Application Type	BLA
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Division / Office	OTAT
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Priority Review	Yes
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Review Completion Date / Stamped Date	
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Applicant	ProMetic BioTherapeutics, Inc.
Established Name	Plasminogen (Human)
(Proposed) Trade Name	RYPLAZIM™
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	For intravenous use through a syringe disc filter after reconstitution
Dosing Regimen	6.6 mg/kg body weight given every two to four days
Indication(s) and Intended Population(s)	Replacement therapy in adults and children with congenital plasminogen deficiency.

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Glossary

AE	Adverse event
BP	Blood pressure
CGI-I	Clinical Global Impression-Global Improvement
FAS	Full Analysis Set
HL	Hispanic or Latino

IA	Interim Analysis (population)
IV	Intravenous
Lys-plasminogen	Modified plasminogen with an N-terminal lysine
MedDRA	Medical Dictionary for Regulatory Activities
NHL	Not Hispanic or Latino
PK	Pharmacokinetic(s)
SAE	Serious adverse event
SMC	Safety Monitoring Committee
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event

1. Executive Summary

There are no approved therapies to treat plasminogen deficiency (hypoplasminogenemia). ProMetic Bio Therapeutics, Inc. developed Plasminogen (Human) Intravenous Lyophilized Solution for the treatment of hypoplasminogenemia. The product is derived from pooled plasma donated by US blood donors and has undergone multiple steps of viral testing and inactivation. This submission is intended to support marketing approval for children and adults under an accelerated approval pathway via Study 2002C011G.

Study 2002C011G is an ongoing, Phase 2/3, single arm, open-label, repeat-dose study of the pharmacokinetics, efficacy, and safety of prometic plasminogen intravenous infusion in subjects with hypoplasminogenemia. The study consists of a screening period and three treatment segments. The primary surrogate endpoint for accelerated approval, PK, is the percent of subjects who achieve the target plasminogen activity trough levels for at least 3 biweekly measurements in 12 weeks during Segment 2. Efficacy data is also presented with the 12-week PK data. The primary efficacy endpoint of the complete study is overall clinical success, defined as 50% of subjects with visible lesions achieving at least a 50% improvement at 48 weeks in an average lesion size in subjects with lesions or functionality impact from baseline.

Of the 14 subjects (9 adult and 5 pediatric) enrolled in the study at the time of this interim analysis, 10 subjects (6 adult and 4 pediatric) are evaluable for the PK surrogate endpoint. All 10 subjects achieved the target plasminogen activity trough levels for at least 3 biweekly measurements in 12 weeks. In addition, the efficacy endpoint was achieved in all 10 subjects as evidenced by an overall clinical success rate of 100% (95% CI: 0.7411, 1)in subjects with visible lesions (eyes, nose, and gingiva) at baseline.

The primary safety endpoints were treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs). In addition to safety data from Study 2002C011G, safety data from Studies 2002C005G, (b) (6) and the Named Patient were also provided in support of the BLA. Study 2002C005G was a Phase 1, open-label, single-arm, single-ascending dose study of the PK and safety/tolerability of Plasminogen (Human) in adolescent and adult subjects with hypoplasminogenemia. Studies (b) (6) and the Named Patient were single subject studies. TEAEs occurred in all subjects, but no subject had a TEAE that resulted in permanent discontinuation of

study drug. Two subjects had severe TEAEs in Study 2002C011G and one subject in Study 2002C005G. There were no TESAEs in any subject across the four studies.

In summary, there were no statistical analysis issues in this submission. The indication of Plasminogen (Human) for replacement therapy in adults and children with plasminogen deficiency appears to be supported by the efficacy data provided. The small sample size and high variability of disease presentation did not allow formal statistical analyses for the efficacy endpoints.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Hypoplasminogenemia or type I plasminogen deficiency is a rare autosomal recessive genetic disorder that leads to a variety of significant clinical manifestations primarily associated with fibrous depositions on mucous membranes throughout the body. It is a multisystem disease that can affect the eyes, ears, nasal and oral cavities, sinuses, tracheobronchial tree, genitourinary tract, gastrointestinal tract, and gingiva. The most common clinical manifestation is ligneous conjunctivitis, which is characterized by thick, woody (ligneous) growths on the conjunctiva of the eye. If left untreated, ligneous conjunctivitis can lead to blindness. Most affected cases are infants and children showing their first clinical manifestation at a median age of approximately 10 months. In addition to ligneous conjunctivitis, hypoplasminogenemia can cause tracheobronchial lesions including abnormal membranes with poor pulmonary toilette that can result in chronic obstruction of the affected pulmonary segment or even respiratory failure. Hydrocephalus occurs in approximately 10% of children with severe hypoplasminogenemia, apparently related to the deposition of fibrin in the cerebral ventricular system.
Hypoplasminogenemia is listed as a rare disease by the National Institutes of Health (NIH) Office of Rare Diseases Research. Prevalence for hypoplasminogenemia is estimated at approximately 1.6 per 1,000,000.

