits, OR
- any 3 of 5 CSM (excluding enzymes) worsening by ≥ 30% on 2 consecutive visits.

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

Secondary Efficacy Endpoints

- 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 CDASI.
- 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:
  o SF-36v2 Health Survey;
  o 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 patients in each treatment arm who met 'confirmed deterioration' criteria up to (including) Week 16

Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI)

The CDASI is a clinician-scored 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 three activity measures (erythema, scale, and erosion/ulceration) and two 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. Activity and Damage Subscale scores range from 0 to 100 and 0 to 32, respectively, where higher scores indicate greater disease severity.

Safety (throughout the entire First and Extension Period):

- Occurrence of all adverse events (AEs) with particular emphasis on 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).

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Determination

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

A total sample size of 84 subjects was estimated to be required to show a significant difference in the proportion of responders between the Octagam 10% and placebo groups with a power of 80%, under the assumption that the true proportions of

responders are 0.6 in the Octagam 10% group and 0.3 in the placebo group. The sample size calculation was based on Pearson's chi square test using a two-sided alpha level of 0.05. To allow for unexpected dropouts and in consideration of a stratified analysis, 94 evaluable subjects into the study were planned for enrollment.

Handling of Dropouts or Missing Data
In general, missing data were not imputed, with a few exceptions. For the covariance (ANCOVA) analysis of changes from baseline to Week 16, last observation carried forward (LOCF) was used in the 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 were not included in the analysis).

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

A worst-case approach was taken for AEs or medications with partially or completely missing dates in that it was assumed that AEs were treatment emergent and medications were concomitant unless it could be shown otherwise.

Multiple Comparisons/Multiplicity
Not applicable. It was clearly distinguished between primary efficacy analysis, supporting analyses for the primary endpoint, and secondary efficacy analyses. Secondary efficacy analyses were not controlled for multiplicity and no p-values for subgroup analyses were reported.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The safety analysis set (SAF) includes all subjects who received at least part of one 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.

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 had an impact on the analysis of the primary endpoint. Seven subjects were excluded from the PP1 (4 subjects in the Octagam 10% group and 3 in the placebo group).

- In the Octagam 10% group, 3 subjects were excluded due to interruptions in azathioprine dosing and 1 was excluded due to visit window deviations.
- In the placebo group, 2 subjects were excluded as they switched to Octagam 10% without having confirmed deterioration and 1 subject was excluded due to incorrect study treatment.

The per-protocol set 2 (PP2) consists of all subjects of the FAS who received at least part of one infusion of Octagam 10%, excluding those with significant protocol deviations which may have had an impact on the evaluation of the treatment effects of Octagam

10%. This set of subjects was defined to allow the assessment of Octagam 10% throughout the study and was not used for comparisons with the placebo group. A total of 19 subjects (12 in the Octagam 10% group and 7 in the placebo group) were excluded from the PP2. In the Octagam 10% group, all 4 subjects who were excluded from the PP1 were also excluded from the PP2, 7 subjects discontinued from the study or were lost to follow-up, and 1 subject did not have efficacy assessments done at the end of the study visit. In the placebo group, 2 subjects who were excluded from the PP1 were also excluded from the PP2 because they discontinued from the study, an additional 4 subjects discontinued from the study or were lost to follow-up, and 1 subject did not have assessments done at the end of study visit.

A total of 95 subjects were randomized to the two study groups: 47 to the Octagam 10% group and 48 to the placebo group. Both the SAF and the FAS included all 95 subjects. The PP1 included 88 subjects and the PP2 included 76 subjects.

6.1.10.1.1 Demographics
Subjects were between 22 and 79 years of age, with a median age of 55 years in the Octagam 10% group and 51.5 years in the placebo group. Overall, the majority of subjects were female (74.7%) and white (90%). Key demographic characteristics are summarized in Table 1.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Table 6 summarizes baseline disease characteristics of the enrolled subjects.

Table 6 Summary of Dermatomyositis Medical History (Safety Analysis Set, N=95)

	octagam 10% N=47	Placebo N=48	Total N=95
Time since Diagnosis (years)			
Mean (SD)	5.34 (8.715)	3.86 (3.915)	4.59 (6.736)
Median	2.35	2.86	2.57
Min, Max	0.1, 48.7	0.1, 18.4	0.1, 48.7
Bohan and Peters criteria [N (%)]			
Symmetric proximal muscle weakness	47 (100.0%)	48 (100.0%)	95 (100.0%)
Muscle biopsy evidence of myositis	23 (48.9%)	23 (47.9%)	46 (48.4%)
Elevation of serum skeletal muscle enzymes	43 (91.5%)	44 (91.7%)	87 (91.6%)
Electromyographic finding consistent with myositis	31 (66.0%)	26 (54.2%)	57 (60.0%)
Typical skin rash of DM	47 (100.0%)	48 (100.0%)	95 (100.0%)
Classification of Dermatomyositis [N (%)]			
Definite	34 (72.3%)	33 (68.8%)	67 (70.5%)
Probable	13 (27.7%)	15 (31.3%)	28 (29.5%)

