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Division / Office	DB/OBE
Committee Chair	Wenyu (Andy) Sun, M.D.
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Priority Review	No
Reviewer Name(s)	Yuqun Abigail Luo, Ph.D. Yuqun Luo -S Digitally signed by Yuqun Luo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yuqun Luo -S, Date: 2021.06.14 16:16:33 -04'00'
Review Completion Date / Stamped Date	June 14, 2021
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Applicant	OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Established Name	Immune Globulin Intravenous (Human), 10%, S/D
(Proposed) Trade Name	Octagam 10%
Pharmacologic Class	Immunoglobulins
Formulation(s), including Adjuvants, etc	Immune Globulin Infusion (Human) 10%
Dosage Form(s) and Route(s) of Administration	Liquid solution containing 10% IgG (100 mg/mL), for intravenous use only
Dosing Regimen	2 g/kg divided in equal doses given over 2-5 consecutive days every 4 weeks
Indication(s) and Intended Population(s)	Treatment for dermatomyositis (DM) in adults

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GLOSSARY

AE	Adverse Event
ALAT	Alanine Aminotransferase
ASAT	Aspartate Aminotransferase
BLA	Biologics License Application
BMI	Body Mass Index
CBER	Center for Biologics Evaluation and Research
CDASI	Cutaneous Dermatomyositis Disease Area and Severity Index
CI	Confidence Interval
CSM	Core Set Measure
CSR	Clinical Study Report
DM	Dermatomyositis
eCRF	electronic Case Report Form
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
GDA	Global Disease Activity
HAQ	Health Assessment Questionnaire
HTR	Hemolytic Transfusion Reaction
IgG	Immunoglobulin G
IGIV	Intravenous Immunoglobulin
IIMs	Idiopathic Inflammatory Myopathies
IMP	Investigational Medicinal Product
IRT	Interactive Response Technology
ITP	Immune Thrombocytopenic Purpura
LDH	Lactate Dehydrogenase
Max	Maximum
MDAAT	Myositis Disease Activity Assessment Tool
Min	Minimum
MMT-8	Manual Muscle Testing-8
PP	Per Protocol
QoL	Quality of Life
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-36v2	Short Form 36 Items Health Status Version 2
TEAE	Treatment Emergent Adverse Event
TEE	Thromboembolic Event
TIS	Total Improvement Score
US	United States
VAS	Visual Analog Scale

1. EXECUTIVE SUMMARY

This is a biologics license application (BLA) efficacy supplement intended to expand the indication of octagam 10% to include treatment of dermatomyositis in adults.

Octagam 10% is a 10% (100 mg/mL) human normal immunoglobulin G for intravenous administration. It was originally approved by the FDA in 2014 for the treatment of chronic immune thrombocytopenic.

This submission included the results from one pivotal study, Study GAM10-08, to provide the primary evidence of efficacy and safety in support of the proposed expanded indication of octagam 10% in dermatomyositis.

Study GAM10-08 was a prospective, placebo-controlled, double-blind, randomized, multicenter Phase 3 study in adults with active dermatomyositis (DM), with a 16-week comparative efficacy period (First Period) followed by a 24-week open-label extension period (Extension Period) during which all eligible subjects received the investigational product octagam 10%. The primary objective of the study was to provide confirmatory data on the beneficial effect of 2.0 g/kg octagam 10% given every four weeks compared with placebo in DM subjects based on the percentage of responders at Week 16. A responder is 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.

A total of 95 subjects with DM aged between 22 and 79 years were randomized: 47 to the octagam and 48 to the placebo groups. For the primary analysis of the primary efficacy endpoint, 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 the response rate between the two groups was 35% with a 95% confidence interval (CI) of (16.7%, 53.2%) and a p-value of 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 (68.1% vs. 22.9%) and with major improvement (31.9% vs. 8.3%), where moderate and major improvement were defined as ≥40 points and ≥60 points on the TIS, respectively.

Longer-term effect was evaluated in the Extension Period. Of the 47 and 48 subjects randomized to the two study groups, 45 and 46 continued into the Extension Period and received octagam 10%, respectively. Efficacy appeared to be maintained into Week 40 for those randomized to the octagam group, with 32 (32/47 = 68.1%) responders at Week 40. Placebo subjects who continued into the Extension Period also received the treatment of octagam 10%; of those subjects, the response rate after 24 weeks of treatment was 69.1% (32/46).

No deaths occurred during the study. Further analysis of safety data is deferred to the clinical team.

The efficacy results of Study GAM10-08 provided sufficient statistical evidence to support expanding the indication of octagam 10% to treatment of dermatomyositis in adults.

2. CLINICAL AND REGULATORY BACKGROUND

BLA 125062 Supplement 674 is an efficacy supplement submitted by Octapharma to expand the indications for octagam 10% (Immune Globulin Intravenous, Human, 10% S/D) to include treatment of dermatomyositis (DM) in adults.