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

Treatment options are limited as there are no approved therapies to treat this disease. Surgical intervention is confounded by the rapid regrowth of lesions, and local use of immunosuppressive, anti-inflammatory, antibiotic, or anticoagulant agents in patients with ligneous conjunctivitis has resulted in little clinical success.

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

Plasminogen is a normal component of human blood that is synthesized in the liver and is involved in both intravascular and extravascular fibrinolysis, wound healing, cell migration, tissue remodeling, angiogenesis, and embryogenesis. There are several reports of the systemic use of modified plasminogen with an N-terminal lysine (Lys-plasminogen) as potential replacement therapy in patients with ligneous conjunctivitis. However, Lys-plasminogen is no longer available and would be a more limited treatment option due to its relatively short half-life and difficulty of maintaining normal or near normal levels of plasminogen activity in the blood.

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

A pre-IND meeting was held between representatives of ProMetic BioTherapeutics, Inc. and the FDA on October 24, 2014, under CRMTS #9540-PS002306. At this meeting the FDA stated that the increase in the plasminogen activity trough level by at least 10% (absolute, not relative change) appears to be an adequate surrogate endpoint for licensure using the accelerated approval pathway given it is reasonably likely to predict clinical benefit. However, under this program, post-licensure confirmatory studies must be conducted to verify the clinical benefit of the surrogate endpoint.

A pre-BLA meeting was held on June 16, 2016, under IND 16186/CRMTS #10257. CMC issues were mainly addressed at this meeting. In addition, the FDA clarified that accelerated approval would be based on the 12-week endpoints of PK and safety. ProMetic stated available efficacy data would be presented with the 12-week PK data in the BLA.

On April 4, 2017, FDA received BLA 125647 for this same product/indication. On June 1, 2017, the FDA issued the Refuse to File letter for CMC and Pharmacology/Toxicology deficiencies. The revised BLA was submitted to the FDA on August 14, 2017 and was filed under the number BLA 125659 on October 12, 2017. Along with this original BLA submission, the sponsor submitted a request for Priority Review for the BLA. The product was granted Priority Review designation on October 12, 2017 for treatment of type I plasminogen deficiency.

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

5.1 Review Strategy

The applicant submitted data from four clinical studies: Phase 2/3 repeat-dose pharmacokinetics (PK), efficacy, and safety Study 2002C011G (IND 16186); Phase 1 dose escalation and pharmacokinetic Study 2002C005G; single patient repeat-dose Study (b) (6) in an adult with hypoplasminogenemia; and treatment of a 22-month-old infant with hypoplasminogenemia in Named Patient study. No other clinical studies were conducted for this product. Studies 2002C005G, (b) (6) , and Named Patient did not address efficacy.

The provided material for Study 2002C011G is the basis for the statistical review and is discussed in Section 6. The study is ongoing, and the cut-off date for the interim analysis presented in this BLA is November 30, 2016; this interim dataset is used for the efficacy and safety evaluation in the submission.

Section 8 integrates the safety data for Studies 2002C011G, 2002C005G, (b) (6) and the Named Patient.

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

BLA 125659/0

Module 1.14.1.3	Draft Labeling Text
Module 2.5	Clinical Overview
Module 2.7.3	Summary of Clinical Efficacy
Module 2.7.6	Synopses of Individual Studies
Module 2.7.4	Summary of Clinical Safety
Module 2.7.6	Synopses of Individual Studies
Module 5.2	Tabular Listing of All Clinical Studies
Module 5.3.5.2	2002C011G – A Phase 2/3, Open-Label, Repeat-Dose Study of the Pharmacokinetics, Efficacy: Study Report Body, Protocol or Amendment, Statistical Methods Interim Analysis Plan, Demographic Data, Data Tabulation Data, Data Analysis Data
Module 5.3.3.2	2002C05G - A Phase 1, Dose Escalation and Pharmacokinetic Study: Study Report Body, Protocol or Amendment, Demographic Data

5.3 Table of Studies/Clinical Trials

The clinical development program for Plasminogen (Human) is summarized in Table 1.