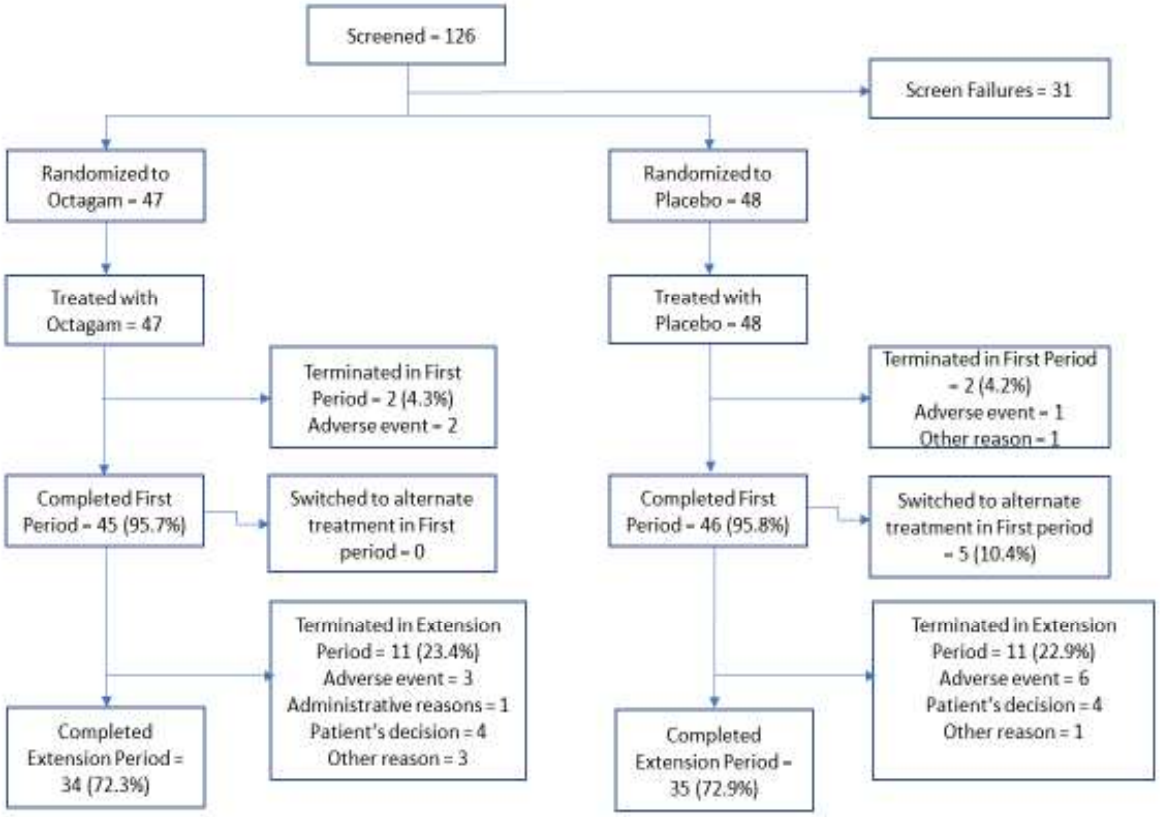
Source: Table 14.1.3.1
DM=dermatomyositis; Max=maximum; Min=minimum; N=number of patients; SD=standard deviation.

Source: Original sBLA 125062/674; Clinical Study Report, page 51

6.1.10.1.3 Subject Disposition

Figure 2 summarizes disposition of enrolled subjects.

Figure 2: Subject Disposition



Note: In both groups, all subjects who completed the First Period entered the Extension Period.
(Source: Original sBLA 125062/674; Clinical Study Report, p.45)

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Efficacy was based on the proportion of responders at Week 16. Using the FAS, the proportion of responders was 78.7% (37/47) in the Octagam 10% group vs. 43.8% (21/48) in the placebo group. The difference in the proportion of responders was 35.0%, which was statistically significant (p = 0.0008) with a 95% CI of (16.7%, 53.2%) (Table 7).

Table 7 Total Improvement Score: Proportions of Responders by Improvement Categories at Week 16 (Full Analysis Set: N=95)

Total Improvement Score (TIS) Response Category	Octagam 10% N=47 Number of Subjects (%)	Placebo N=48 Number of Subjects (%)	Difference in Responder Proportions Octagam 10% – Placebo Point Estimate [95% CI] p-value[a]
At Least Minimal Improvement (TIS ≥ 20) (Primary Efficacy Endpoint)	37 (78.7%)	21 (43.8%)	35.0% [16.7%, 53.2%] 0.0008
At Least Moderate Improvement (TIS ≥ 40)[b]	32 (68.1%)	11 (23.0%)	45.2% [27.3%, 63.0%] < 0.001
At Least Major Improvement (TIS ≥ 60)[b]	15 (32.0%)	4 (8.3%)	23.6% [8.1%, 39.0%] 0.0062

[a] Cochran-Mantel-Haenszel Test
[b] There was no plan of multiplicity control on inference of additional endpoints other than the primary efficacy endpoint, i.e., proportion of responders with at least minimal improvement. The p-values and 95% CIs in the last two rows are at nominal levels and were not multiplicity-adjusted p-values and CIs.
Source: FDA statistical reviewer's analysis

The results were supported by analysis using the PP1 set with 76.7% responders in the Octagam 10% group and 42.2% in the placebo group with a difference in response rates of 34.5% (95% CI: 15.4, 53.7).

Reviewer Comment: The primary endpoint of the study was met. The high response rate (43.8%) in the placebo control group at 16 weeks is not uncommon in this type of therapeutic clinical trial and could be due to the following reasons: more intensive treatment and care in the context of a clinical trial, improved compliance with medications, treatment effect from concomitant medications (corticosteroids, immune-suppressants), spontaneous remission, and placebo effect.

6.1.11.2 Analyses of Secondary Endpoints

TIS responders by improvement category at Week 16 and Week 40

At Week 16, there was a higher proportion of responders in the Octagam 10% group compared to placebo with at least moderate and major improvement at Week 16 (Table 7).

At Week 40, at the end of the Extension Period in which all subjects received Octagam 10%, the proportion of subjects who were responders was similar in the two treatment groups (Table 8).

Table 8 Total Improvement Score – Proportions of Responders by Improvement Categories at Week 40

Total Improvement Score (TIS) Response Category	Octagam 10% Number of Responders (%) [95% CI] N=45	Placebo Number of Responders (%) [95% CI] N=46
At Least Minimal Improvement (TIS ≥ 20)	32 (71.1%) [57.9%, 84.4%]	32 (69.6%) [56.2%, 82.9%]
At Least Moderate Improvement (TIS ≥ 40)	26 (57.8%) [43.4%, 72.2%]	28 (60.9%) [46.7%, 75.0 %]
At Least Major Improvement (TIS ≥ 60)	17 (37.8%) [23.6%, 51.9%]	14 (30.4%) [17.1%, 43.7%]

