BLA Clinical Review Memorandum

Application Type	Original BLA
STN	125659/0
CBER Received Date	August 14, 2017
PDUFA Goal Date	June 5, 2021
Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Gavin Imperato, M.D., Ph.D. Medical Officer, GMB2/DCEPT/OTAT
Review Completion Date / Stamped Date	May 27, 2021
Supervisory Concurrence	Jasmine Gatti, M.D. Team Lead, GMB2/DCEPT/OTAT Lei Xu, M.D., Ph.D. Chief, GMB2/DCEPT/OTAT Ilan Irony, M.D. Deputy Director, DCEPT/OTAT
Applicant	Prometic BioTherapeutics
Established Name	plasminogen, human-tvmh
Trade Name	RYPLAZIM
Pharmacologic Class	Blood Component
Formulation(s), including Adjuvants, etc.	Lyophilized Glu-plasminogen (68.8 mg per vial) reconstituted with 12.5 mL Sterile Water for Injection and passed through a syringe disc filter contains 5.5 mg/mL Glu-plasminogen in (b) (4) sodium citrate, (b) (4) sodium chloride, (b) (4) glycine, and (b) (4) sucrose.
Dosage Form(s) and Route(s) of Administration	6.6 mg/kg of plasminogen, human as a 10- to 30-minute IV infusion using a syringe
Dosing Regimen	One infusion administered every 2 to 4 days
Indication(s) and Intended Population(s)	Treatment of patients with plasminogen deficiency type I (hypoplasminogenemia)
Orphan Designated (Yes/No)	Yes

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GLOSSARY

ADR	Adverse Drug Reaction
AE	Adverse Event
AUC	Area under the curve
BIMO	CBER Bioresearch Monitoring Program
BLA	Biologics license application
Cmax	Maximum concentration
CBC	Complete blood count
CBER	Center for Biologics Evaluation and Research
CGI-I	Clinical Global Impression – Global Improvement Scale
CI	Confidence interval (95%, unless otherwise specified)
CMC	Chemistry, manufacturing, and controls
CT	CAT scan
DCEPT	Division of Clinical Evaluation and Pharmacology/Toxicology
FFP	Fresh Frozen Plasma
GCP	Good Clinical Practices
HL	Hispanic or Latino
IND	Investigational New Drug application
IV	Intravenous
kg	Kilogram
mg	Milligram
MRI	Magnetic resonance imaging
NHL	Not Hispanic or Latino
OTAT	Office of Tissues and Advanced Therapies
PDUFA	Prescription Drug User Fee Act
PFT	Pulmonary function test
PI	Prescribing Information; Package Insert
PK	Pharmacokinetics
PLG	Plasminogen
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PREA	Pediatric Research Equity Act
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
TEAE	Treatment-emergent adverse event
US	United States

1. EXECUTIVE SUMMARY

Plasminogen, human-tvmh (proprietary name: RYPLAZIM) is a lyophilized preparation of purified, human plasma-donor derived Glu-plasminogen, which is the native form of plasminogen that contains a glutamic acid residue at the N-terminus. The proposed indication for RYPLAZIM is for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia), a rare disease primarily affecting the pediatric population.

Plasminogen deficiency type 1 is a rare autosomal recessive genetic disorder of hemostasis. Plasminogen is a normal component of human blood that is cleaved to form plasmin, which is the main effector of fibrinolysis in human circulation. Biallelic mutations in the *plasminogen* (*PLG*) gene result in reductions in both the serum plasminogen antigen and activity level. Patients with plasminogen deficiency type 1 due to these mutations experience substantial disease-related morbidity from ligneous lesions, which are thick, woody deposits that primary affect the eye (ligneous conjunctivitis), and can cause life-threatening loss of organ function depending on the anatomical location and severity of the lesions. Ligneous lesions recur despite surgical removal, and there are no approved therapies for the treatment of plasminogen deficiency type 1.

RYPLAZIM is intended to be reconstituted, passed through a syringe disc filter, and administered by intravenous (IV) infusion at a dose of 6.6 mg/kg body weight. Due to its short *in vivo* half-life, RYPLAZIM is intended to be administered every two to four days to have durable clinical effects on ligneous lesions.

The efficacy of RYPLAZIM in pediatric and adult patients with plasminogen deficiency type 1 was evaluated in a single-arm, open-label Phase 2/3 clinical trial (Study 2002C011G). A total of 15 subjects with plasminogen deficiency type 1 due to biallelic mutations in the *PLG* gene were enrolled. All subjects had a baseline plasminogen activity level between <5% and 45% of normal. Fourteen subjects had disease manifestations starting during childhood ranging from infancy to 10 years of age. One subject was diagnosed at age 22 years with unknown age of symptom onset. The age range of these subjects was 4 to 42 years, including 6 pediatric subjects age 4 to 16 years, and 9 adults. Eleven subjects were female. All subjects were White. All subjects received RYPLAZIM at a dose of 6.6 mg/kg administered every 2 to 4 days for 48 weeks to treat the clinical manifestations of the disease and to achieve at least an increase of individual trough plasminogen activity by an absolute 10% above baseline.

Efficacy was established on the basis of overall rate of clinical success at Week 48. Overall rate of clinical success is defined as 50% of subjects with visible or other measurable non-visible lesions achieving at least a 50% improvement in lesion number or size, or improvement in spirometry for subjects with pulmonary lesions causing impaired pulmonary function compared to baseline. Eleven subjects, including 3 pediatric subjects, had lesions at baseline. All subjects with any lesion at baseline had at least 50% improvement in the number/size of their lesions after 48 weeks of treatment with RYPLAZIM. One subject with pulmonary lesions had abnormal spirometry at baseline which normalized after 12 weeks of treatment.