Table 1: Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK and Safety	2002C005G	5.3.3.2.1	Define PK; IMM; Assess safety/ tolerability	Open-label, single-arm, no control	Plasminogen (Human); 2 mg/kg and 6 mg/kg single dose, IV	12 [a] (7 unique)	Hypoplasminogenemia	Single dose	Complete; Full
Efficacy and Safety	2002C011G	5.3.5.2.1	12-week PK of PLG activity; 48-week efficacy; IMM; Safety	Open-label, single-arm, no control	Plasminogen (Human); 6.6 mg/kg IV, every second, third, or fourth day	14 [b]	Hypoplasminogenemia	12 weeks (interim analysis) 48 weeks (full analysis)	Ongoing; Interim (data cut-off date of 30Nov2016)
Single-Patient Efficacy and Safety	(b) (6) (Expanded Access [compassionate-use])	NA	Treat subject with hypoplasminogenemia	Single-patient, expanded access, open-label, no control	Plasminogen (Human); 6 mg/kg [c] IV, every second, third, or fourth day	1	Hypoplasminogenemia	48 weeks	Ongoing; Narrative
Single-Patient Efficacy and Safety	Named Patient (compassionate-use)	NA	Treat subject with hypoplasminogenemia	Single-patient, Named Patient, open-label, no control	Plasminogen (Human); 6.5 mg/kg [c] IV, every second, third, or fourth day	1	Hypoplasminogenemia	Not specified	Ongoing; Narrative

MM = immunogenicity; IV = intravenous; NA = not applicable; PK = pharmacokinetics.
[a] The same 5 subjects received a single dose of 2 mg/kg and a single dose of 6 mg/kg; 2 additional subjects received a single dose of 6 mg/kg.
[b] Includes 6 subjects who also participated in Cohort 2 (6 mg/kg) of the Phase 1 study 2002C005G.
[c] After efficacy was established in these studies, the dose was switched to 6.6 mg/kg
Source: "BLA 125659/1, Module 5.2, Tabular Listing of All Clinical Studies, Table 5.2.1"

6. Discussion of Individual Studies/Clinical Trials

Insert text here

6.1 Trial #1

Study 2002C011G is entitled "A Phase 2/3, Open-Label, Repeat-Dose Study of the Pharmacokinetics, Efficacy, and Safety of Prometic Plasminogen Intravenous Infusion in Subjects with Hypoplasminogenemia."

6.1.1 Objectives (Primary, Secondary, etc)

The primary objectives of the study are:

- To achieve an increase of individual plasminogen activity trough levels by at least an absolute 10% (i.e., 10 U/dL) for at least three biweekly measurements above baseline in adult and pediatric subjects with hypoplasminogenemia during the 12 weeks of plasminogen replacement therapy in Segment 2
- To evaluate the efficacy of plasminogen replacement therapy on clinically evident or visible symptoms of hypoplasminogenemia during the 48 weeks of dosing in Segments 2 and 3.

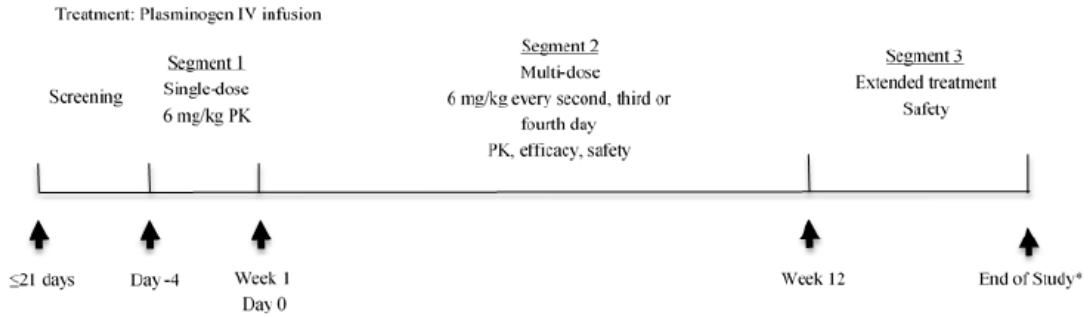
The secondary objectives of the study are:

- To evaluate the safety and tolerability of plasminogen replacement therapy during the 48 weeks of dosing
- To evaluate the efficacy of plasminogen replacement therapy on clinically evident or visible symptoms of hypoplasminogenemia during the 12 weeks of dosing in Segment 2
- To evaluate the effect of plasminogen replacement therapy on PK and immunogenicity during the 48 weeks of dosing.