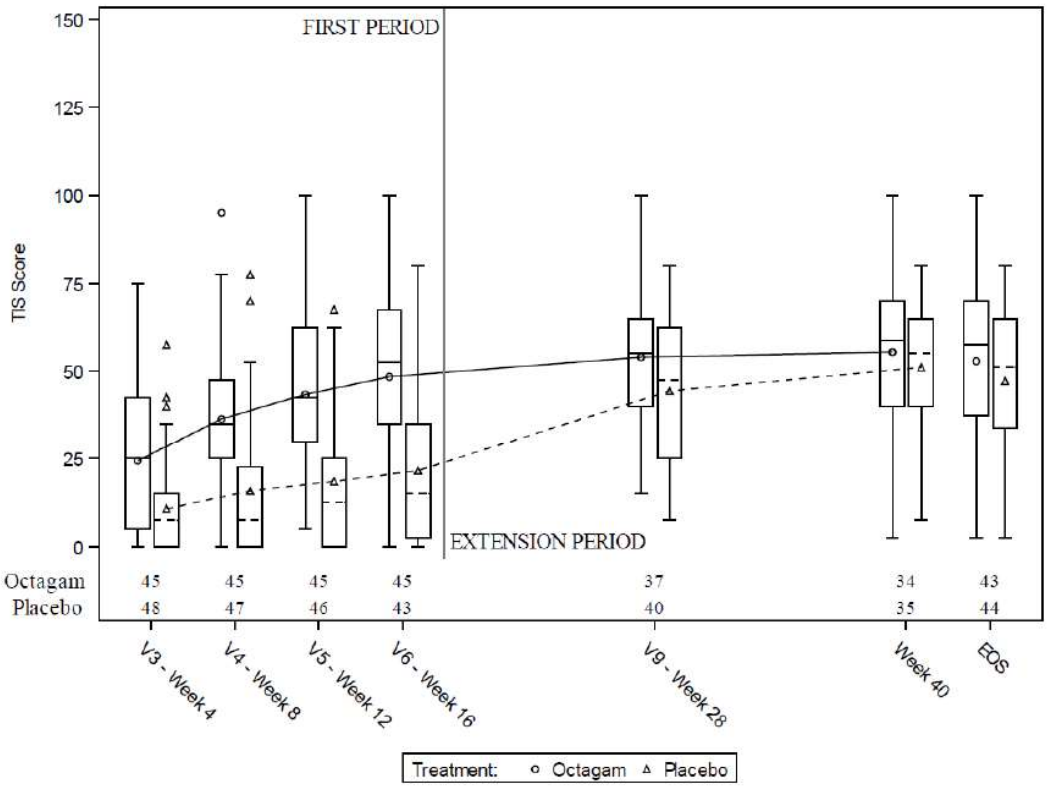
Source: Original sBLA 125062/674; Summary Clinical Efficacy, p.6

Reviewer Comment: There was no plan of multiplicity control on inference of these secondary endpoints. The 95% CIs are at nominal levels and were not multiplicity adjusted.

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)

Mean TIS from Week 0 to Week 40 is summarized in Figure 3. Mean and median TIS values at Weeks 16 and 40 are summarized in Table 11. The results are consistent with the results on TIS response categories summarized above. The placebo subjects who switched to Octagam 10% showed similar TIS values compared to the Octagam 10% group by Week 40.

Figure 3. Boxplot of Total Improvement Score by Visit (Full Analysis Set: N=95)



Source: Original sBLA 125062/674, Clinical Study Report GAM10-08, Figure 3, p.62.

Table 9 Total Improvement Score – Summary of Absolute Values at Week 16 and Week 40 (Full Analysis Set: N=95)

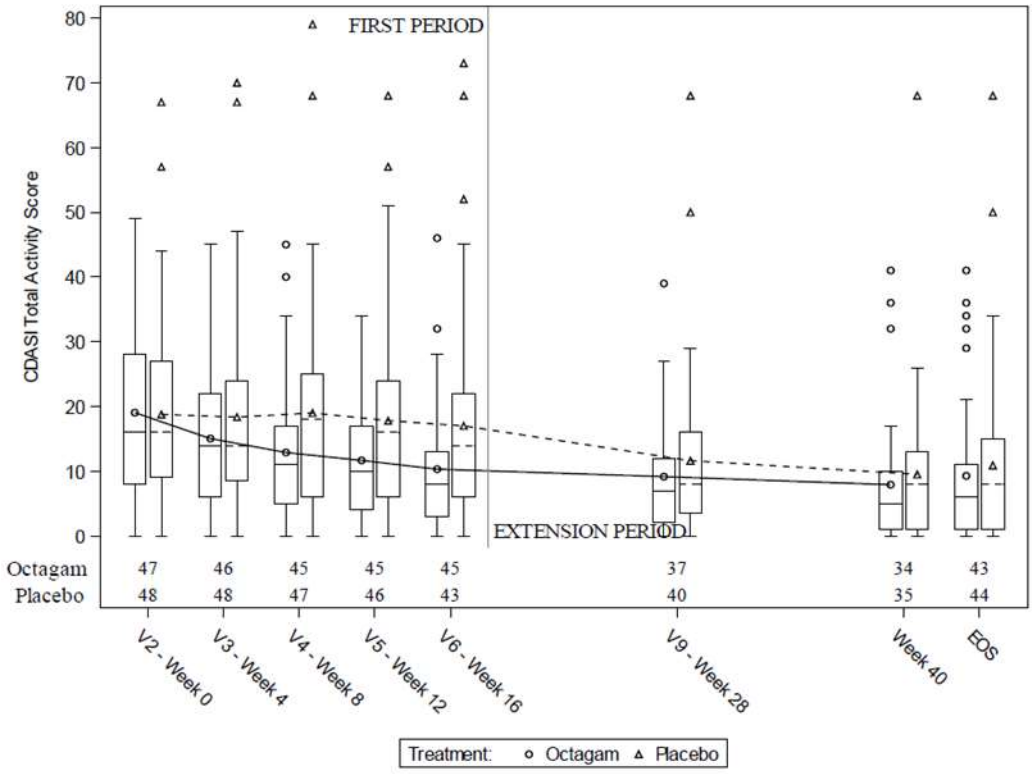
	Week 16		Week 40	
	Octagam 10% N=47	**Placebo N=48**	**Octagam 10% N=47**	**Placebo N=48**
Number of Included Subjects	45	43	34	35
Mean (SD)	48.4 (24.4)	21.6 (20.2)	55.4 (21.7)	51.1 (18.3)
Median	52.5	15.0	58.8	55.0
Min, Max	0.0, 100.0	0.0, 80.0	0.0, 100.0	0.0, 80.0

Source: FDA statistical reviewer's analysis.

CDASI total activity score

At Week 16, there was improvement in the CDASI total activity score, with a mean decrease of 9.4 (SD:10.5) points in the Octagam 10% group versus approximately 1.2 (SD:7.0) point in the placebo group. The mean values in the Octagam 10% group and the placebo group from Week 0 to Week 40 are shown in Figure 4.

Figure 4: Boxplot by Visit of Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) - Total Activity Score, Study GAM10-08 (Full Analysis Set, N=95)



[Reference: Module 5, Section 5.3.5.1, CSR Study GAM10-08, Section 14: Figure 14.4.2.1.1] The connecting lines between visits are plotted between the mean values. Source: sBLA 125062/674; Summary Clinical Efficacy, p.8

Reviewer Comment: CDASI assesses the skin disease activity and damage of DM, which is clinically relevant. Based on literature, the minimally clinically meaningful change is estimated to be about 4-5 points[5].