Octagam 10% (100 mg/mL) is an intravenous immunoglobulin (IGIV) liquid, which has undergone a three-stage viral inactivation, including solvent/detergent (S/D) treatment. It is a sterile preparation of highly purified human normal immunoglobulin G (IgG) derived from large pools of human plasma.

2.1 Disease or Health-Related Condition(s) Studied

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. Adult DM is one of the most common subsets of IIM.

DM is a rare disease with a prevalence of ~5.9 patients per 100,000 persons in the United States (US). DM is seen in both children and adults and the early symptoms include distinct skin manifestations accompanying or preceding muscle weakness. The lesions are photosensitive and may be aggravated by ultraviolet radiation. Although a spectrum of severity exists for DM, it is often associated with rapid and aggressive myositis. Patients with DM have increased morbidity related to severe muscle weakness and visceral involvement, with gastrointestinal, pulmonary, and cardiac dysfunction. Between 20% and 40% of treated patients with DM will achieve disease remission, but the majority (60% to 80%) will experience a chronic disease course, either in cycles or continuous. The overall mortality is three times higher in DM patients compared with the general population.

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

Corticosteroids are the mainstay of treatment and are often combined with another immunosuppressive agent, such as methotrexate, azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil, cyclophosphamide or rituximab.

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

In the US, octagam 10% was approved in 2014 for chronic immune thrombocytopenic purpura in adults. This BLA supplement is to obtain marketing authorization for the indication of treatment of DM in adults. There was no pre-BLA meeting for this supplement submission.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

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

All documents and data are included in the applicant's electronic Common Technical Document submission in FDA/CBER docuBridge.

5.1 Review Strategy

The applicant submitted one pivotal study (Study GAM10-08) in support of this BLA supplement application. This review memo focuses on the efficacy and safety analyses of Study GAM10-08.

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

The documents reviewed in submission STN 125062/674 include:

- Draft Labeling (Module 1.14.1)
- Clinical Overview (Module 2.5)
- Summary of Clinical Efficacy (Module 2.7.3)
- Summary of Clinical Safety (Module 2.7.4)
- Listing of Clinical Studies (Module 5.2)
- Clinical Study Report (CSR) for Study GAM10-08 (Module 5.3.5.1)
- Study protocol for Study GAM10-08 (Version 12, 18-Jun-2019) (Module 5.3.5.1)
- Statistical Analysis Plan for Study GAM10-08 (SAP, Version 4.0, 18-Jun-2019) (module 5.3.5.1)

Analyses performed within this review are based on the following analysis-ready datasets provided by the applicant: adsl.xpt, adae.xpt, adeff.xpt, addv.xpt, adtis.xpt, and adtte.xpt (module 5.3.5.1).

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Study GAM10-08 was a Phase 3 trial conducted under IND 16925, intended as the primary evidence for the efficacy and safety of octagam 10% in treatment of DM in adults. The study was titled "Prospective, Double-Blind, Randomized, Placebo-Controlled Phase III Study Evaluating Efficacy and Safety of octagam 10% in Patients

with Dermatomyositis (ProDERM Study)". It was initiated on February 27, 2017 and completed on November 5, 2019.

6.1.1 Objectives (Primary, Secondary, etc)

The primary objective of the study was to provide confirmatory data on the beneficial effect of 2.0 g/kg octagam 10% given every four weeks compared with placebo in subjects with active DM, measured in terms of the percentage of responders at Week 16.

The secondary objectives were:

- 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 also at Week 40;
- to evaluate the safety and tolerability of octagam 10% in patients with DM.

6.1.2 Design Overview

The study was a prospective, placebo-controlled, double-blind, randomized, multicenter Phase 3 study in adult subjects with active DM, with a 16-week comparative efficacy period (First Period) followed by a 24-week open-label extension period (Extension Period) during which all eligible subjects received octagam 10%. See Figure 1 for the study design and Table 1 for the schedule of assessments.

A total of 95 eligible subjects were randomized at a 1:1 ratio 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 consisted of 2 to 5 days over which the study drug was administered. Randomization was stratified on three strata according to the seriousness of disease before enrollment based on the Physician's Global Disease Activity (GDA) assessment on a visual analog scale (VAS) scale:

- mild: GDA value of 0-3
- moderate: GDA value of 4-6
- major: GDA value of 7-10.