6.1.2 Design Overview

Study 2002C011G is a Phase 2/3, open-label, single-arm, repeat-dose study evaluating the PK, safety, and efficacy of replacement therapy with Plasminogen (Human) Intravenous in adult and pediatric subjects with hypoplasminogenemia. The study consists of a screening period and three treatment segments as illustrated in Figure 1. Subjects who had documented individual PK profiles with the Applicant (due to their participation in Study 2002C005G, where they received a 6 mg/kg dose of study drug) did not need to undergo Segment 1 and proceeded directly to Segment 2. At the end of Segment 2, subjects have the option to participate in Segment 3. The duration of the study for subjects consists of 21 days of screening, 4 days for Segment 1, 48 weeks of treatment (12 weeks for Segment 2 and 36 weeks for Segment 3), and 30 days for safety follow-up.

Figure 1: Study 2002C011G Design Schematic



IV = intravenous; PK = pharmacokinetic(s); The actual dose was 6.6 mg/kg not 6 mg/kg. *End of study = Week 48 in Norway and product licensing or study termination by Applicant in the USA. A Safety Follow-up visit is required 30 days after the last dose of study drug in any segment.
"Source: BLA 125659, Module 5.3.5.2, 2002C011G - A Phase 2/3, Open-Label, Repeat-Dose Study of the Pharmacokinetics, Efficacy, and Safety of Prometic Plasminogen Intravenous Infusion in Subjects With Hypoplasminogenemia; Protocol and Protocol Amendment, Figure 1"

Segment 1

Subjects who did not have documented individual PK profiles with the Applicant received a single dose of study drug on Day 4. Blood samples for PK analysis were to be collected prior to infusion and subsequently through 96 hours after completion of the infusion to establish individual PK profiles. The sample collected prior to infusion (Day 4) was used to measure the subject's baseline plasminogen activity, plasminogen antigen, and D-dimer levels. The last PK sample (96 hours post infusion) was to be collected on Week 1, Day 0, before the administration of the first dose in Segment 2. The resulting PK profile was used to determine each subject's dosing interval in Segment 2.

Segment 2
Subjects were to receive repeat doses of study drug every second, third, or fourth day for 12 weeks during Segment 2 for a total of approximately 21 to 42 doses.

For subjects who do not participate in Segment 1 and directly enter Segment 2, baseline assessments were conducted before the first dose of Plasminogen IV infusion, including a blood sample to measure the baseline plasminogen activity and antigen as well as D-dimer levels. Their dosing intervals were every second, third, or fourth day, depending on each subject's PK profile on file.

Subjects who have gone through Segment 1 started with the every-third day dosing interval until their individual PK results become available. This initial dosing regimen is based upon the aggregate PK obtained from the Phase 1 study. Once each subject's individual PK profile became available, his or her dosing interval was adjusted to every second, third, or fourth day accordingly.

The first dose of study drug in Segment 2 was administered at the study site on Week 1, Day 0. Subjects visited the study sites every four weeks and received study drug. The infusions between study visits were to be administered at the study site or an ancillary site by study personnel or, for USA subjects only, at the subject's home by a home health nurse, by the subject (i.e., self-administration), or by a caregiver/family member. The final dose at the Week 12 visit (or at study discontinuation) was to be administered at the study site to allow for a repeat PK profile.

At the end of Segment 2, subjects have the option to participate in Segment 3. Subjects for whom there was no perceived or anticipated benefit from further dosing were not to be enrolled in Segment 3 at the Investigator's discretion and based on discussion with the Safety Monitoring Committee (SMC) and the Applicant. Any subject who discontinued the study during or at the end of Segment 2 was to return to the study site for a Safety Follow-up visit 30 days after the final dose of study drug.

Segment 3
Subjects who participate in Segment 3 will continue receiving study drug for an additional 36 weeks in Norway, and until product licensing or study termination by the Applicant for subjects in the USA. Subjects will return to the study sites for assessments every 12 weeks to monitor clinical status and plasminogen activity trough levels. Subjects will be given a diary to record the dates of study drug administration, any AEs, concomitant medication, and other relevant information. All subjects in Segment 3 will return to the study site for a Safety Follow-up visit 30 days after the final dose of study drug.