Time to minimal, moderate and major improvement in TIS

The median time to response (minimal improvement) was 35 days in the Octagam 10% group, with longer median times to moderate improvement (85 days) and major improvement (283 days). Because the placebo group subjects switched to Octagam 10% at the end of the First Period, if eligible, no time-to-event analysis is conducted for those subjects.

5 Ahmed et al., The validity and utility of the Cutaneous Disease Area and Severity Index (CDASI) as a clinical outcome instrument in dermatomyositis: A comprehensive review. Seminars in Arthritis and Rheumatism 50, 458-462, 2020.

Confirmed deterioration

The number of subjects with confirmed deterioration was low, with only 1 subject in the Octagam 10% group in the Extension Period, and 3 subjects in the placebo group in the First Period with confirmed deterioration.

6.1.11.3 Subpopulation Analyses

The results of subgroup analyses by age, sex, randomization strata are shown in Table 10. Analysis by the race subgroups was not conducted as over 90% of the subjects were White. There is no substantial difference across the various subgroup categories.

Table 10 Total Improvement Score – Proportions of Responders with at Least Minimal Response at Week 16 by Subgroups (Full Analysis Set: N=95)

Subgroup	Octagam 10% N = Number of Responders (%)	Placebo N = Number of Responders (%)	Difference in Responder Proportions Octagam 10% – Placebo Point Estimate [95% CI][a]
Age			
18 to ≤ 45 years	N=14 11 (78.6%)	N=14 7 (50.0%)	28.6% [-5.3%, 62.5%]
> 45 years to ≤ 60 years	N=17 13 (76.5%)	N=22 10 (45.5%)	31.0% [2.0%, 60.0%]
> 60 years	N=16 13 (81.3%)	N=12 4 (33.3%)	47.9% [15.1%, 80.7%]
Sex			
Female	N=36 29 (80.1%)	N=35 14 (40.0%)	40.1% [19.8%, 61.3%]
Male	N=11 8 (72.7%)	N=13 7 (53.9%)	18.9% [-18.9%, 56.7%]
Randomization Stratum: Global Disease Activity			
Mild	N=11 8 (72.7%)	N=15 4 (26.7%)	46.1% [11.5%, 80.6%]
Moderate	N=29 23 (79.3%)	N=27 14 (51.9%)	27.5% [3.5%, 51.4%]
Severe	N=7 6 (85.7%)	N=6 3 (50.0%)	35.7% [-12.0%, 83.4%]
Region			
US	N=14 13 (92.9%)	N=13 9 (69.2%)	23.6% [-4.9%, 52.1%]
Non-US	N=33 24 (72.7%)	N=35 12 (34.3%)	38.4% [16.6%, 60.3%]

[a] There was no plan of multiplicity control on inferences of additional endpoints other than the primary efficacy endpoint of proportion of responders with at least minimal improvement at Week 16. The 95% CIs are at nominal levels, and are not multiplicity-adjusted.
Source: FDA statistical reviewer's analysis

6.1.11.4 Dropouts and/or Discontinuations

There were no missing data for the primary endpoint at Week 16. No sensitivity analysis was performed.

6.1.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.1.12 Safety Analyses

In the First Period, the 47 subjects randomized to Octagam 10% plus 5 subjects who switched from placebo underwent 189 infusion cycles with Octagam 10%. The 48 subjects randomized to placebo underwent 184 infusion cycles with placebo. In the Overall Period (the First Period followed by the Extension Period), there were 641 infusion cycles with Octagam 10% at a dose of 2.0 g/kg and 23 infusion cycles at a dose of 1.0 g/kg (664 infusion cycles in total); there were 475 infusion cycles with Octagam 10% in the Extension Period. In total, 96,315.54 g (963,155 mL) of Octagam 10% was administered during the study.

6.1.12.1 Methods

- The condition of subjects was monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs were elicited using a standard non-leading question.
- Any AE or adverse drug reaction (ADR) that occurred during the study was noted in detail on the appropriate pages of the eCRF. If the subject reported several signs or symptoms, which represented a single syndrome or diagnosis, the latter was to be recorded in the eCRF.
- The investigator graded the severity of all AEs or ADRs (mild, moderate, or severe), the seriousness (nonserious or serious) and causality. The Applicant was responsible to assess the expectedness of each ADR (expected or unexpected).
- In the event of clinically significant abnormal laboratory findings other than those related to the basic disease, the tests were confirmed and the subject was followed-up until the values returned to normal and/or an adequate explanation was available.
- The intensity/severity of all AEs was 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.
- Diseases, signs and symptoms and/or laboratory abnormalities already present before the first administration of IMP were not considered as AEs when observed at a later stage unless they represented an exacerbation in intensity or frequency (worsening).
- The investigator had to provide detailed information concerning any abnormalities and the nature of and reasons for any necessary action(s), as well as any other observations or comments which were useful for the interpretation and understanding of the subjects' AEs or ADRs.

6.1.12.2 Overview of Adverse Events

In the First Period, 52 subjects received Octagam 10% (47 subjects randomized to Octagam 10% plus the 5 subjects randomized to placebo who switched to Octagam

10%), and there were 48 subjects in the placebo group (as randomized). The proportions of subjects experiencing AEs were higher in the Octagam 10% subjects than in the placebo group:

- Treatment-emergent adverse events (TEAEs) (80.8% versus 58.3%)
- Related TEAEs (57.7% versus 22.9%)
- Infusional TEAEs (65.4% versus 39.6%)
- Suspected adverse drug reactions (ADRs) (75.0% versus 43.8%)
- Majority of AEs were mild in intensity (142/196 [72.4%] in the Octagam 10% group and 102/135 [75.6%] in the placebo group),
- 6 events of severe intensity reported in 4 subjects (7.7%) in the Octagam 10% group and no severe events reported in the placebo group.
- The incidence of serious TEAEs was similar in the two treatment groups, with 3 subjects (5.8%) experiencing 5 serious TEAEs in the Octagam 10% group and 2 subjects (4.2%) experiencing 4 serious TEAEs in the placebo group. None of the serious TEAEs had a fatal outcome.
- TEAEs leading to discontinuation of study drug only occurred in the Octagam 10% group, with 3 subjects (5.8%) experiencing 8 such events.
- Thromboembolic events (TEEs) were also only reported in the Octagam 10% group, with 1 subject experiencing 2 TEEs in the First Period. No hemolytic transfusion reactions (HTRs) were reported in the First Period.

