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CLINICAL MEMORANDUM

From:	Laurence Landow MD, Medical Officer, CRS/DBCD/OBRR
To:	Orieji Illoh MD, Division Director, CRS/DBCD/OBRR
And:	Wendy Paul MD, Deputy Division Director, CRS/DBCD/OBRR
Through:	Salim Haddad MD, Team Lead, CRS/DBCD/OBRR
Re:	PAS (CSR for LAS-213 and revised draft labeling)
BLA:	125416/167
Applicant:	Octapharma Pharmazeutika Produktionsges.m.b.H.
Product:	Octaplas (Pooled Plasme (Human), Solvent/Detergent Treated

EXECUTIVE SUMMARY

This supplement includes a clinical study report for Study LAS-213 and draft labeling. Study LAS-213 was an open-label, multicenter (n=7), single-arm, PMR study to investigate the safety and tolerability of blood type-specific Octaplas™ in the management of male and female subjects (N=41) aged ≥2 to ≤20 years requiring therapeutic plasma exchange (TPE).[1] Young children aged 2 to <12 years were classified as **Group 1** (N=15), adolescents aged 12 to <17 years as **Group 2** (N=13), and young adults aged ≥17 to ≤20 years as **Group 3** (N=13). A major aim of the study was to assess whether this pooled plasma product was associated with increased risk of thrombotic (TE) or thromboembolic (TEE) adverse events in a young population. Of note, efficacy was not a study endpoint.

Subjects were followed for one week (7 days) during their therapy, which consisted of one or more TPE procedures at a dose of 40 to 60 mL/kg. The primary study endpoint was serious adverse events (SAEs), adverse reactions (ARs),[2] adverse events (AEs), TEs, and TEEs. Secondary endpoints included Safety laboratory parameters (Complete Blood Count (CBC), a Chemistry 7 lab panel (Chem 7), and ionized calcium), and the investigator's assessment of overall safety. A Follow-up visit was performed 24 hours after each TPE procedure at which time the investigator provided an assessment of overall safety and blood was drawn for ionized calcium levels to assess for citrate toxicity. TPEs starting after the 7-day time point were not considered part of the Treatment Period. An independent data monitoring committee (iDMC)

[1] The original BLA referred to the name of the product as OctaplasLG; however, the proprietary name of the U.S. marketed product is Octaplas™. For the purposes of this memo, the product will be designated as Octaplas.
[2] ARs are TEAEs considered to be causually related to the product.

was set up which reviewed safety line listings and narratives periodically during the study and gave advice on the continuation, modification or termination of the study.

Results
41 subjects were screened and 41 subjects received ≥1 Octaplas infusion during the Study period. No TEs or TEEs were reported or identified by the iDMC during their review of the data.

One subject experienced an unrelated serious adverse event (SAE) with a fatal outcome, i.e, multiple organ failure secondary to sepsis, in a 5 year old female patient with B-cell acute lymphocytic leukemia. No treatment-related SAEs were reported.

No ARs occurred in young children (Group 1). In contrast, 5 ARs occurred in Group 2 (N=3) during TPE #1 (n=4) and TPE #4 (n=1), and 3 ARs occurred in Group 3 (N=1) during TPE #1 (n=2) and TPE #2 (n=1). Frequency of ARs was highest in subjects with a medical history of renal and urinary disorders. The most frequent AR was mild citrate toxicity (1 subject each) in Group 2 (N=2). Other ARs (1 subject each) included headache, pyrexia and urticaria in Group 2, and elevations in C-reactive protein and procalcitonin in Group 3. All were of mild intensity (except for pyrexia, which was of moderate intensity) and all resolved by study end.

No vital signs of note were identified.

Safety was assessed by the investigators as 'excellent' for more than 90% of subjects 24 hours after each TPE based on prespecified definitions;[3] the overall safety was assessed as 'moderate' for the 4 subjects who experienced ADRs.

Assessment
Overall, the evaluation of SAEs, ADRs, laboratory results, and vital signs supported the safety profile of Octaplas and did not indicate any safety signals, including risk of TEs or TEEs, in the pediatric population requiring TPE. Investigator assessment of overall safety indicated that the drug was well tolerated.

Recommendation
Approval of the PAS.

[3] Excellent: Treatment was well tolerated by the patient; Moderate: AR(s) were observed, but easily resolved or not clinically significant; Poor: AR(s) were observed requiring significant medical intervention

STUDY PROTOCOL (overview)

1. **Background**

Octaplas is a solvent/detergent (S/D) treated human plasma prepared from units of fresh frozen plasma (FFP) pooled according to their ABO blood group. It contains the normal constituents of FFP and does not contain red blood cells (RBCs), leukocytes and platelets. Octaplas was developed as an alternative to plasma to reduce the risk of virus transmission.

The original BLA included data from16 prospective clinical studies and 9 retrospective studies with different formulations of the product. Of the 16 prospective studies, 2 focused on safety aspects only, and of the 9 retrospective studies, 3 mainly studied efficacy. In total, approximately 545 subjects were enrolled in prospective and retrospective efficacy studies.

2. **Clinical Protocol Review**

2.1. Design

Prospective, open-label, multicenter, interventional, PMR, phase 4, safety and tolerability study.

2.2. Primary endpoints

SAEs, ARs, TEs, and TEEs

2.3. Secondary endpoints

- Safety laboratory parameters (complete blood count [CBC][4], Chem 7 laboratory panel [Chem 7][5], and ionized calcium).
- Investigator's assessment of overall safety

2.4. Dosing regimen

40 to 60 mL/kg at an infusion rate not to exceed 0.020 to 0.025 mmol/kg body weight.