6.1.3 Population

- Subject was male or female between the ages of 2 and 80 years (inclusive).
- Subject had a documented history of lesions and symptoms consistent with a diagnosis of hypoplasminogenemia.

- Subject had plasminogen activity level ≤ 45%.

6.1.4 Study Treatments or Agents Mandated by the Protocol

In Segment 1, per the protocol a single dose of 6 mg/kg Plasminogen was to be administered to each subject. After the start of this study, Plasminogen (Human) Intravenous underwent further manufacturing process characterization resulting in a change of the stated plasminogen concentration. Consequently, the stated Plasminogen (Human) Intravenous dose levels also had to be changed from 6 mg/kg to 6.6 mg/kg in order to not have an actual change in the dose administered (as reported in Section 9.8.2 of the Main Study Report). However, the protocol was not amended to prevent confusion. Therefore, the actual dose was 6.6 mg/kg not 6 mg/kg.

In Segment 2, per the protocol repeated doses of 6 mg/kg Plasminogen was to be administered every second, third, or fourth day, depending on individual PK profile. As in Segment 1, the actual dose was 6.6 mg/kg not 6 mg/kg.

The dosage and dosing interval in Segment 3 will be the same as Segment 2, with the option of modification based on clinical response and plasminogen activity trough levels. In the event a subject does not achieve the expected or optimum clinical response by the completion of Segment 2, the Principal Investigator will reduce the dosing interval during Segment 3 by 1-day increments until the plasminogen activity trough level exceeds 45%.

6.1.6 Sites and Centers

This study is being conducted at one site each in the USA and Norway; however, the interim analysis (IA) only includes subjects at the USA site as none of the subjects in Norway completed Segment 2 dosing.

6.1.8 Endpoints and Criteria for Study Success

The primary PK endpoint, percent of subjects who achieve the target plasminogen activity trough levels for at least 3 measurements in 12 weeks during Segment 2, will be reviewed by the clinical pharmacologist.
The primary efficacy endpoint was the overall clinical success in number and size of lesions, as measured by photographic or other imaging modality depending on the organ system affected, or change in affected organ functionality at 48 weeks.

Overall clinical success was defined as 50% of subjects with visible or other measurable lesions achieving at least a 50% improvement in lesion number/size or functionality impact from baseline.

Clinical success was further described as a graded evaluation of potential clinical responses: 1) Excellent response: > 75% decrease; 2) Good response: > 50% and < 75% reduction; 3) Moderate response: > 25% to < 50% reduction; 4) Minimal response: < 25% reduction; and 5) No response: an increase or no reduction in the size of the lesion. Clinical responses were determined by the Principal Investigator for the assessment of clinical success.

Secondary endpoints

1) the overall clinical success in number and size of lesions as measured by photographic or other imaging modality depending on the organ system affected or change in affected organ functionality at 12 weeks;
2) Clinical Global Impression-Global Improvement (CGI-I) scores at 12 and 48 weeks; and
3) quality of life scores at 12 and 48 weeks. CGI-I and quality of life data were presented descriptively by individual subjects.

Safety Endpoints

The primary safety endpoints were treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs). Safety endpoints included also all vital signs.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

Approximately 15 subjects aged 2 to 80 years with hypoplasminogenemia were to be enrolled to ensure a sample size of at least 10 PK-evaluable subjects, with at least 2 pediatric subjects 2 to 18 years of age.

No formal calculation was made for sample size because of the rarity of the disease. The sample size is based on known subjects who have hypoplasminogenemia.

Analysis Populations

There were four analysis populations:

• Full Analysis Set (FAS) Population: Included any subject who received at least one dose of study drug and provided data for at least one post-baseline efficacy assessment. The FAS Population was used for the final analysis of efficacy.

• IA Population: Included any subject who completed Segment 2 dosing and provided data for at least one post-baseline efficacy assessment. The IA population was used for the interim analysis of efficacy.

• PK Population: Included any subject who had completed Segment 2 dosing and had provided at least 3 blood samples to measure plasminogen activity trough levels. The PK Population was used for all PK analyses.