In the Overall Period (including any events reported by subjects following Octagam 10% treatment in the First Period and any events from all subjects in the Extension Period, but not including any events reported by subjects in the placebo group in the First Period),

- 84 subjects (88.4%) experienced 545 TEAEs following treatment with Octagam 10%.
- 62 subjects (65.3%) experienced 282 TEAEs that were considered related to Octagam 10%.
- 351 infusional AEs were reported in 76 subjects (80.0%).
- 508 suspected ADRs were reported in 82 subjects (86.3%).
- The majority of events were mild in intensity (405/545 events [74.3%]), with 22 events of severe intensity reported in 10 subjects (10.5%).
- Following Octagam 10% treatment, 22 serious TEAEs were reported in 14 subjects (14.7%), 25 TEAEs leading to discontinuation of Octagam 10% were reported in 13 subjects (13.7%),
- 8 TEEs were reported in 6 subjects (6.3%).
- None of the serious TEAEs had a fatal outcome.
- No HTRs were reported at any time in the study.

Reviewer Comment: The proportion of subjects who received Octagam 10% in the overall period and experienced TEAEs, adverse reactions, or infusional AEs was higher compared to the Octagam 10% group in the First Period. This is likely due to longer exposure of Octagam 10% for those subjects in the overall period.

The most frequent adverse reactions (ARs) that occurred in > 5% of subjects with DM are summarized in Tables 11 and 12.

Table 11 Drug-related Adverse Reactions Experienced by >5% of Subjects

Reactions	No. of Subjects (% of Subjects [n=95])
Headache	40 (42)
Pyrexia	18 (19)
Nausea	15 (16)
Vomiting	8 (8)
Chills	7 (7)
Musculoskeletal pain	7 (7)
Blood pressure increased	6 (6)

Source: sBLA 125062/674, PI

Table 12 ARs in >5% of Subjects During and Within 72 Hours After End of Infusion Cycle, Irrespective of Causality

Reactions	No. of Subjects (% of Subjects [n=95])
Headache	44 (46)
Pyrexia	19 (20)
Nausea	16 (17)
Vomiting	8 (8)
Blood pressure increased	8 (8)
Chills	7 (7)
Musculoskeletal pain	5 (5)
Heart Rate Increased	5 (5)
Dyspnea	5 (5)
Infusion site reactions	5 (5)

Source: sBLA 125062/674, PI

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events

In the First Period, 3 subjects (5.8%) in the Octagam 10% group experienced 5 serious TEAEs, and 2 subjects (4.2%) in the placebo group experienced 4 serious TEAEs. Two serious TEAEs reported in 1 subject (1.9%) in the Octagam 10% group, muscle spasms and dyspnoea, were considered to be related to study drug.

In the Overall Period, 14 subjects (14.7%) experienced 22 serious TEAEs (all in the 2.0 g/kg cohort). In the Extension Period, 7 serious TEAEs in 6 subjects were considered to be related to study drug (2 events of pulmonary embolism, and 1 event each of deep vein thrombosis, loss of consciousness, cerebrovascular accident, cerebral infarction, and hypoaesthesia).

All serious adverse events (SAEs) were individually reviewed, and narratives for SAEs happened in the Octagam 10% group are summarized below:

First Period

(b) (6) A 69-year-old white male subject with ongoing tooth abscess was randomized to Octagam 10% and had received 1 infusion cycle of Octagam 10% before the SAEs leading to discontinuation occurred. Thirteen (13) days after the last infusion of Octagam 10%, the subject was admitted to hospital for sepsis due to left leg cellulitis and tooth abscess and received multiple IV antibiotics treatment. Fifty-one (51) days after the last infusion of Octagam 10%, the subject was admitted to the hospital for a large saddle pulmonary embolism involving both upper and lower arterial branches bilaterally. A Doppler examination was performed that showed bilateral popliteal and bilateral calf DVTs. The subject was discharged one week after in stable condition.

Reviewer Comment: Reviewer agrees that the SAE of sepsis was due to left leg cellulitis and tooth abscess. The SAE of pulmonary embolism (PE) was more likely due to the subject's comorbidity, such as cellulitis and sepsis, which might lead to decreased mobilization and increased risk of deep venous thrombosis and PE. The role of Octagam 10%, which have known risk for TEEs, in the SAE of PE cannot be ruled out; however, considering the long lapse of time (51 days) since his last infusion, it is less likely to be due to Octagam 10%.

(b) (6) A 56-year-old male subject experienced infusion reactions including severe muscle spasms and dyspnea after Octagam 10% infusion rate had been increased to 0.04 mL/kg/min (1 hour and 20 minutes after the infusion started). There were also non-serious AEs of moderate sinus tachycardia, mild child, mild fever (38.2), elevated blood pressure, and moderate lower back pain. The Octagam 10% infusion was stopped and treatment was given, 3 hours later all AEs were resolved. This subject was originally randomized to placebo, but he was switched to Octagam 10% for the fourth cycle due to deterioration of DM. However, the treatment cycle was not completed due to SAEs and non-serious AEs.

Reviewer Comment: Reviewer agrees that the SAEs (severe muscle spasms and dyspnea) were likely related to Octagam 10%.

(b) (6) A 43-year-old white female subject received the first episode of the 3rd infusion cycle on (b) (6) the 2nd episode on (b) (6) and the 3rd episode on (b) (6) A routine electrocardiogram (ECG) was performed on the morning of (b) (6) before the 3rd infusion. Since the subject had no clinical signs or complaints related to the arrhythmia and was hemodynamically stable, the third episode of the study drug infusion was administered as scheduled. The ECG evaluation of ventricular extrasystoles was provided to the subject's doctor in the afternoon of the same day. The planned fourth infusion episode was not administered due to reported SAE. No further AEs were reported for this subject. ECGs were repeated on (b) (6) and on (b) (6) showing no premature ventricular contractions or trigeminy.

Reviewer Comment: The event of ventricular extrasystoles was unlikely related to Octagam 10% as cardiac involvement including conduction abnormalities and arrhythmia is well described in patients with DM.

Extension Period

(b) (6) A 67-year-old white male subject with a medical history of chronic heart failure who was randomized to placebo group during the First Period had received 2 cycles of Octagam 10% in the Extension Period before the SAEs occurred. One day after his last infusion, he had increased shortness of breath and increased heart rate followed by a short episode of hypotension. His computed tomography (CT) confirmed a pulmonary embolism and an ultrasound of the lower extremities confirmed a deep vein thrombosis.

Reviewer Comment: Although congestive heart failure is associated with a relatively high risk of venous thromboembolism, the SAEs of pulmonary embolism and deep vein thrombosis were probably related to Octagam 10% because IGIV is known for increasing risk of TEEs and the SAEs occurred within a reasonable time frame after infusion. Pulmonary embolism is likely secondary to deep vein thrombosis in his lower extremities.