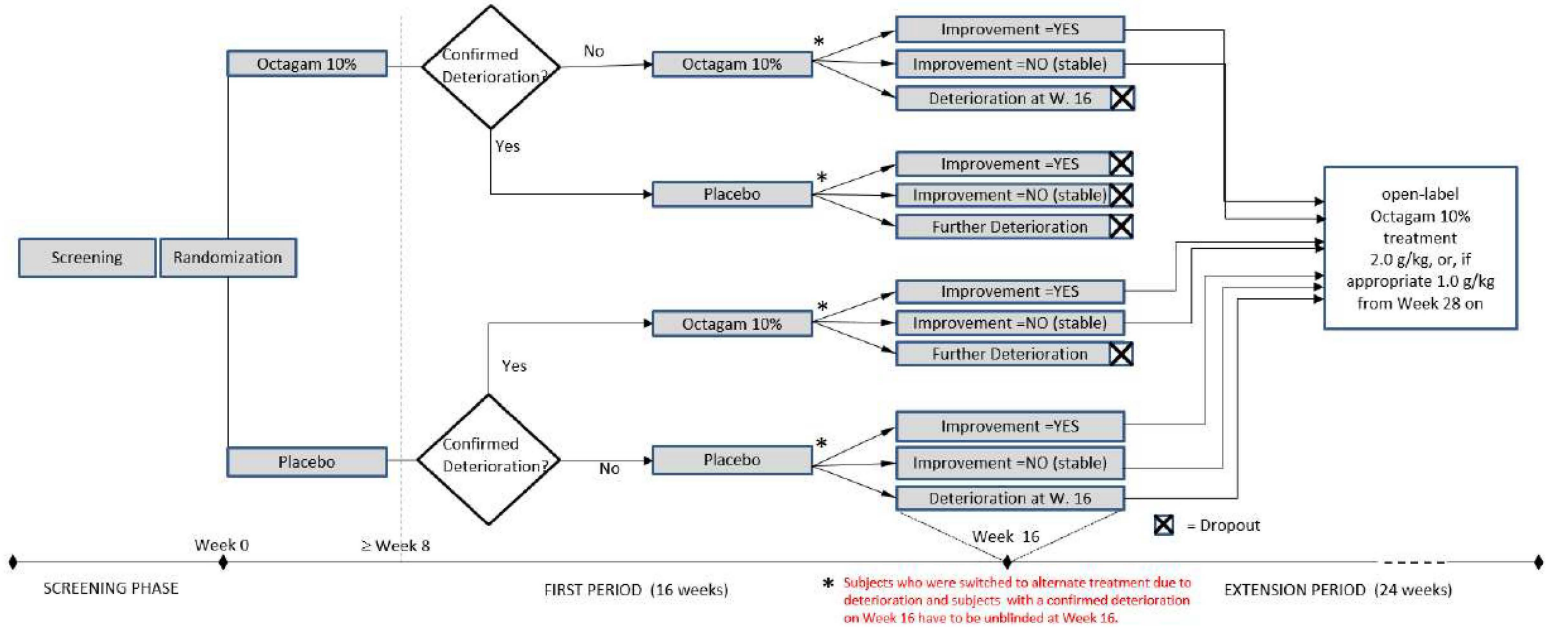
During the First Period (Weeks 0 through 16), subjects were followed every 4 weeks (±4 days, Visits 2 through 6). Subjects received four cycles of the assigned investigational medicinal product (IMP, placebo or octagam) at Weeks 0, 4, 8, and 12 (Visits 2 through 5). In case of confirmed deterioration (i.e. deterioration at two consecutive visits, see definition under the endpoint section) during the First Period, subjects were switched to the alternate treatment. After response assessment at Week 16 (Visit 6), this subgroup of subjects was unblinded.

After response assessment at Week 16, all subjects who had not deteriorated after receiving octagam during the First Period continued to receive 2.0 g/kg of octagam 10% during the subsequent 24-week (6-month) Extension Period in 4-week cycles. At Week 28, a subject might be switched to 1.0 g/kg octagam 10%, if they previously had been

stable on the 2.0 g/kg (20 mL/kg) octagam 10% dose. Efficacy variables were assessed at Weeks 28 and 40.

No interim analysis was planned.

Figure 1. Study Design



Source: Original sBLA 125062/674, GAM10-08 Protocol, Figure 1, p.22.

Table 1. Schedule of Events

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 sBLA 125062/674, GAM10-08 Protocol, Table 1, p.ix.

6.1.3 Population

Key inclusion criteria were:

- Subjects with diagnosis of definite or probable DM according to the Bohan and Peter criteria.
- Subjects under treatment with corticosteroids and/or maximally 2 immune-suppressants and being on stable therapy for at least 4 weeks

  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.
- Subjects with active disease, assessed and agreed upon by an independent adjudication committee.
- Manual Muscle Testing-8 (MMT-8) score <142, with at least 2 other abnormal Core Set Measures (CSM) (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).
- Males or females ≥ 18 to < 80 years of age.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Octagam 10% is a 10% immunoglobulin intravenous (IGIV) ready for intravenous administration; 1 mL of solution contains 100 mg protein of which ≥95% or ≥96% (depending on regulatory requirements) is human normal immunoglobulin. 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) during the First Period. After the response assessment at Week 16, all subjects who were eligible to continue received 2.0 g/kg (20 mL/kg) of octagam 10% at 4-week intervals during the subsequent 6-month, open-label Extension Period, for 6 infusion cycles (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.