2.5. Study conduct/schedule

The study consisted of a Screening Period, a 1-week Treatment Period consisting of 1 or more therapeutic plasma exchanges (TPE), and a Follow-up Assessment 24 hours after the last TPE procedure in the Treatment Period. Screening included a CBC, Chem 7 panel, ionized calcium and a pregnancy test.

Between 30 minutes and 3 hours after the completion of each TPE procedure, vital signs were assessed, and blood was drawn for safety laboratory assessments (CBC and Chem 7). Within 24 hours before each TPE procedure, vital signs were assessed, and blood was drawn for CBC, Chem 7, and ionized calcium levels. The investigator provided an assessment of overall safety 24 hours after each TPE, and blood was drawn for ionized calcium levels to assess for citrate toxicity. All AEs observed during the study that did not meet the definition of a serious adverse event (SAE) were NOT captured in the eCRF; however, all serious and non-serious TEs and TEEs

[4] CBC: White Blood Cell Count; Red Blood Cell Count; Hemoglobin; Hematocrit; Mean Corpuscular Volume; Mean Corpuscular Hemoglobin; Mean Corpuscular Hemoglobin Concentration; Red Cell Distribution Width

[5] Chem 7 Panel: Blood Urea Nitrogen; CO2 (bicarbonate); Serum Chloride; Serum Creatinine; Glucose; Serum Potassium; Serum Sodium

were captured in the eCRF. An independent DMC monitored subject safety and reviewed quarterly safety line listings and SAE narratives periodically.

2.5.1. Schedule of assessments

Table 1 shows assessments conducted pre-, during, and post-TPE.

Table 1: Schedule of Assessments

Time-Points	Screening (≤ 14 Days Prior to 1st TPE)	1-Week (7-Day) Study Treatment Period[1]			Follow-Up[10, 11]
		Within 24 Hours Before Each TPE Procedure	Study Treatment (During Each TPE Procedure)[2]	Between 30 Minutes and 3 Hours After Each TPE Procedure	24 Hours After Each TPE Procedure
Obtain Informed Consent	X				
Review of inclusion/exclusion criteria	X				
Physical examination	X				
Medical history (including relevant current concomitant medications, and blood group type [ABO] recording)	X				
Demographics	X				
Vital signs[3] (heart rate, respiratory rate, temperature, and blood pressure assessment)		X		X	
Blood draw CBC and Chem 7[4]	X	X		X	
Blood draw for ionized calcium		X	X[9]		X[8]
Record total volume of Octaplas infused at each infusion episode			X		
Record the type of machine used for TPE (filtration or centrifugation)			X		
Record any SAEs, ADRs (including transfusion reactions), TEs, TEEs, and concomitant medication use[5]			←----------Continuously----------→		
Pregnancy test for females of childbearing potential[6]	X				
Investigator's overall assessment of safety[7]					X

ADR=adverse event reaction; CBC=complete blood count; SAE=serious adverse event; TE=thrombotic event; TEE=thromboembolic event; TPE=therapeutic plasma exchange.

1. Study treatment period was a maximum of 1 week (7 days) and consisted of 1 or more TPEs. In the event that a TPE began within the 7-day Treatment Period and ran past the maximum 7-day time point, the entire TPE was followed and all relevant TPE assessment procedures performed (even if lasting longer than 7 days). New TPEs starting after the 7-day time point were not be considered part of the Treatment Period.
2. Subsequent treatment was determined at the investigator's discretion and depended upon the clinical setting including the patient's response to treatment.
3. Vital signs included heart rate, respiratory rate, temperature, and blood pressure assessments. If multiple vital sign assessments were taken before and/or after each TPE, the vital signs that were assessed closest before the start and after the end of each TPE were recorded.
4. Refer to Section 9.5.1.7.2 for list of safety blood parameters analyzed. For the first TPE it was mandatory that pre- and post-TPE samples for CBC and Chem 7 were tested. If subsequent infusion episodes were performed, pre- and post-TPE samples were drawn unless considered not medically necessary by the investigator (eg, the timing of the pre-TPE sample was close to or overlapped with the timing of the post-TPE sample). In the event a pre- or post-TPE laboratory sample was not drawn, the reason for not obtaining the sample was recorded in the eCRF. CBC and/or Chem 7 parameters may have been assessed at any other time point as medically indicated. If multiple laboratory assessments were made before and after the TPE, the assessment taken most proximal to the start (pre) and after the end (post) of the infusion was recorded in the eCRF.
5. For outpatients, follow-up was done via a telephone interview to assess for any ADRs.
6. Confirmation that patients of child bearing potential were not pregnant was established by a negative pregnancy test result obtained during Screening.
7. Investigator's evaluation of overall safety was performed 24 (+/-2) hours after each TPE procedure.
8. If it was impractical to obtain a blood sample for ionized calcium during Follow-up (eg, an outpatient situation), a post-study treatment sample to test for ionized calcium was skipped.
9. The first sample was drawn within 90 minutes after start of the TPE.
10. Follow-up procedures (ionized calcium sample and Investigator's Assessment) were performed 24 (+/-2) hours after the TPE concluded. Follow-up procedures may have been performed sooner if it was not practical to obtain these during the 24-hour post-TPE period. If it was not practical to obtain a blood sample for testing ionized calcium, the laboratory assessment could be skipped. If Follow-up assessments were not performed, the reason was clearly documented (eg, patient discharged prior to 24 hours after the end of the last TPE).
11. If plasma was needed for administration during the study Follow-up Period, Octaplas was given. After the end of the Follow-up, if plasma was needed, this was provided according to institutional standard of care.