• Safety Population: Included any subject who received at least one dose of study drug and provided safety data for at least one non-screening visit. Safety analysis was based on the Safety Population. The first safety analyses were based on Segment 2 (Week 12) data after Segment 2 was complete. The second safety analyses were to be based on combined Segment 1, 2 and 3 data at the end of Week 48, and the final safety analyses were to be based on all subjects who completed the final safety visit or remained in the study in Segment 3 (USA subjects only).

Statistical Methods

Summary statistics were used for the primary (PK and efficacy), secondary efficacy and safety endpoints.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 14 subjects (9 adult and 5 pediatric) have enrolled in the study through the data cut-off date at one site in the USA (n = 11) and one site in Norway (n = 3). Ten subjects (6 adult and 4 pediatric) completed Segment 2 and had at least 3 measurements of plasminogen activity trough (PK Population; see Table 2). These same 10 subjects had efficacy assessments through Week 12 (IA Population). All 14 subjects received at least one dose of study drug and had at least one post-baseline safety assessment (Safety Population). The FAS Population was not applicable to the IA.

Table 2: Summary of Data Analysis Populations

Data Analysis Population	Subject Population		
	Adult	Pediatric	Combined
PK	6	4	10
Interim Analysis	6	4	10
Safety	9	5	14
Full Analysis Set	9	4	13

Source: "BLA 125659, Module 5.3.5.2, 2002C011G - A Phase 2/3, Open-Label, Repeat-Dose Study of the Pharmacokinetics, Efficacy, and Safety of Prometic Plasminogen Intravenous Infusion in Subjects With Hypoplasminogenemia; Study Report Body; Main Study Report, Table 12"

Three adult subjects and one pediatric subject were excluded from the PK and IA Populations because they had not completed Segment 2 dosing as of the data cut-off date (see Table 3). Subject (b) (6) was also excluded from the FAS Population because he did not have a post-baseline efficacy assessment as of the data cut-off date.

Table 3: Listing of Subjects Excluded from the PK and IA Populations

Subject ID	Site	Reason Subject Was Excluded from PK/IA Populations
(b) (6) (Pediatric)	USA	Segment 2 not completed; no post-baseline efficacy assessment
(Adult)	Norway	Segment 2 not completed
(Adult)	Norway	Segment 2 not completed
(Adult)	Norway	Segment 2 not completed

Site 01 = USA; Site 02 = Norway.
Source: "BLA 125659, Module 5.3.5.2, 2002C011G - A Phase 2/3, Open-Label, Repeat-Dose Study of the Pharmacokinetics, Efficacy, and Safety of Prometic Plasminogen Intravenous Infusion in Subjects with Hypoplasminogenemia; Study Report Body; Main Study Report, Table 13"

6.1.10.1.1 Demographics

There were nine adult subjects and five pediatric subjects; of the five pediatric subjects, three were children and two were adolescents. The mean age (range) of the combined

subject population was 24.4 years (5-42 years); most subjects were female (71.4%) and non-Hispanic or Latino (92.9%), and all subjects were White.

- In the adult population, the mean age (range) was 31.9 years (20-42 years); most were female (66.7%), and all were White and non-Hispanic or Latino.
- In the pediatric population, the mean age (range) was 10.8 years (5-16 years); most were female (80.0%) and not-Hispanic or Latino (80.0%), and all were White (see Table 4).

Table 4: Demographics and Baseline Characteristics (Segment 1 and 2) (Safety Population) Adult and Pediatric Population Combined

Demographics and Baseline Characteristics	Overall (N=14)
Age (Years)	
N	14
Mean (SD)	24.4 (12.39)
Median	24.0
Min, Max	5, 42
Age Group (Years)	
2 - 11	3 (21.4%)
12 - 17	2 (14.3%)
> 17	9 (64.3%)
Gender	
Male	4 (28.6%)
Female	10 (71.4%)
Ethnicity	
Hispanic or Latino	1 (7.1%)
Not Hispanic or Latino	13 (92.9%)
Race	
American Indian or Alaska Native	0
Asian	0
White	14 (100%)
Black or African American	0
Native Hawaiian or Other Pacific Islander	0
Other	0

"Source: "BLA 125659, Module 5.3.5.2, 2002C011G - A Phase 2/3, Open-Label, Repeat-Dose Study of the Pharmacokinetics, Efficacy, and Safety of Prometic Plasminogen Intravenous Infusion in Subjects with Hypoplasminogenemia; Study Report Body, Tables: Table 14.1.2a"

6.1.10.1.2 Medical /Behavioral Characterization of the Enrolled Population

All subjects had past and/or concomitant diseases or past surgeries, but none of these medical histories met any of the exclusion criteria for the study. Medical history also captured some past/current symptoms/lesions of hypoplasminogenemia (e.g., eye and ear disorders, infections, and lung problems) but not for all subjects.