6.1.6 Sites and Centers

About 55 sites worldwide were planned with emphasis on (Eastern) European countries and North America. The sponsor did not expect that any single center would enroll more than about 5 subjects. In total, subjects were enrolled at 36 study sites as follows: 17 sites in the US, 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. US subjects accounted for 28.4% (27/95) of the randomized subjects. Three sites randomized more than 6 subjects each, at 12, 10, 8 subjects, respectively. Together these three non-US sites accounted for 31.6% (30/95) of the randomized subjects.

6.1.7 Surveillance/Monitoring

See Table 1 for schedule of assessments.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

- Proportion of responders in the 2.0 g/kg octagam 10% group and the placebo group at Week 16. A responder is 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 at 2 consecutive visits, as defined below, up to (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 is a scale, with a range of 0 to 100, calculated as the sum of sub-scores of changes in the six CSMs as shown in Table 2. The level of improvement was always 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, ≥40 to 59 defined as moderate improvement, and ≥60 points defined as major improvement.

Reviewer Comment #1. Note that TIS does not differentiate between stable and worsening subjects. A subject with a TIS score of 0 has "worsening to 5% improvement" in each of the six CSMs.

Table 2. 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	0
	>5% to 15% improvement	7.5
	>15% to 25% improvement	15
	>25% to 40% improvement	17.5
	>40% improvement	20
Patient Global Activity	Worsening to 5% improvement	0
	>5% to 15% improvement	2.5
	>15% to 25% improvement	5
	>25% to 40% improvement	7.5
	>40% improvement	10
Manual Muscle Testing (MMT)	Worsening to 2% improvement	0
	>2% to 10% improvement	10
	>10% to 20% improvement	20
	>20% to 30% improvement	27.5
	>30% improvement	32.5
Health Assessment Questionnaire (HAQ)	Worsening to 5% improvement	0
	>5% to 15% improvement	5
	>15% to 25% improvement	7.5
	>25% to 40% improvement	7.5
	>40% improvement	10
Enzyme (most abnormal)*	Worsening to 5% improvement	0
	>5% to 15% improvement	2.5
	>15% to 25% improvement	5
	>25% to 40% improvement	7.5
	>40% improvement	7.5
Extra Muscular Activity	Worsening to 5% improvement	0
	>5% to 15% improvement	7.5
	>15% to 25% improvement	12.5
	>25% to 40% improvement	15
	>40% improvement	20
	Improvement Category	**Total Improvement Score**
Adult Threshold	Minimal	20
	Moderate	40
	Major	60

Source: Adapted from - Original sBLA 125062/674, GAM10-08 SAP, p.9.

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 will be determined by comparing to baseline values (Week 0).

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

CDASI

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 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.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

The sample size calculation was 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 groups at the end of the 16-week efficacy period (First Period). A total sample size of 84 subjects was required to show a significant difference in the proportion of responders between the octagam and placebo groups with a power of 80%, under the assumption that the true proportions of responders were 0.6 in the octagam group and 0.3 in the placebo group, using a two-sided alpha level of 0.05. The sample size was increased to 94 to allow for a safety margin. The study eventually randomized 95 subjects.

Analysis Sets

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

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

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. Protocol deviations in the open-label extension period are irrelevant for the definition of this population. The difference between the FAS and the PP1 was expected to be small.

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

Analysis of the safety endpoints was based on the safety set.

The primary endpoint was evaluated using FAS for the primary analysis and using PP1 for supplemental analysis.

All other analyses used the FAS set and/or the appropriate PP set.

Analysis of Efficacy Endpoints

The primary analysis of the primary efficacy endpoint was a comparison of the responder proportions between the octagam and the placebo groups using the Cochran-Mantel-Haenszel test, stratified by global disease activity (GDA), i.e., the randomization stratification factor. The primary analysis would be considered a success if the proportion of responders is significantly higher in the octagam group compared to the placebo group, at a two-sided alpha level of 0.05. In addition, an exact two-sided 95% confidence interval (CI) was also constructed for the overall difference in the proportion of responders between the octagam and the placebo groups.

Secondary efficacy endpoints were also analyzed. There was no multiplicity consideration in these analyses.

Missing Data Handling

For the primary analysis of the primary endpoint, subjects who did not meet the responder definition, including those who discontinued from the study prior to Week 16, were counted as non-responders.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

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 Safety Analysis Set (SAF) and the Full Analysis Set (FAS) included all these 95 subjects, while the Per-protocol Set 1 (PP1) included 88 subjects and the Per-protocol Set 2 (PP2) included 76 subjects (Table 3).