Source: Table 3, CSR, page 29/707, 16 Jan 2020

2.6. Eligibility Criteria

2.6.1. Inclusion Criteria

- Subjects in whom therapeutic plasma exchange was required
- Male or female ≥2 years to ≤20 years of age
- Patient or patient's legal representative(s)/guardian(s) gave voluntarily written and signed informed consent before any study-related procedure were performed. If children are old enough (age usually deemed by each institution) to understand the risks and benefits of the study, they were informed and provided their written assent.

2.6.2. Exclusion Criteria

- Known homozygous congenital deficiency of protein S
- History of severe hypersensitivity reaction to plasma-derived products or to any excipient of the investigational product
- Known immunoglobulin A (IgA) deficiency with documented antibodies against IgA
- Participating in another interventional clinical study or had participated during the 1 month prior to study inclusion.
- Patient was pregnant
- Use of Angiotensin-Converting-Enzyme-inhibitors within 72 hours of the start of the first infusion episode or planned used of these medications while on study

2.7. Safety Monitoring and Treatment Modifications

Definitions of possible thromboembolic events (TEE), e.g., acute myocardial infarction, cerebral vascular events, deep venous thrombosis, ischemic stroke, transient ischemic attack, thrombophlebitis, infusion site thrombosis, were prespecified.

To determine/confirm if an event was a thrombotic event (TE) or thromboembolic event (TEE), the following adjudicators were involved:
Adjudicator 1 (Investigator), Adjudicator 2 (Octapharma Central Drug Safety Unit, CDSU), and Adjudicator 3 (Independent Data Monitoring Committee, IDMC).
The IDMC received anonymized case reports and/or lists of all reported adverse reactions. SAEs, along with probably or possibly related and suspected TEs/TEEs (as determined by Adjudicator 1 and/or Adjudicator 2), were reviewed on an ad-hoc basis; other events such as unrelated AEs and unrelated SAEs were reviewed on a quarterly basis. The IDMC then voted on all new cases (simple majority), recorded their judgment, and returned their decisions back to data management. Even if the adjudicators disagreed, provided that at least 1 adjudicator determined that an event was a TE or TEE, it was entered as such in the database.

2.8. Statistical Analysis

All data collected were summarized and presented descriptively to facilitate the review of population homogeneity and general patterns within and between age groups. Missing data were not imputed. For calculations concerning BW and

calculating the administered dose per kg, the latest available BW measurement was used. No analyses of the patterns of missing data were done

Study Populationss

- Safety (SAF) population: all subjects who received at least one infusion of octaplas.
- Full analysis set (FAS): all subjects of the SAF with any information available on the primary endpoint.
- Per-protocol (PP) population: all subjects who completed the infusion episode(s) and the final examination without major protocol deviations that would have had an effect on the evaluation of the primary endpoint.

2.9. Protocol Amendments

There were 6 amendments to the original study protocol (Protocol v.1 dated 29 August 2013), which was submitted to FDA for review and input. All sites received Protocol v2 as their original protocol and was the version submitted to their IRBs for approval prior to site initiations or patient recruitment. Subsequent versions were as follows.

2.9.1. Protocol v3 dated 14 March 2014

- Serious Adverse Events and Adverse Event Collections, Section 7.3.2 and Section 7.3.3 was modified. In Protocol v.2 only ARs that were temporally associated with administration of octaplas, and ADRs that fell into the category of TEs and TEEs, were collected. In order to capture additional ADRs that could have been classified as serious, obligatory reporting of all SAEs was added.
- Exclusion Criterion #1 (Patient requires RBC priming for his/her plasma exchange machine) was removed, as this requirement was redundant with Inclusion Criterion #3 (Patient must be a minimum of 15 kg and not require RBC priming for his/her plasma exchange machine)
- Dose Rationale, Section 1.2 was replaced with the reference to the current package insert of the investigational product.
- Study Procedures Follow-Up, Section 6.1.3, was modified to allow flexibility in the timing of blood sampling for ionized calcium levels, in order to accommodate outsubjects or other subjects who may not have been available to provide a blood sample during the Follow-up time period
- Permitted Concomitant Therapy, Section 4.2.1, was modified to clarify that all concomitant therapies were permitted except those that would interfere with the objectives of the study.
- Adverse Event Causality, Section 7.3.2.4 was clarified providing causality definitions of both AEs and ARs, in order to be consistent with pharmacovigilance system already in place at Octapharma.
- Plasma-Associated and Transfusion-Associated Reactions, Section 7.3.4, was deleted, as invariably all ARs would be reported in the study.