6.1.10.1.3 Subject Disposition

Of the 14 subjects enrolled, eight subjects completed Segment 1 and 10 subjects completed Segment 2 as of the data cut-off date (see Table 5). All 10 subjects who completed Segment 2 were enrolled at the USA site.

Table 5: Summary of Subject Disposition by Segment, All Enrolled

Parameter	Segment 1			Segment 2		
	Subject Population			Subject Population		
	Adult	Pediatric	Combined	Adult	Pediatric	Combined
Subjects enrolled	4	4	8	9	5	14
Screen failures	0	0	0	0	0	0
Completed segment	4	4	8	6	4	10
Discontinued study	0	0	0	0	0	0

"Source: "BLA 125659, Module 5.3.5.2, 2002C011G - A Phase 2/3, Open-Label, Repeat-Dose Study of the Pharmacokinetics, Efficacy, and Safety of Prometic Plasminogen Intravenous Infusion in Subjects With Hypoplasminogenemia; Study Report Body; Main Study Report; , Table 10"

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary PK endpoint will be reviewed by the clinical pharmacologist.

6.1.11.2 Analyses of Secondary Endpoints

Of the 10 subjects included in the IA population, 6 subjects (4 adult and 2 pediatric) had 15 visible lesions and 2 subjects had non-visible lesions only. Since assessment of non-visible lesions was to be performed at the investigator's discretion, only 6 non-visible lesions in 4 subjects (3 adult and 1 pediatric) were assessed as part of the interim analysis. Overall clinical success was achieved as all 6 subjects with visible lesions at baseline achieved at least a 50% improvement in an average lesion size in subjects with visible lesions from baseline after 12 weeks of treatment; this equated to a 100% response rate, meeting the success criterion. Of the 15 visible lesions at baseline, 14 lesions (93.3%) completely resolved and one lesion (right eye, upper lid) showed nearly complete resolution as the lesion was too small to measure. In addition, no new lesions appeared during this time (see Table 6).

Table 6: Effect of Plasminogen (Human) Intravenous on Adult and Pediatric Subjects with Visible Measurable or Visible Non-Measurable Lesions through Week 12, IA Population

Lesion Assessment	Subject Population											
	Adult				Pediatric				Combined Adult and Pediatric			
	BL [a] (N=4)	Wk4 (N=4)	Wk8 (N=4)	Wk12 (N=4)	BL [a] (N=2)	Wk4 (N=2)	Wk8 (N=2)	Wk12 (N=2)	BL [a] (N=6)	Wk4 (N=6)	Wk8 (N=6)	Wk 12 (N=6)
Visible lesions	12	0	0	0	3	2	1	1 [c]	15	2	1	1 [c]
New lesions	---	0	0	0	---	0	0	0	---	0	0	0
Resolved	---	12	12	12	---	1	2	2	---	13	14	14
% Resolved	---	100	100	100	---	33.3	66.7	66.7	---	86.7	93.3	93.3
Measurable visible lesions	3	0	0	0	3	2	1	0	6	2	1	0
New lesions	---	0	0	0	---	0	0	0	---	0	0	0
Response [b]												
Excellent (≥ 75% resolved)	---	3 100%	3 100%	3 100%	---	3 100%	3 100%	3 100%	---	6 100%	6 100%	6 100%

--- = no data available; BL = baseline; N = number of subjects with a visible lesion at baseline; Wk = Week.
[a] Baseline is defined as Day 4 for subjects started in Segment 1 or Day 0 for new subjects started in Segment 2.
[b] Response is defined as the percent change of the total area of raw measurements of visible lesions.
[c] Lesion changed from visible, measurable (5 mm × 2 mm) to visible, non-measurable.
Note: Visible lesions that had both a length and width were referred to as "measurable lesions," and visible lesions that were too small to measure (length and/or width could not be measured) were referred to as "non-measurable lesions."
Source: "BLA 125659, Module 5.3.5.2, Study Report Body; Main Study Report; Table 26"

6.1.11.3 Subpopulation Analyses

No subgroup analyses were necessary since the success rate was 100%.