Table 3. Analysis Sets (Safety Analysis Set: N=95)

	octagam 10% N=47 N (%)	**Placebo N=48 N (%)**	**Total N=95 N (%)**
Safety Analysis Set	47 (100.0%)	48 (100.0%)	95 (100.0%)
Full Analysis Set	47 (100.0%)	48 (100.0%)	95 (100.0%)
Per-protocol Set 1	43 (91.5%)	45 (93.8%)	88 (92.6%)
Per-protocol Set 2	35 (74.5%)	41 (85.4%)	76 (80.0%)

Source: Adapted from - Original sBLA 125062/674, Clinical Study Report GAM10-08, Table 7, p.49

Reviewer Comment #2. Recall that PP1 excluded those subjects with significant protocol deviations that occurred before the Week 16 primary endpoint assessments, and which may have an impact on the analysis of the primary endpoint. In contrast, PP2 excluded those subjects with significant protocol deviations which may have an impact on the evaluation of the treatment effects of octagam. PP2 was defined to allow the assessment of the effect of octagam throughout the study. There is a noticeable difference between the number of subjects excluded from PP2 between the two study groups: 12 (25.5%) in the octagam group vs. 7 (14.6%) in the placebo group. It is not clear what led to this noticeable difference in subjects with significant protocol deviations across study groups.

6.1.10.1.1 Demographics

The demographic characteristics are summarized by study groups for the FAS in Table 4. Subjects aged between 22 and 79 years. Around 75% of subjects were female. Around 90% of subjects were White. Median body mass index (BMI) was 26.7 with a range of (16.5, 39.4). The demographics of the two study groups were similar, except that all five "Hispanic or Latino" subjects were in the placebo group.

Table 4. Demographics (Full Analysis Set: N=95)

	octagam 10% N=47	Placebo N=48	Total N=95
Age [Years]			
Mean (SD[a])	54.0 (13.8)	51.4 (13.0)	52.7 (13.4)
Median	55.0	51.5	52.0
Min[a], Max[a]	22, 77	22, 79	22, 79
Sex [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%)
Ethnicity [N (%)]			
Hispanic or Latino	0 (0.0%)	5 (10.4%)	5 (5.3%)
Not Hispanic or Latino	47 (100.0%)	43 (89.6%)	90 (94.7%)
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, 117	52, 110	45, 117
Height [cm]			
Mean (SD)	166.3 (8.7)	168.1 (9.7)	167.2 (9.2)
Median	165.0	167.0	167.0
Min, Max	152.0, 186.0	150.0, 190.5	150.0, 190.5
BMI [kg/m^2]			
Mean (SD)	26.9 (5.0)	27.6 (4.9)	27.2 (4.9)
Median	26.7	26.7	26.7
Min, Max	16.5, 37.0	19.7, 39.4	16.5, 39.4
Region [N (%)]			
US	14 (29.8%)	13 (27.1%)	27 (28.4%)
Non-US	33 (70.2%)	35 (72.9%)	68 (71.6%)

[a] SD: Standard Deviation. Min: Minimum. Max: Maximum.
Source: Adapted from - Original sBLA 125062/674, Clinical Study Report GAM10-08, Table 8, pp.49-50

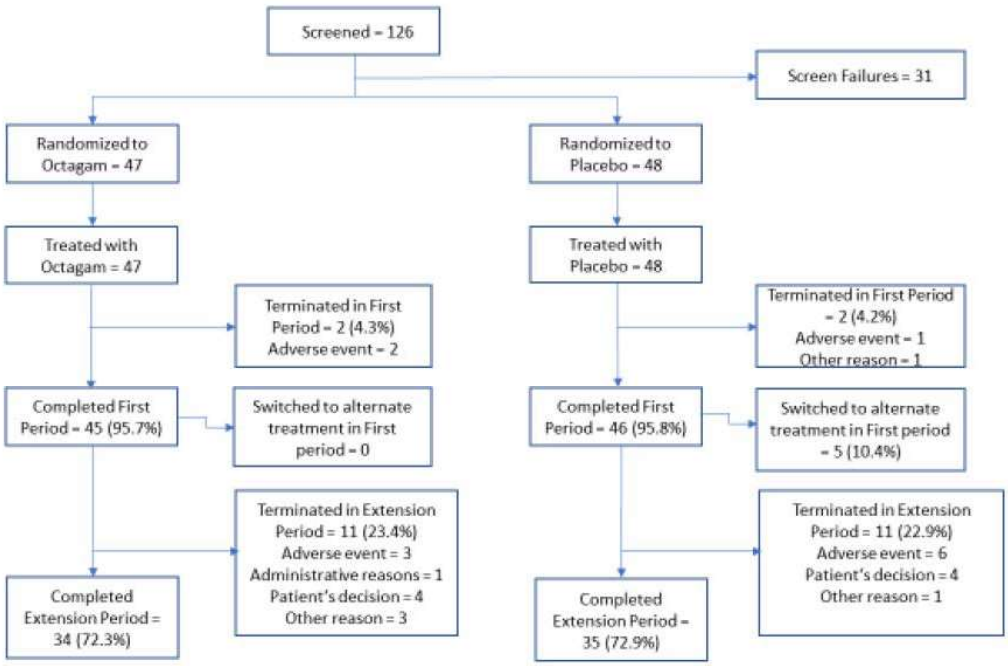
6.1.10.1.3 Subject Disposition

Figure 2 summarizes subject disposition. In total, 126 subjects were screened of whom 31 were screen failures and 95 were randomized. All randomized subjects received study treatment.