2.9.2. Protocol v4 dated 23 April 2015

- Exclusion Criterion #6 was clarified to explicitly exclude subjects that received any other plasma product, other than Octaplas (or albumin) in the previous 21 days.
- Dose and Dosing Schedule, Section 5.4, was modified to include language allowing hanges in the protocol-specified dosing regimen from the general recommendation, depending on the therapeutic treatment plan and the investigator's evaluation of the respective clinical situation
- Ionized calcium measurement was added during the TPE
- Conditions for Storage and Use, Section 5.3, was updated to reflect the new octaplas prescribing information which had extended the time periods in which octaplas could be used after thawing.
- Preparation and Method of Administration, Section 5.5, was changed to allow for the administration of blood group-compatible octaplas to subjects in urgent cases and in circumstances that the same blood group is not available.
- The NIH clinical center guideline for blood draw for research purpose (M95-9, rev 06/05/2009) was added as a reference and implemented in order to provide direction on the maximum blood volume allowed to be drawn during the study

2.9.3. Protocol v5 dated 19 September 2017

- Exclusion Criterion #6 (Patient is currently undergoing TPE with regular plasma (no exclusion for subjects treated with albumin) was deleted, in order to facilitate access to the
  required study population.
- An Exclusion Criterion (Use of Angiotensin-Converting-Enzyme-inhibitors within 72 hours of the start of the first infusion episode or planned used of these medications while on study) was added, as use of ACE-inhibitors is contraindicated in combination with plasma exchange.
- The Study Flow Chart, Section 3.1.2, was modified to more precisely define the duration between the last study drug administration and the safety Follow-up visit (changed from "6 hours to 24 hours" to "24 [±2] hours").
- Prior and Concomitant Therapy, Section 4.2, was updated to specify that only relevant concomitant medications should be reported. A list of relevant medications, for the purposes of this study, was provided as guidance to the investigator.

2.9.4. Protocol v6 dated 19 October 2018

- Removal of patient age category requirements within each age category to an overall minimum requirement of 40 subjects between 2 years and 20 years of age.

STUDY SUBJECTS

1. Demographics

Table 2 shows that the safety population consisted primarily of non-Hispanic White subjects with a median age of 13 years (range: 2 to 20 years of age) in which females slightly outnumbered males.

Table 2: Demographic Characteristics (Safety Population, N=41)

Parameter	Group 1 Age 2 to <12 N=15 (%)	Group 2 Age 12 to <17 N=13 (%)	Group 3 Age ≥17 N=13 (%)	All Subjects N=41 (%)
Age				
Mean (SD)	5.1 (2.3)	13.8 (1.5)	18.1 (1.0)	12.3 (5.4)
Median	6.0	14.0	18.0	13.0
Range	2-10	12-16	17-20	2-20
Sex				
Male	3 (20.0%)	6 (46.2%)	9 (69.2%)	18 (43.9%)
Female	12 (80.0%)	7 (53.8%)	4 (30.8%)	23 (56.1%)
Race (N, %)				
White	13 (87.7%)	9 (69.2%)	10 (76.9%)	32 (78.0%
African American	2 (13.3%)	2 (15.4%)	3 (23.1%)	7 (17.1%)
American Indian	0	2 (15.4%)	0	2 (4.9%)
Ethnicity				
Hispanic	0	0	1 (7.7%)	1 (2.4%)
Non-Hispanic	15 (100.0%)	12 (92.3%)	12 (92.3%)	39 (95.1%)
Missing	0	1 (7.7%)	0	1 (2.4%)
Diagnosis				
Immune system disorders	2 (13.3%)	5 (38.5%)	7 (53.8%)	14 (34.1%)
Infections	3 (20.0%)	1 (7.7%)	0	4 (9.8%)
Nervous system disorders	9 (60.0%)	2 (15.4%)	1 (7.7%)	12 (29.3%)
Renal and urinary disorders	0	4 (30.8%)	4 (30.8%)	8 (19.5%)
Other	1 (6.7%)	1 (7.7%)	1 (7.7%)	3 (7.3%)

Adapted from Table 14.1.5-1, page 91 of 707, Study report, Oct 18, 2019

2. Past Medical History

Study subjects had a notable past medical history (PMH), defined (arbitrarily by this reviewer) as an incidence ≥10% overall. As depicted in Table 3, a notable PMH was present in three organ systems: surgical-medical procedures (e.g., transplant, nephrectomy), cardiac disorders (e.g., cardiomyopathy), and renal-urinary disorders (e.g., chronic kidney disease).

Table 3: Past Medical History by SOC and Preferred Term >10% (Safety Population, N=41)

System Organ Class Preferred Term	Group 1 Age 2 to <12 N=15 (%)	Group 2 Age 12 to <17 N=13 (%)	Group 3 Age ≥17 N=13 (%)	All Subjects N=41 (%)
Surgical-medical procedures	5 (33.3%)	10 (76.9%)	9 (69.2%)	24 (58.5%)
Heart transplant	2 (13.3%)	2 (15.4%)	5 (38.5%)	9 (22.0%)
Renal transplant	0	4 (30.8%)	5 (38.5%)	9 (22.0%)
Nephrectomy	0	5 (38.5%)	3 (23.1%)	8 (19.5%)
Cardiac disorders	2 (13.3%)	1 (7.7%)	4 (30.8%)	7 (17.1%)
Renal and urinary disorders	0	5 (38.5%)	1 (7.7%)	6 (14.6%)

Adapted from Table 14.1.6-1, page 106 of 707, Study report, October 18, 2019

3. Concomitant Diseases

Study subjects also had notable concomitant diseases for many organ systems, as indicated in Table 4.