(b) (6) A 50-year-old white female subject with a medical history of obesity and hypertension who was randomized to placebo during the First Period had received 1 cycle of Octagam 10% before the SAE occurred. The subject had experienced AEs of chills, dizziness and pyrexia (38.0 °C) during the infusion one day before her SAE. 9 hours after her last infusion episode, she had a 5-minute transient loss of consciousness. There were no symptoms of stroke and her blood pressure was 140/80 mmHg. The subject was hospitalized the next day with fever, otherwise all findings were normal during the 4-day stay for observation in hospital.

Reviewer Comment: It's not clear what's the exact underlying etiology for the subject's transient loss of consciousness. Her SAE was possibly related to Octagam 10% given the close time relationship and other AEs she experienced around the same time.

(b) (6) A 79-year-old white female subject with a history of myocardial ischemia, hypertension, and hyperlipidemia who was randomized to placebo in the First Period had received 3 infusion cycles Octagam 10% before the SAE "cerebrovascular accident" occurred. On the day of the last infusion episode, she experienced moderate vertigo and mild blurred vision. Three weeks after, the subject developed mild aphasia and ataxia. The subject improved following IV thrombolysis-active therapy and acetylsalicylic acid. Her head CT scan and carotid ultrasonography were reported normal.

Reviewer Comment: Although the subject has multiple risk factors for cerebrovascular accident/ischemic stroke, the SAE was possibly related to Octagam 10% because of the temporal relationship and the known thrombotic risk of IGIV.

(b) (6) A 70-year-old white female subject with a medical history of hypertension randomized to placebo in the First Period had received 6 infusion cycles Octagam 10% before the SAE "cerebral infarction" occurred. 12 days after the last infusion cycle of Octagam 10%, the subject was admitted to hospital for experiencing dysarthria and loss of balance. Brain MRI revealed cerebral infarction of the left parietal area.

Reviewer Comment: The SAE "cerebral infarction" was possibly related to Octagam 10% infusion because of the temporal relationship and the fact IGIV increases the risk of thrombosis.

(b) (6) A 67-year-old white female subject with a history of supraventricular arrhythmia and hyperlipidemia had received 6 infusion cycles of Octagam 10% before the SAE "hypoesthesia" occurred. 9 days after the last infusion of Octagam 10%, the subject developed mild hypoesthesia, with numbness of the left half of the body that resolved after rest. A Doppler ultrasound of carotid arteries showed normal results as did a Holter ECG examination. Acetylsalicylic acid prophylaxis was started.

Reviewer Comment: This SAE should be reclassified as a cerebrovascular accident. The underlying etiology of the subject's cerebrovascular accident is not clear. Although the subject had other stroke risk factors (history of supraventricular arrhythmia, hyperlipidemia, old age), given the temporal relationship, the SAE was possibly related to Octagam 10%.

(b) (6) A 62-year-old white male patient had received 7 infusion cycles of Octagam 10% before the SAE occurred. 15 days after his last infusion of Octagam 10%, he experienced hemoptysis. 4 days after, he was treated with antibiotics for cough and chest pain. 22 days after his last infusion, he was hospitalized for further workup. His CT pulmonary angiogram confirmed pulmonary embolism and left pulmonary infarction.

Reviewer Comment: The SAE "pulmonary embolism" is likely related to Octagam 10%. Risk of thrombosis is labeled in the WARNING section of Octagam 10% PI.

(b) (6) A 69-year-old white male had received a total of 10 treatment cycles of Octagam 10% before the SAEs occurred. The subject began receiving care from his primary care physician for pneumonia one day after his last Octagam 10% infusion. About two weeks after he was hospitalized for a multi-lobar pneumonia bilaterally with a small eft pleural effusion. In the meantime, an echocardiogram showed an ejection fraction around 20%, suggestive of systolic heart failure. Approximately 3 weeks after his last infusion, a cardiac catheterization was performed and subject was found to have severe left main and 3-vessel coronary artery disease and significant aortic stenosis. The subject underwent a quadruple cardiac bypass graft (CABG) and aortic valve replacement. Post procedure, the subject developed the following complications: sepsis (11 days post procedure), acute renal failure (13 days post procedure), and acute respiratory failure (14 days post procedure). The subject was discharged from the hospital to a rehabilitation facility 20 days after his surgery.

Reviewer Comment: The subject's SAEs of worsening pneumonia, congestive heart failure, sepsis, acute renal failure, and acute respiratory failure were unlikely related to Octagam 10%. The risk of opportunistic infections is increased in patients with dermatomyositis, and dermatomyositis is also associated with increased risk of cardiac involvement mainly due to atherosclerosis and myocarditis. There's no evidence that IGIV can contribute to either congestive heart failure or coronary artery disease.

(b) (6) A 64-year-old white female subject with a history of type 2 diabetes mellitus had received 5 cycles of Octagam 10% before the SAE occurred. 18 days after her last Octagam 10% infusion, the subject developed fever, tachycardia, and elevated lactic acid level. Blood cultures were positive for extended spectrum beta lactamase positive bacteria. The subject was hospitalized for IV antibiotics treatment.

Reviewer Comment: The SAE of Escherichia bacteremia was unlikely related to Octagam 10%. Dermatomyositis is associated with increased risk of opportunistic infection.

(b) (6) A 74-year-old white male subject with a medical history of basal cell carcinoma of nose and bladder cancer was administered the 5th infusion cycle of Octagam 10% on (b) (6) over 2 days. 28 days after his last infusion, he had a routine appointment with his dermatologist who discovered that the subject had 2 neoplasms of the skin, one on the right temple and the other on the left arm. A biopsy of both sites showed squamous cell carcinoma. Both neoplasms were excised successfully and without incident.

Reviewer Comment: The SAE of squamous cell carcinoma was unlikely related to Octagam 10%. It's reported that DM is associated a 6-fold higher risk of malignancy compared with the general population.

(b) (6) A 49-year-old (b) (6) female subject with a medical history of Sjogren's syndrome and rheumatoid arthritis received 8th infusion cycle of Octagam 10% 28 days before the SAEs "Condition aggravated" and "Atypical pneumonia" occurred.

Reviewer Comment: The SAEs "Condition aggravated" and "Atypical pneumonia" were unlikely related to Octagam 10%. Lung infection is a common complication of DM, and lung infection certainly worsen her DM symptoms.