Two patients from each group withdrew from the study during the First Period: except for one placebo subject who withdrew for other reasons, the remaining three subjects had an AE leading to discontinuation. Thus 45 octagam and 46 placebo subjects, respectively, completed the First Period. Five placebo subjects switched to receive octagam 10% treatment during the First Period. Two of the five subjects were switched due to confirmed deterioration at two consecutive visits as planned in the protocol, and three were switched in error. None of the patients in the octagam 10% group switched to receive placebo.

Eleven subjects in each treatment group terminated the study during the Extension Period; 34 subjects (72.3%) completed the study in the octagam 10% group and 35 (72.9%) in the placebo group. No subject terminated the study due to pregnancy.

Figure 2. Subject Disposition



Source: Original sBLA 125062/674, Clinical Study Report GAM10-08, Figure 2, p.45

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary efficacy endpoint was the proportion of responders at week 16. A responder was defined as a subject with an improvement of ≥20 points (i.e., at least minimal improvement) on the TIS at Week 16 compared to baseline and who did not meet the "Confirmed Deterioration" criteria at two consecutive visits up to and including Week 16. Table 5 summarizes the primary analyses of the primary endpoint and analyses of additional categories of responders defined as secondary endpoints. Using the FAS, the proportion of responders with at least minimal improvement was 78.7% (37/47) in the octagam group vs. 43.8% (21/48) in the placebo group, resulting in a difference of 35.0%. The difference in the responder proportions was statistically significant (p = 0.0008) with a 95% confidence interval (CI) of (16.7%, 53.2%). Analysis results using PP1 agrees with the primary analysis results using FAS. Proportions of responders in terms of moderate and major improvements were also higher in the octagam group than in the placebo group (Table 5).

Table 5. 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**	**Placebo N=48**	**Difference in Responder Proportions octagam 10% – Placebo**
	Number of Subjects (%)	**Number of Subjects (%)**	**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.

6.1.11.2 Analyses of Secondary Endpoints

Reviewer Comment #3. Analyses of all secondary endpoints are descriptive. There was not plan for multiplicity control in the analyses of secondary endpoints. In what follows I

will focus on additional analyses of the TIS to further characterize the efficacy in TIS at Week 16 for comparison in the First Period and at Week 40 for effect maintenance in the Extension Period, and analyses proposed in the draft labeling which the clinical team deemed important. For some analyses, nominal p-values and CI are provided and noted as such.

First Period: TIS Response at Week 16 by Improvement Categories

Table 5 summarizes TIS response at Week 16 in three different improvement categories: at least minimal improvement (the primary endpoint), at least moderate improvement, and at least major improvement. In addition to the primary endpoint, the last two categories also show more responders in the octagam group compared to the placebo group, with the difference in responder proportions being 45.2% and 23.6%, respectively.

Extended Period: TIS Response at Week 40 by Improvement Categories

Table 6 summarizes TIS response at Week 40 in the three different improvement categories to assess longer-term effect of octagam. The response rates are similar between those who continued octagam treatment from the First Period and those who switched to octagam treatment from placebo treatment from the First Period. The octagam response rates at Week 40 is higher than the placebo response rates at Week 16, showing that octagam continued to be effective into Week 40. The octagam response rate at Week 40 is lower than that at Week 16 (68.1% vs. 78.7%), which may partly be explained by subject attrition.

Table 6. Total Improvement Score – Proportions of Responders by Improvement Categories at Week 40 (Full Analysis Set: N=95)

	Number of Responders (%) [95% CI] [a]	
Total Improvement Score (TIS) Response Category	**octagam 10% N=47**	**Placebo N=46**
At Least Minimal Improvement (TIS ≥ 20)	32 (68.1%) [52.9%, 80.9%]	32 (69.6%) [54.2%, 82.3%]
At Least Moderate Improvement (TIS ≥ 40)	26 (55.3%) [40.1%, 69.8%]	28 (60.9%) [45.4%, 74.9 %]
At Least Major Improvement (TIS ≥ 60)	17 (36.2%) [22.7%, 51.5%]	14 (30.4%) [17.7%, 45.8%]

[a] 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 95% CIs are at nominal levels and were not multiplicity adjusted.
Source: FDA statistical reviewer's analysis.