Table 4: Concomitant Diseases by SOC and Preferred Term >10% (Safety Population, N=41)

System Organ Class Preferred Term	Group 1 Age 2 to <12 N=15 (%)	Group 2 Age 12 to <17 N=13 (%)	Group 3 Age ≥17 N=13 (%)	All Subjects N=41 (%)
Renal and urinary disorders	3 (20.0%)	7 (53.8%)	9 (69.2%)	19 (46.3%)
Acute kidney injury	2 (13.3%)	1 (7.7%)	4 (20l.8%)	7 (17.1%)
Focal segmental glomerulosclerosis	0	4 (30.8%)	3 (23.1%)	7 (17.1%)
Chronic kidney disease	0	3 (23.1%)	2 (15.4%)	5 (12.2%)
Vascular disorders	2 (13.3%)	8 (61.5%)	7 (53.8%)	17 (41.5%)
Hypertension	1 (6.7%)	7 (53.8%)	5 (38.5%)	13 (31.7%)
Nervous system disorders	10 (66.7%)	4 (30.8%)	2 (15.4%)	16 (39.0%
Immune system disorders	3 (20.0%)	4 (30.8%)	8 (61.5%)	15 (36.6%)
Blood and lymphatic system disorders	4 (26.7%)	5 (38.5%)	5 (38.5%)	14 (34.1%)
Anemia	0	3 (23.1%)	2 (15.4%)	5 (12.2%)
Cardiac disorders	5 (33.3%)	5 (38.5%)	4 (30.8%)	14 (34.1%)
Tachycardia	4 (26.7%)	2 (15.4%)	1 (7.7%)	7 (17.1%)
Respiratory disorders	5 (33.3%)	4 (30.8%)	5 (38.5%)	14 (34.1%)
Acute respiratory failure	3 (20.0%)	1 (7.7%)	1 (7.7%	5 (12.2%)
Metabolism and nutrition disorders	3 (20.0%)	5 (38.5%)	3 (23.1%)	11 (26.8%)
Infections and infestations	4 (26.7%)	2 (15.4%)	4 (30.8%	24.4%)
Gastrointestinal disorders	2 (13.3%)	4 (30.8%)	2 (15.4%)	8 (19.5%)
Congenital disorders	1 (6.7%)	3 (23.1%)	3 (23.1%)	7 (17.1%)
Endocrine disorders	1 (6.7%)	3 (23.1%)	3 (23.1%)	7 (17.1%)
Investigations	1 (6.7%)	2 (15.4%)	2 (15.4%)	5 (12.2%)
Skin and subcutaneous tissue disorders	1 (6.7%)	3 (23.1%)	1 (7.7%)	5 (12.2%)

Adapted from Table 14.1.6-2, page 114 of 707, Study report, October 18, 2019

4. Clinically significant findings at Screening

As shown in Table 5, the most common abnormal physical findings at Screening were neurological and respiratory abnormalities (20.0% each, green-shaded boxes) in the youngest age cohort (children aged 2 to <12 years). Less common were abnormalities of the cardiovascular and musculoskeletal systems, and the head, eyes, ears, nose and throat and endocrinological systems.

Table 5: Clinically Abnormal Findings at Screening (Safety Population, N=41)

Body System	Group 1 Age 2 to <12 N=15 (%)	Group 2 Age 12 to <17 N=13 (%)	Group 3 Age ≥17 N=13 (%)	All Subjects N=41 (%)
Neurological	3 (20.0%)	0	0	3 (7.3%)
Respiratory	3 (20.0%)	0	0	3 (7.3%)
Cardiovascular	1 (6.7%)	0	1 (7.7%)	2 (4.0%)
Musculoskeletal	1 (6.7%)	1 (7.7%)	0	2 (4.0%)
HEENT	1 (6.7%)	0	0	1 (2.4%)
Endocrinological	0	1 (7.7%)	0	1 (2.4%)
Other	0	1 (7.7%)	0	1 (2.4%)

Adapted from Table 14.1.8, page 151 of 707, Study report, October 18, 2019

5. Disposition

All 41 enrolled subjects completed the study.

Table 6: Disposition of Subjects (Safety Population, N=41)

	Group 1 Age 2 to <12 N=15 (%)	Group 2 Age 12 to <17 N=13 (%)	Group 3 Age ≥17 N=13 (%)	All Subjects N=41 (%)
Screened	15	13	13	41
Eligible but never treated	0	0	0	0
Enrolled	15	13	13	41
Treated	15	13	13	41

Adapted from Table 14.1.1, page 87 of 707, Study report, October 18, 2019

6. Protocol Violations

One major protocol deviation (dosing error) was reported for subject # (2.4%), a 14-year-old white female, blood group O, with an underlying diagnosis of septic shock. She was excluded from the PP Population due to a dosing error (she received a combination of Octaplas and FFP during TPE #3). No other major protocol deviations were reported.

There were 55 minor protocol violations. In subject # a screening pregnancy test was not performed, although a preganacy test prior to TPE 1 was negative. A Screening Chem 7 was not drawn in subject # the patient was screened on the same date as their TPE 1 and a Chem 7 was drawn prior to the initiation of TPE 1. The remaining 53 minor protocol deviations included 20 clinical laboratory samples drawn outside of the protocol window and 13 vital sign assessments that were not preformed. The iDMC reviewed all of the safety data including these minor protocol deviations.

7. Exposure to Study Drug

Overall, 102 TPEs were administered to 41 subjects. Table 7 shows that most subjects underwent 2 TPEs (median) via centrifugation at an infusion rate of 0.4 mL/kg/min. Adolescents received higher total doses (mL/kg) than children aged 2 to <12 years or young adults aged ≥17 years (green-shaded cell).