(b) (6) A 44-year-old white female subject had received a total of 5 cycles of Octagam 10% before the SAE "condition aggravated" occurred. 8 days after her last Octagam 10% infusion, she reported muscle weakness, swallowing disability, and significant weight loss.

Reviewer Comment: Her worsening symptoms were observed on previous visits; therefore, the SAE was likely due to the underlying disease DM and unlikely related to Octagam 10%.

6.1.12.5 Adverse Events of Special Interest (AESI)

The following TEEs are of special interest:

- In the First Period, 1 subject (1.9%) in the Octagam 10% group had 2 events, including pulmonary embolism and deep vein thrombosis – probably not related.

- In the Extension Period: 1 subject had events of pulmonary embolism and deep vein thrombosis, and 1 subject each had events of cerebrovascular accident, cerebral infarction, pulmonary embolism, and hypoaesthesia - all were considered related to Octagam 10%.

Reviewer Comment: TEEs have been associated with IGIV products and Boxed Warning is in place in all the PIs of IGIV products. Octagam 5% was voluntarily withdrawn from the US market in 2010 in response to an increased number of TEE reports associated with its use. Octagam was re-introduced to the US market in late 2011. A safety postmarketing requirement (PMR) study completed in 2020 did not

identify an increased risk of TEE after Octagam 5% compared to other US-licensed IGIV products.

In the DM study that used Octagam 10%, Reviewer considers that 6 of the 8 TEEs that occurred in 5 subjects were probably/possibly related to the study drug. The two other TEEs, pulmonary embolus and deep vein thrombosis that occurred in a subject 51 days after the last Octagam 10% infusion, were less likely to be related to the study drug, although cannot be ruled out.

A recent meta-analysis suggests that PM/DM is associated with increased risk of venous thromboembolism, primarily consisting of pulmonary embolism and deep venous thrombosis. It's speculated that systemic inflammation is associated with venous stasis, increased blood coagulation, and damage to the vessel walls.[6]

During the study, there was a protocol amendment based on an FDA recommendation that the maximum allowed infusion rate was reduced from 0.12 mL/kg/min to 0.04 mL/kg/min. The exposure-adjusted incidence rates of TEEs in the study was lower after the change (1.54/100 patient months before the reduced rate versus 0.54/100 patient months after the reduced rate).

Risk of TEE is in the Boxed WARNING section of the package insert, As patients with dermatomyositis are at increased risk for thromboembolic events, the PI has been further modified to emphasize monitoring the risk of TEE carefully and not exceeding an infusion rate of 0.04 ml/kg/min.

6.1.12.6 Clinical Test Results

Hematology results showed consistent decreases in median counts for leukocytes and for neutrophils up to Week 16 in the Octagam 10% group, and median values remained below the baseline value in the Extension Period; median values were consistently lower compared to the placebo group. For clinical chemistry parameters there were similar results in the two treatment groups with no marked trends over time.

There were individual subjects with clinically significant laboratory values during the study, including, in the Octagam 10% group, clinically significant low values of hemoglobin, red blood cells, hematocrit, lymphocytes, and sodium, and high values of glucose, creatinine and platelets; and in the placebo group, clinically significant low values of hemoglobin, lymphocytes, leukocytes, red blood cells, hematocrit, and neutrophils, and high values of urea and creatinine. In a shift table analysis, changes to a clinically significant value were observed only for a small number of subjects in both treatment groups and did not indicate any safety concerns. There were also individual subjects with abnormal markers for hemolysis (e.g., positive Coombs' test or abnormal haptoglobin or plasma free hemoglobin), but the majority were not clinically significant and no subject met the criteria for HTR during the study.

All tests for viral markers (HBV, HCV, HIV) were negative and there were no shifts to abnormal values from Baseline to the End of Study.

6 Lee YH, Song GG. Idiopathic inflammatory myopathy and the risk of venous thromboembolism: a meta-analysis. Rheumatol Int. 2017 Jul;37(7):1165-1173.

There were no marked changes in mean and median values for heart rate, systolic and diastolic blood pressure, respiratory rate, or body temperature during the study, and the maximum changes during and after the infusion compared to pre-infusion were minor. There were no marked differences between the two treatment groups. Few subjects had clinically significant abnormal findings in the physical examination that were newly diagnosed or had worsened, with similar proportions in the two treatment groups.

6.1.12.7 Dropouts and/or Discontinuations

In the First Period, there were 3 subjects (5.8%) in the Octagam 10% group who experienced 8 TEAEs that led to discontinuation of study drug, and none in the placebo 'at risk' group. There was also 1 subject (1.9%) in the Octagam 10% group who experienced 2 TEEs (pulmonary embolism and deep vein thrombosis) 52 days after the last Octagam 10% administration, hence assessed as being not related to study drug.

In the Overall Period, there were 13 subjects (13.7%) in the Octagam 10% 2.0 g/kg cohort who experienced 25 TEAEs that led to discontinuation of study drug. The only events reported in more than 1 subject that led to discontinuation of study drug were condition aggravated reported in 3 subjects (3.2%) and pulmonary embolism reported in 2 subjects (2.1%).The following events led to discontinuation of study drug in the Extension Period and were reported in 1 subject (1.1%) each: vertigo, vision blurred, nausea, vomiting, hypersensitivity, Escherichia bacteremia, myalgia, cerebrovascular accident, dizziness, headache, paraesthesia, and deep vein thrombosis.

6.1.13 Study Summary and Conclusions

The efficacy of Octagam 10% in subjects with DM was supported by the primary endpoint and secondary endpoints. There was a higher proportion of responders at 16 weeks in the Octagam 10% group than in the placebo group (78.7% versus 43.8%) and the difference in response rates was statistically significant: 35.0%, 95% CI: 16.7, 53.2; p=0.0008. Through Week 40, the response in the Octagam 10% group from the First Period was maintained. The placebo group attained a similar response after switching to Octagam 10% in the Extension Period. The evaluation of TEAEs, routine laboratory examination, vital signs and physical examination showed that administration of Octagam 10% was generally well tolerated in this DM population and no new safety signals were identified.

7. INTEGRATED OVERVIEW OF EFFICACY

An Integrated Overview of Efficacy was not performed because only one clinical trial was conducted in patients with DM using Octagam 10%.