6.1.11.4 Dropouts and/or Discontinuations

No subject completed or discontinued the study as of the data cut-off date.

6.1.12 Safety Analyses

6.1.12.3 Deaths

There were no deaths in the study.

6.1.12.4 Nonfatal Serious Adverse Events

No SAE or TESAE was reported.

6.1.12.5 Adverse Events of Special Interest (AESI)

Two subjects experienced severe TEAEs. One of them experienced one severe TEAE and another experienced seven severe TEAEs.

8. Integrated Overview of Safety

No statistical analysis plan was provided by the applicant for this analysis.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

In addition to safety data from Study 2002C011G, safety data from Studies 2002C005G, (b) (6) and the Named Patient were also provided in support of the BLA. Study 2002C005G was a Phase 1, open-label, single-arm, single-ascending dose study of the PK and safety/tolerability of Plasminogen (Human) in adolescent and adult subjects with hypoplasminogenemia. Studies (b) (6) and the Named Patient were single subject studies; summaries of all four studies can be found in Table 1.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The pooled data for all four studies are presented in Table 7.

Table 7: Pooled Demographics and Exposure Data

Study	2002C011G N=14	2002C005G N=7	(b) (6) N=1	Named Patient N=1
Age(years)				
median	24	23	33	1.8
range	5 - 42	13 – 37[1]	33	1.8
Sex				
male	4	2	1	1
female	10	5	0	0
Race				
white	14	7	1	1
Dose				
2mg/kg		5		
6mg/kg	14	7[2]	1	1
Exposure	every 2, 3, or 4 days. Duration 12 weeks (interim analysis) 48 weeks (full analysis)	1 day	every 2, 3, or 4 days during 12 months	every 2 days Duration not specified

[1] Two subjects, who were both exposed to 2 mg/kg and 6mg/kg, were adolescents.
[2] There were seven unique subjects. Five subjects were exposed to 2 mg/kg and 6mg/kg, and two additional subjects were exposed to 6 mg/kg dose only.

8.4 Safety Results

8.4.1 Deaths
No deaths were observed.

8.4.2 Nonfatal Serious Adverse Events
There were no TESAEs in any subject across the four studies.

8.4.8 Adverse Events of Special Interest

Three subjects experienced severe TEAEs. One subject experienced one severe TEAE, one subject experienced seven severe TEAEs and one subject experienced two severe TEAEs. No subject had a TEAE that resulted in permanent discontinuation of study drug. No subject had a TEAE that was considered possibly, probably, or definitely related to study drug.

10. Conclusions

10.1 Statistical Issues and Collective Evidence

Efficacy

Only one phase 2/3 efficacy and safety study was implemented (Study 2002C011G). The study consisted of 48 weeks of treatment (4 days for Segment 1, 12 weeks for Segment 2, and 36 weeks for Segment 3), and 30 days for safety follow-up. For subjects in the USA, treatment could continue after 48 weeks until product approval or Applicant decision. A total of 14 subjects (9 adult and 5 pediatric) have enrolled in the study up to the data cut-off date for the IA (November 30, 2016). Of the 10 subjects included in the IA population, 6 subjects (4 adult and 2 pediatric) had 15 visible lesions.

The primary PK endpoint of the IA, a surrogate primary endpoint for the accelerated approval pathway, is reviewed by the clinical pharmacologist.

The clinical efficacy endpoint for the accelerated approval pathway was achieved in both adult and pediatric subjects as evidenced by an overall clinical success rate of 100% (6/6 subjects) in subjects with visible lesions (eyes, nose, and gingiva) at baseline following 12 weeks of treatment with 6.6 mg/kg Plasminogen (Human) Intravenous administered every second, third, or fourth day.

Safety

There were no deaths or TESAEs in any subject across the four studies (2002C011G, 2002C005G, (b) (6) and Named Patient) in the clinical development program for Plasminogen (Human). Furthermore, there were no TEAEs that resulted in permanent discontinuation of Plasminogen (Human) in any subject across the four studies; none of the TEAEs were considered possibly, probably, or definitely related to study drug. However, three subjects experienced severe TEAEs (two subjects in Study 2002C011G and one subject in 2002C005G).

10.2 Conclusions and Recommendations

There were no statistical issues in this submission. Results of Study 2002C011G appear to support the use of Plasminogen (Human) (RYPLAZIM™) as a replacement therapy in adults and children with congenital plasminogen deficiency.