Table 7: Exposure to Study Drug (Safety Population, N=41)

	Group 1 Age 2 to <12 N=15 (%)	Group 2 Age 12 to <17 N=13 (%)	Group 3 Age ≥17 N=13 (%)	All Subjects N=41 (%)
Number of TPEs				
n	15	13	13	41
Mean (SD)	2.5 (1.4)	2.5 (1.8)	2.5 (1.5)	2.5 (1.5)
Median	2.0	1.0	2.0	2.0
Range	1-5	1-6	1-5	1-6
Volume of study drug administered				
n				
Mean (SD)	15	13	13	41
Median	1750.9	4838.1	3536.8	3296.0
Range	(2241.9)	(3602.8)	(2779.0)	(3107.31)
	800.0	3056.0	2779.0	2200.0
	200-7937	600-11891	500-9220	200-11891
Actual dose (mL/kg)				
n	15	13	13	41
Mean (SD)	67.4 (78.67)	96.8 (90.0)	49.9 (37.8)	71.2 (73.4)
Median	36.4	58.9	41.6	41.0
Range	4-275	10-283	7-135	4-283
Infusion rate (mL/kg/min)				
n	15	13	13	41
Mean (SD)	0.4 (0.1)	0.4 (0.1)	0.3 (0.1)	0.4 (0.1)
Median	0.4	0.4	0.3	0.4
Range	0.2-0.7	0.3-0.5	0.2-0.4	0.2-0.7
Type of machine used for TPE				
Filtration				
Centrifugation	2 (13.3%)	1 (7.7%)	0	3 (7.3%)
	13 (86.7%)	12 (92.3%)	13 (100.0%)	38 (92.7%)

Adapted from Table 14.1.10, page 158 of 707, Study report, October 18, 2019

8. Safety

8.1. Adverse events

TEs or TEEs were not found in any study subject. An unrelated SAE fatality was experienced by subject # following multiple organ failure secondary to sepsis (see 6.2 of this memo for additional information).

Overall, 8 ARs were reported in 4 subjects (9.8%). Table 8 shows that ARs (green shaded box) most commonly occurred in adolescent subjects (23.1%), and to a much lesser extent, young adults (7.7%).

Table 8: Summary of Safety Events by Age Group (Safety Populations, N=41)

	Group 1 Age 2 to <12 N=15 (%)	**Group 2 Age 12 to <17 N=13 (%)**	**Group 3 Age ≥17 N=13 (%)**	**All Subjects N=41 (%)**
Number of SAEs	**1**	**0**	**0**	**1**
No. of subjects with SAEs	1 (6.7%)	0	0	1 (2.4%)
95% CI	0.2%, 31.9%	N/A	N/A	0.1%, 13.0%
No. of SAEs/Number of TPEs	1/37	0/32	N/A	1/102
Number of ARs	**0**	**5**	**3**	**8**
No. of subjects with ADRs	0	3 (23.1%)	1 (7.7%)	4 (9.8%)
95% CI	N/A	5.0, 53.8	0.2, 36.0	2.7, 23.1
No. of ADRs/Number of TPEs	0/37	5/32	3/33	8/102
Number of TEs or TEEs	**0**	**0**	**0**	**0**
No. of TEs or TEEs/No. of TPEs	0/37	0/32	0/33	0/102
Number of ARs, SAEs, TEs and TEEs leading to Withdrawal	**1**	**0**	**0**	**1**
No. of subjects with ARs, SAEs, TEs and TEEs leading to death	1 (6.7%)	0	0	1 (2.4%)
95% CI	0.2%, 31.9%	N/A	N/A	0.1%, 12.9%
No. of ADRs, SAEs, TEs and TEEs leading to death/Number of TPEs	1/37	0/32	0/33	1/102

Adapted from Table 14.3.1.1-1.1, page 160 of 707, Study report, October 18, 2019

Table 9 shows that most ARs occurred early on during the study (green-shaded cells).

Table 9: Summary of Safety Events by TPE Number (Total TPEs: n=102)

	Group 1 Age 2 to <12 N=15 (%)	Group 2 Age 12 to <17 N=13 (%)	Group 3 Age ≥17 N=13 (%)	All Subjects N=41 (%)
TPE #1				
Number of subjects	15	13	13	41
Number of ARs	0	4 (31%)	2 (15%)	6
Number of subjects with ARs	0	0	0	4 (9.8%)
TPE #2				
Number of subjects	11	4	2	6
Number of ARs	0	0	1 (11.1%)	1 (3.8%)
Number of subjects with ARs	0	0	0	0
TPE #3				
Number of subjects	6	6	6	18
Number of ARs	0	0	0	0
Number of subjects with ARs	0	0	0	0
TPE #4				
Number of subjects	3	4	3	1
Number of ARs	0	1 (25.0%)	0	1
Number of subjects with ARs	0	0	0	1 (10.0%)
TPE #5				
Number of subjects	2	2	2	6
Number of ARs	0	0	0	0
Number of subjects with ARs	0	0	0	0
TPE #6				
Number of subjects	0	1	0	1
Number of ARs	0	0	0	0
Number of subjects with ARs	0	0	0	0

Adapted from Table 14.3.1.1-1.3, page 164 of 707, Study report, October 18, 2019

Table 10 shows that most ARs occurred in subjects with a medical history of renal and urinary disorders (green-shaded cell)

Table 10: Summary of Safety Events by Underlying Diagnosis (Safety Population, N=41)

	Immune Disorders N=14	Nervous Disorders N=12	Renal & Urinary Disorders N=8	Infections N=4	Other N=4	All Subjects N=41
Number of SAEs	0	0	0	1	0	1
No. of subjects with SAEs	0	0	0	1 (25.0%)	0	1 (2.4%)
Number of ARs	0	0	8	0	0	8
No. of subjects with ADRs	0	0	4 (50%)	0	0	4 (9%)
95% CI	N/A	N/A	15.8, 84.3	N/A	N/A	2,7, 23.1
Number of TEs or TEEs	0	0	0	0	0	0
Number of ARs, SAEs, TEs and TEEs leading to Withdrawal	0	0	0	0	0	0
Number of ARs, SAEs, TEs and TEEs leading to death						
No. of subjects with ADRs, SAEs, TEs and TEEs leading to death	0	0	0	1	0	1
	0	0	0	1 (25.0%)	0	1 (2.4%)

Adapted from Table 14.3.1.1-1.2, page 162 of 707, Study report, October 18, 2019

Table 11 summarizes ARs by age group and preferred term. Citrate toxicity was found only in adolescent subjects.