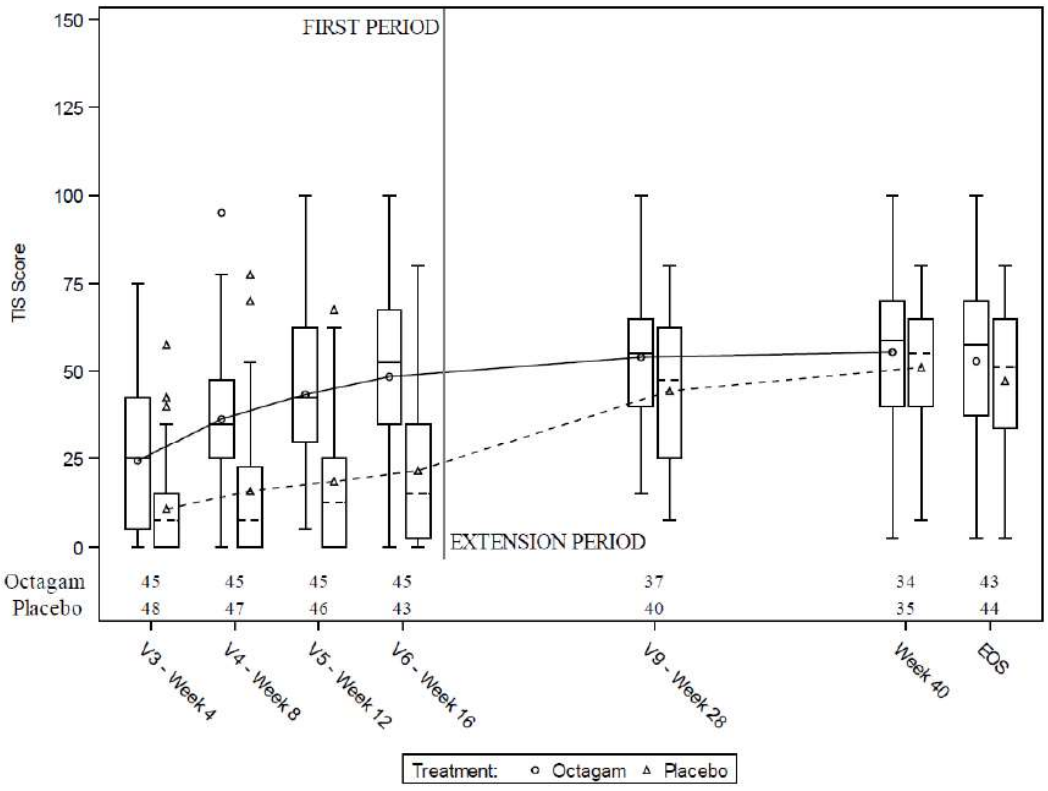
Reviewer Comment #4. My approach to analyzing Week 40 TIS response rate differs subtly from that in the submission. Specifically, the applicant used 45, while I used 47 as

the denominator when calculating the response rate in the octagam 10% column in Table 6. To interpret this column as an estimate of the response rate at Week 40, we need to include in the denominator all subjects who, when started the trial, had a chance to be a responder at Week 40, including the two subjects who discontinued due to AE prior to Week 16. There in the denominator I included these two discontinued subjects who the applicant excluded. Another difference is that the applicant also calculated a "total" response rate by pooling the two columns in Table 6. I consider the two columns addressing different questions, and therefore should not be pooled. The placebo column in Table 6 estimated the response rate for subjects who had been treated with octagam for 24 weeks, while the octagam column estimated that for subjects who had been treated with ocatagam for 40 weeks.

Absolute TIS values: Both Periods

Figure 3 summarizes the absolute TIS values over time. Table 7 summarizes the absolute TIS values at Weeks 16 and 40. The results are consistent with the results on TIS response categories summarized above.

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 7. 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.

Confirmed Deterioration

No patients in the octagam 10% group had confirmed deterioration during the First Period, and one patient had confirmed deterioration in the Overall Period. This was Patient (b) (6) who was a non-responder at Week 16, and withdrew following deterioration in the Extension Period. In the placebo group, three patients had confirmed deterioration during the First Period, and no further patients had confirmed deterioration during the Overall Period.

First Period: Time to TIS Response

The median time to minimal improvement in the octagam 10% group was 35.0 days with a 95% CI of (29.0, 58.0). Because the placebo group subjects switched to receive octagam 10% at the end of the First Period, if eligible, no time-to-event analysis is conducted for the placebo group subjects.

CDASI Total Activity Score

At Week 16, CDASI had a mean decrease of 9.4 points (SD=10.5) in the octagam 10% group, and a mean decrease of 1.2 points (SD=7.0) in the placebo group.

6.1.11.3 Subpopulation Analyses

Table 8 summarizes the subgroup analyses by age, sex, randomization stratum, and region. Note that because over 90% of the subjects were White, analysis by the race subgroups was not conducted. There is no substantial difference across the various subgroup categorizations.

Table 8. Total Improvement Score – Proportions of Responders with at Least Minimal Response at Week 16 by Subgroups (Full Analysis Set: N=95)

Subgroup	N = Number of Responders (%)		Difference in Responder Proportions octagam 10% – Placebo Point Estimate [95% CI][a]
	octagam 10%	Placebo	
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

Since there were no missing data for the primary efficacy endpoint, no sensitivity analyses were performed.