8. INTEGRATED OVERVIEW OF SAFETY

An Integrated Overview of Safety was not performed because only one clinical trial was conducted in patients with DM using Octagam 10%.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No human reproduction and pregnancy data are available to indicate the presence or absence of drug-associated risk. Animal reproduction studies have not been conducted with Octagam 10%. It is not known whether Octagam 10% can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Immune globulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation. Octagam 10% should be given to pregnant women only if clearly needed. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

9.1.2 Use During Lactation

No human data are available to assess the presence or absence of Octagam 10% in human milk, the effects of Octagam 10% on the breastfed child, and the effects of Octagam 10% on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Octagam 10% liquid and any potential adverse effects on the breastfed infant from Octagam 10% liquid or from the underlying maternal condition. Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.

9.1.3 Pediatric Use and PREA Considerations

The safety and effectiveness of Octagam 10% has not been established in pediatric patients with DM.

9.1.4 Immunocompromised Patients

The safety and effectiveness of Octagam 10% in immunocompromised patients have not been established.

9.1.5 Geriatric Use

Patients > 65 years of age may be at increased risk for developing certain adverse reactions such as thromboembolic events and acute renal failure. Do not exceed recommended doses in this population, and the applied infusion rate should be the minimum practicable. Clinical studies of Octagam 10% did not include sufficient number of subjects > 65 years to determine whether they respond differently from younger subjects. During the First Period (placebo-controlled) of the DM trial, 11 subjects over 65 years were treated with Octagam 10%.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not applicable.

10. CONCLUSIONS

The substantial evidence of effectiveness is based on significant improvements in clinically meaningful efficacy outcomes following IV administration of Octagam 10%

observed in Study GAM10-08, an adequate and well-controlled study, for adults with dermatomyositis.

The known risk of thromboembolic events (TEEs) of IGIV products seems to be more frequent in patients with DM. No other new safety issues were observed. The known risks such as TEEs can be mitigated by adequate risk mitigation information in the PI, pharmacovigilance plan and specific adverse reaction follow-up questionnaire for TEEs. Review of the submitted data indicates that Octagam 10% appears safe and effective for the treatment of adults with DM.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Risk-benefit considerations for Octagam 10% are summarized in Table 13.

Table 13 Risk / Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Dermatomyositis (DM) is a rare disease affecting multiple organs, such as skeletal muscles, skin, joints, lung, and heart. • DM is associated with increased mortality and morbidity.	. • Dermatomyositis is a serious condition
Unmet Medical Need	• Corticosteroids are the only FDA-approved therapy for treatment of muscle manifestation of DM. • Immunosuppressive drugs, such as methotrexate, azathioprine, cyclosporine-A are considered as steroid sparing alternatives; however, high quality randomized and controlled clinical trials are lacking to assess the efficacy and safety of these drugs. • Long-term administration of corticosteroids and immunosuppressive drugs may cause infections and other serious complications.	• There is an unmet medical need for treatment of DM.
Clinical Benefit	• The efficacy of Octagam 10% in adults with DM was evaluated in a Phase 3 study consisting of two parts: a 16-week, randomized, double-blind, placebo-controlled First Period, and a 6-month, open-label Extension Period. In the First Period, 47 subjects received 2 g/kg Octagam 10% and 48 subjects received placebo every 4 weeks for 4 infusion cycles. In the Extension Period, 91 subjects received 6 infusion cycles of Octagam 10%. • The proportion of subjects achieving a clinically meaningful response (an improvement of ≥20 points on the TIS) at 16 weeks was higher in the Octagam 10% group than in the placebo group (78.7% versus 43.8%). The difference in response rates was statistically significant: 35.0% (95% CI: 16.7, 53.2; p=0.0008).	• Overall, substantial evidence indicates clinical benefit of Octagam 10% for treatment of DM, based on compelling results from one adequate and well-controlled study and supported by additional data from the natural history of the disease that provides confirmatory evidence.
Risk	• The following related serious adverse reactions were reported: Non-TEE: muscle spasms and dyspnea in one patient and loss of consciousness in one patient. TEE: one patient experienced deep vein thrombosis and pulmonary embolism, and one patient each experienced cerebrovascular accident, cerebral infarction, hypoesthesia, and pulmonary embolism. • The most common adverse reactions (ARs) reported in >5% of subjects were headache, fever, nausea, vomiting, increased blood pressure, chills, musculoskeletal pain, increased heart rate, dyspnea, and infusions site reactions. • No death	• The risk of TEEs known to IGIV products seems to be higher in the DM population. • No unexpected risks were identified.
Risk Management	The risk management plan includes: • Routine pharmacovigilance plan, • Specific adverse reaction follow-up questionnaire for thromboembolic events • Adequate information provided in Prescribing Information (PI)	• The risks can be mitigated through the proposed pharmacovigilance plan, medical management, and adequate PI. • The data do not warrant the need for a REMS or a safety PMR study.

11.2 Risk-Benefit Summary and Assessment

The overall risk-benefit is favorable for intravenous administration of Octagam 10% at the dose of 2 g/kg every 4 weeks to adults with dermatomyositis.

An unmet medical need exists for the treatment of dermatomyositis. A Phase 3 adequate and well-controlled study provides substantial evidence of effectiveness of Octagam 10% with meaningful clinical benefit with regard to minimal, moderate, and major improvement on Total Improvement Score (TIS).

Available evidence indicates that the major known and potential risks associated with IGIV products, including Octagam 10% can be prevented or mitigated by the pharmacovigilance plan, routine medical practice and suitable prescribing information.

The Applicant has provided substantial evidence of effectiveness and safety from an adequate and well-controlled study, and the benefit/risk profile is favorable for Octagam 10% for the proposed indication.

11.3 Discussion of Regulatory Options

The regulatory options include (1) traditional approval; or (2) Complete Response (CR). The submission provides substantial evidence of effectiveness from an adequate and well controlled trial with compelling results supported by confirmatory evidence from the natural history of the disease, supportive of approval.

11.4 Recommendations on Regulatory Actions

Based on review of the clinical data, the clinical reviewer recommends that Octagam 10% be approved for the treatment of dermatomyositis in adults.

11.5 Labeling Review and Recommendations

FDA made substantial changes to sections of the Prescribing Information (PI) related to DM, based on available clinical trial data, as well as FDA guidance on product labeling. The Clinical Reviewer and APLB consider the revised PI to be acceptable.

The overall content of the PI suitably conveys known information regarding safety and efficacy results demonstrated in clinical studies of Octagam 10%

The overall content of the PI contains adequate warnings for medical practitioners, as well as for caregivers, considering Octagam 10% for treatment of DM.

11.6 Recommendations on Postmarketing Actions

Based on review of the safety data, neither a REMS nor a safety PMR study is required. The postmarketing risk mitigation plans proposed by the Applicant are acceptable, including PI, routine pharmacovigilance and specific adverse reaction follow-up questionnaire for TEEs.