Table 11: Adverse Reactions by Age (Safety Population, N=41)

Preferred Term	Group 1 Age 2 to <12 N=15 (%)		Group 2 Age 12 to <17 N=13 (%)		Group 3 Age ≥17 N=13 (%)		All Subjects N=41 (%)	
	Subject N (%)	ARs n	Subjects N (%)	ARs n	Subjects N (%)	ARs n	Subjects N (%)	ARs n
Any AR	0	0	3 (23.1%)	5	1 (7.7%)	3	4 (9.8%)	8
Citrate toxicity	0	0	2 (15.4%)	2	0	0	2 (4.9%)	2
Headache	0	0	1 (7.7%)	1	0	0	1 (2.4%)	1
Pyrexia	0	0	1 (7.7%)	1	0	0	1 (2.4%)	1
Urticaria	0	0	1 (7.7%)	1	0	0	1 (2.4%)	1
Inflammatory marker increased	0	0	0	0	1 (7.7%)	1	1 (2.4%)	1
Myalgia	0	0	0	0	1 (7.7%)	1	1 (2.4%)	1
Nausea	0	0	0	0	1 (7.7%)	1	1 (2.4%)	1

Adapted from Table 14.3.1.3-2, page 172 of 707, Study report, October 18 2019

In summary, no ARs occurred in young children (Group 1). In contrast, 5 ARs occurred in Group 2 (N=3) during TPE #1 (n=4) and TPE #4 (n=1), and 3 ARs occurred in Group 3 (N=1) during TPE #1 (n=2) and TPE #2 (n=1). Most ARs occurred in subjects with a medical history of renal and urinary disorders. The most frequent AR was mild citrate toxicity (1 subject each) in Group 2 (N=2). Other ARs (1 subject each) included headache, pyrexia and urticaria in Group 2, and elevations in C-reactive protein and procalcitonin in Group 3. All

were of mild intensity (except for pyrexia, which was of moderate intensity) and all resolved by study end.

8.2. Narrative of Death and other SAEs

One death occurred during the study: subject # died following multiple organ failure secondary to sepsis due to streptococcus pneumonia during which time she received Octaplas from .

This was a 5 year old White female weighing 32.7 kg with B-cell acute lymphocytic leukemia in maintenance cycle 6 who presented with a 3-day history of a cough, increased lethargy, and decreased oral intake. She was admitted to the Pediatric Intensive Care Unit (PICU) on with respiratory failure, septic shock, neutropenia, tachycardia, and impending circulatory failure. A central line was placed the same day. The next day, venous-arterial (VA) extra corporeal membrane oxygenation (ECMO) was initiated for circulatory collapse. She experienced a significant right sided ischemic stroke (demonstrated by CT scan) on prior to ECMO decannulation the next day. An MRI performed on showed middle cerebral artery stroke without brainstem involvement. Continued multiorgan dysfunction was reported in the following days, up to On following discussion with the patient's family, a decision was made to institute comfort care. She was pronounced dead at later that day.
The reporter considered the event (multiple organ failure) as fatal and unrelated to study drug.

Reviewer comment

I concur with the investigator's assessment. The subject was at high risk of sepsis and none of the SAEs potentially associated with the product occurred in the subject.

8.3. Laboratory Values

For all hematology parameters, there were no marked changes from Pre-TPE to Post-TPE in the mean values for individual TPE infusions. Subjects in the renal and urinary disorders group had the lowest WBC counts, whereas subjects in the immune system disorders group had the highest WBC counts, with mean values ranging from 14.5 x 10^9/L to 22.1 x 10^9/L for the first 3 TPEs (elevated WBCs are frequently observed in subjects with immune system disorders taking glucocorticoids, as were most of these subjects).

For all chemistry parameters, there were no marked changes from Pre-TPE to Post-TPE in the mean values for individual TPE infusions. No patterns were observed with values increasing or decreasing or associated with the TPE number. The largest changes were observed for glucose values; these fluctuations were not unexpected as the samples could have been either fasting or non-fasting. No patterns were observed with values increasing or decreasing or associated with the TPE number, and no ADRs were reported associated with glucose results. Subjects in the immune system underlying disease category had the highest glucose levels, with mean values ranging from 159.5 mg/mL to 282.0 mg/mL for the first 3 TPEs as compared to mean values ranging between 94.6 mg/dL to 194.0 mg/dL for all other disease categories. This was not unexpected as elevated glucose levels are associated with

glucocorticoid use; most subjects (11/14, 79%) in the immune system underlying disease category received glucocorticoids during TPEs, as compared with 50% of subjects (4/8) with renal and urinary disorders or 33% of subjects (4/12) with nervous system disorders.

8.3.1. Ionized calcium

As shown in Table 12, no marked changes were observed in mean ionized calcium levels between Pre-TPE to Post-TPE and at the Follow-up Visit (green shading) or in median values for individual TPE infusions.