6.1.12 Safety Analyses

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events

First Period

In the First Period, there were 52 'at risk' subjects in the octagam 10% group (47 subjects randomized to octagam 10% plus the 5 subjects randomized to placebo who switched treatment) and 48 subjects in the placebo group (as randomized).

The incidence of serious treatment emergent adverse event (TEAEs) was similar in the two treatment groups, with 3 subjects (5.8%) experiencing 5 serious TEAEs in the octagam 10% 'at risk' group and 2 subjects (4.2%) experiencing 4 serious TEAEs in the placebo 'at risk' group. None of the serious TEAEs had a fatal outcome. TEAEs leading to discontinuation of study drug only occurred in the octagam 10% 'at risk' group, with 3 subjects (5.8%) experiencing 8 such events.

Overall Period

The Overall Period includes any events reported by subjects 'at risk' following octagam 10% treatment in the First Period and any events from all subjects in the Extension Period, but does not include any events reported by subjects in the placebo 'at risk' group in the First Period. Following octagam 10% treatment, 22 serious TEAEs were reported in 14 subjects (14.7%).

6.1.12.5 Adverse Events of Special Interest (AESI)

AESI included thromboembolic events (TEEs) and hemolytic transfusion reactions (HTRs).

TEEs were only reported in the octagam 10% 'at risk' group, with 1 subject experiencing 2 TEEs in the First Period, and 8 TEEs were reported in 6 subjects (6.3%) in the Overall Period. No HTRs were reported at any time in the study.

Reviewer Comment #5. For the TEE AE, there is a difference of 1 subject with 2 TEEs in the octagam group vs. 0 TEEs in the placebo group during the 16-week First Period, which cannot be concluded as not due to chance. More TEEs were observed in the longer 24-week Extended Period: 6 subjects with 8 TEEs overall. However, because there is no comparison group in the Extended Period, it is impossible to conclude whether octagam treatment would lead to an increase of TEEs. Note that study exclusion criterion #13 excluded 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)." This exclusion criterion should be considered when assessing the relatedness of TEE and octagam treatment. I communicated the TEE issue with the clinical review team and defer to their judgment.

9. ADDITIONAL STATISTICAL ISSUES

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

Reviewer Comment #6. Twenty percent (19/95) of randomizations were from an incorrect randomization stratum (Table 9). All the analyses above used the Physician's Global Disease Activity (GDA) stratum recorded in the screening electronic case report form (eCRF), which was deemed by the applicant to be more accurate, and not the one entered into the interactive response technology (IRT) system used for randomization. While these errors indicate some issues with study conduct, given the large number of study sites involved in the study and consequently limited influence of each study site on the overall study outcome, I determine that this issue alone would not have substantively influenced the study outcome.

Table 9. Discrepancy in Physician's Global Disease Activity between eCRF and IRT

GDA in eCRF	GDA in IRT			
	Mild	Moderate	Severe	Total
Mild	16	10	0	26
Moderate	3	49	4	56
Severe	0	2	11	13

Source: FDA statistical reviewer's analysis.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Study GAM10-08 was a prospective, placebo-controlled, double-blind, randomized, multicenter Phase 3 study in adults with active dermatomyositis (DM), with a 16-week comparative efficacy period (First Period) followed by a 24-week open-label extension period (Extension Period) during which all eligible subjects received the investigational product octagam 10%. The primary objective of the study was to provide confirmatory data on the beneficial effect of 2.0 g/kg octagam 10% given every four weeks compared with placebo in DM subjects based on the percentage of responders at Week 16. A responder is 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.

A total of 95 subjects with DM aged between 22 and 79 years were randomized: 47 to the octagam and 48 to the placebo groups. For the primary analysis of the primary efficacy endpoint, 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 the response rate between the two groups was 35% with a 95% CI of (16.7%, 53.2%) and a p-value of 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 on the TIS) at 68.1% vs. 22.9%; and with major improvement (defined as ≥60 points on the TIS), at 31.9% vs. 8.3%.

Longer-term effect was evaluated in the Extension Period. Of the 47 and 48 subjects randomized to the two study groups, 45 and 46 continued into the Extension Period and received octagam 10%, respectively. Efficacy appeared to be maintained into Week 40 for those randomized to the octagam group, with 32 (32/47 = 68.1%) responders at Week 40. The subjects randomized to the placebo group and continued into the Extension Period also received the octagam 10% treatment for 24 weeks, and the response rate after 24 weeks of treatment was 69.1% (32/46).

No deaths occurred during the study. Further analysis of safety data is deferred to the clinical team.

10.2 Conclusions and Recommendations

The efficacy results of Study GAM10-08 provided sufficient statistical evidence to support expanding the indication of octagam 10% to treatment of dermatomyositis in adults.