Table 12: Ionized Calcium (mmol/L) During the Study (Safety Population, N=41)

Timepoint/Visit	Pre-TPE	During TPE	Follow-Up
TPE 1 N=41			
N	39	38	30
Mean (SD)	1.23 (0.07)	1.13 (0.15)	1.19 (0.09)
Median	1.23	1.14	1.18
Range	1.05-1.34	0.60-1.40	1.06-1.42
Change from Pre-TPE 1			
N	-	36	
Mean (SD)	-	-0.09 (0.16)	-0.03 (0.09)
Median	-	-0.04	-0.04
Range	-	-0.63-0.08	-0.20-0.26
TPE 2 N=26			
N	23	23	16
Mean (SD)	1.21 (0.07)	1.19 (0.12)	1.20 (0.08)
Median	1.20	1.18	1.21
Range	1.07-1.38	1.00-1.53	1.07-1.37
Change from Pre-TPE 2			
N	-	20	14
Mean (SD)	-	-0.00 (0.1)	0.03 (0.12)
Median	-	0.00	0.02
Range	-	-0.17-0.28	-0.15-0.30
TPE 3 N=18			
N	18	15	12
Mean (SD)	1.17 (0.21)	1.18 (0.11)	1.22 (0.09)
Median	1.21	1.20	1.23
Range	0.34-1.31	0.90-1.36	1.07-1.39

8.4. Vital Signs

There were no ARs reported associated with vital signs. However, transfusion reactions (n=3) occurred in two subjects. Subject [redacted] experienced citrate toxicity with TPE 2 (10 Octaplas bags infused), while subject [redacted] experienced an episode of hypotension and citrate toxicity with TPE 1 (10 Octaplas bags infused) and an allergic reaction with TPE 4 (13 Octaplas bags infused).

8.5. Investigator's Assessment of Overall Safety

As shown in Table 13, overall safety assessed by investigators was 'excellent' for most subjects (>90%) 24 hours after each TPE throughout the study. There were 6 assessments of 'moderate' reported among 4 subjects (2 each for subjects #[redacted] and #[redacted] and 1 each for subjects #[redacted] and #[redacted] These were the same 4 subjects with ARs observed during the study. There were no assessments of overall safety as 'poor' for any subject.

Table 13 Investigator's Assessment of Overal Safety (Safety Population, N=41)

	All Subjects N=41
TPE 1 Subjects with investigator's assessment of overall safety (subject's experience with treatment)	41
Excellent	37 (90%)
Moderate	4 (10%)
Poor	0
TPE 2 Subjects with investigator's assessment of overall safety (subject's experience with treatment)	26
Excellent	25 (96%)
Moderate	1 (4%)
Poor	0
TPE 3 Subjects with investigator's assessment of overall safety (subject's experience with treatment)	18
Excellent	18 (100%)
Moderate	0
Poor	0
TPE 4 Subjects with investigator's assessment of overall safety (subject's experience with treatment)	10
Excellent	9 (90%)
Moderate	1 (10%)
Poor	0
TPE 5 Subjects with investigator's assessment of overall safety (subject's experience with treatment)	6
Excellent	6
Moderate	0
Poor	0
TPE 6 Subjects with investigator's assessment of overall safety (subject's experience with treatment)	1
Excellent	1 (100.0%)
Moderate	0
Poor	0

Adapted from Table 14.3.6.2, page 706 of 707, Study report, October 18, 2019

7. Safety Conclusions

This study was performed to evaluate the safety and tolerability of Octaplas administered to pediatric subjects who required TPE. A total of 102 TPEs were given to 41 subjects between 2 and 20 years of age, resulting in a total of 135,137 mL of Octaplas administered study-wide.

No TEs or TEEs were reported by the investigators nor identified by the iDMC during their quarterly review of the data. There were 8 ARs reported among 4 subjects during the study. The most frequently reported AR was mild citrate toxicity, with 2 events reported among 2 adolescent subjects. Other ARs reported in 1 subjects each included headache, inflammatory marker increased, myalgia, nausea, pyrexia, and urticaria. Most ARs (7/8, 87.5%) occurred in adolescent subjects and were mild and resolved by the end of the study. A unique AR of inflammatory marker increase was reported in a young adult whereas no ARs were reported in young children.

All 8 ARs in 4 subjects occurred in the underlying disease category of renal and

urinary disorders. No ARs were reported among subjects who received doses <40 to 60 mL/kg dose and at higher infusion rates than recommended in the protocol and the approved product labeling; these subjects were considered to have received a partial TPE. In the group treated per protocol specifications, the safety profile was as expected. One female subject aged 5 years with B-cell ALL leukemia had an unrelated multiple organ failure SAE with a fatal outcome. She was receiving TPE to treat septic shock. Laboratory assessments did not indicate any safety concerns and the majority of laboratory values were considered normal or abnormal but not clinically significant (NCS) by the investigators. There were transient abnormal clinically significant values (CS) for creatinine, BUN, WBC, potassium, and glucose values reported by the investigators during the study. None of these was related to study drug and was not unexpected in this population. Ionized calcium levels remained relatively stable from Pre-TPEs to Post-TPEs and at the 24-hour Post-TPE Follow-up Visits. There were 3 abnormal CS ionized calcium values reported by the investigators, 1 of which was related to study drug and reported as an ADR. One additional ADR of citrate toxicity was reported without a corresponding low ionized calcium level. No vital signs of note were identified.

The overall safety of Octaplas administered in this study population was assessed by the investigators as ‘excellent’ for more than 90% of subjects 24 hours after each TPE; the overall safety was assessed as ‘moderate’ for the 4 subjects who experienced ARs.