- **<u>External Lesions:</u> Twenty-five of the 32 (78%) external lesions with sites mainly located in the eyes (ligneous conjunctivitis), nose, gingiva (ligneous gingivitis), gums, and ligneous lesions of the hands and feet were resolved by the end of Week 48.**

There were no recurrent or new external lesions in any subject through Week 48.

- **Internal Lesions: Nine of the 12 (75%) assessed internal lesions were resolved by Week 48. The lesion sites were mainly located in the cervix, bronchus, colon, vagina and uterus. No recurrent or new lesions were found on imaging in any subject through Week 48.**

There was no inferential hypothesis testing. The Clinical Reviewer considers the single-arm, open-label Phase 2/3 study an adequate and well-controlled study. Based on the natural history of this rare condition, and phenotypic heterogeneity, sustained significant improvement (e.g., > 50% in lesion size/number) or resolution of disease-associated ligneous lesions is highly unlikely to have occurred spontaneously; additionally, the lack of appearance of new lesions over the 48-week study period is highly unlikely to have occurred by chance alone given the pathophysiology of the condition.

Efficacy of RYPLAZIM was supported by data from Expanded Access protocols (EAPs) in the United States (U.S.) or Compassionate Use protocols outside of U.S. In addition to the 6 pediatric subjects enrolled in Study 2002C011G (4-16 years), 6 pediatric patients (age 11 months to 3 years) who received repeat administrations of RYPLAZIM through these programs showed improvement in lesions.

The safety database consists of 29 subjects with plasminogen deficiency type 1 who received at least one dose of RYPLAZIM in two single-arm, open-label clinical trials as well as through US FDA expanded access programs for investigational drugs or non-US compassionate use programs. Subjects were between 11 months and 42 years of age. There were 17 pediatric subjects and 12 adults. Fifteen subjects were female. Twenty-eight subjects were Caucasian, and one subject was Asian.

No subjects/patients died. One serious adverse reaction of possible worsening of gastrointestinal hemorrhage secondary to gastric ulcers was reported. No subjects discontinued study participation or treatment due to the occurrence of an adverse event (AE). The most frequent adverse reactions (incidence ≥10%) were abdominal pain, gastric dilatation, nausea, fatigue, pain in extremity, hemorrhage, constipation, dry mouth, headache, dizziness, arthralgia, and back pain.

Lesions in the respiratory, renal, gastrointestinal and gynecologic systems may slough following treatment with RYPLAZIM resulting in bleeding or organ obstruction. Patients with tracheobronchial lesions may develop airway obstruction or hemoptysis. Hypersensitivity reactions, including anaphylaxis, may occur with RYPLAZIM. Because RYPLAZIM is derived from human plasma, it carries a risk of transmitting infectious agents. None of these potential risks were observed in clinical trials or under expanded access / compassionate use programs.

The reviewed safety data do not warrant a Risk Evaluation and Mitigation Strategies (REMS), or a safety postmarketing requirement (PMR) study. The postmarketing risk mitigation plans include appropriate Prescribing Information (Package Insert, PI), Patient Information, and routine pharmacovigilance.

In conclusion, plasminogen deficiency type 1 is a serious condition without any FDA-approved therapy. The submitted data from an adequate and well-controlled trial (Study 2002C011G) provide primary evidence of effectiveness for the treatment of adult and pediatric patients with plasminogen deficiency type 1. Efficacy was demonstrated with

respect to percentage of internal and external lesions that were resolved through Week 48. Efficacy was supported by data from Expanded Access and Compassionate Use protocols. Six pediatric patients (age 11 months to 3 years) received repeat administrations of RYPLAZIM through these programs showed improvement in lesions. The potential serious risks associated with IV administration of RYPLAZIM include tissue sloughing, transmission of infectious agents, and hypersensitivity reaction. None of these potentially serious risks were observed in clinical studies. The risks can be mitigated through routine pharmacovigilance plan, medical management, and adequate Package Insert (PI) without requiring other regulatory measures such as REMS or PMR. The efficacy and safety data in the BLA support a favorable benefit-risk profile for pediatric and adult patients with plasminogen deficiency type 1. Therefore, the Clinical Reviewer recommends traditional approval of RYPLAZIM for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia).

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Demographic information for subjects in Study 2002C011G is shown in Table 1. A total of 15 subjects (9 adult subjects and 6 pediatric subjects) with plasminogen deficiency type 1 due to biallelic mutations in the *PLG* gene were enrolled at two clinical sites: Indiana Hemophilia and Thrombosis Center (Indianapolis, IN, USA) and Oslo University Hospital (Oslo, Norway). Fourteen subjects had mutations in the *PLG* gene confirmed at study entry; however, there was heterogeneity regarding the specific disease-causing genetic alterations for individual subjects. Eleven subjects (6 adults and 5 children) were enrolled in the U.S., and 3 subjects (all adults) were enrolled in Norway.

Table 1 Demographics for the Subjects Enrolled in Clinical Study 2002C011G

Characteristic	Overall Subjects (n = 15)
Age (years)	
Mean	23.0
Median	24.0
Minimum, Maximum	4, 42
Sex	
Male	4 (26.7%)
Female	11 (73.3%)
Race	
White	15 (100%)
Ethnicity	
Non-Hispanic or Latino	14 (93.3%)
Hispanic or Latino	1 (6.7%)

Source: modified based on BLA 125659 submission

1.2 Patient Experience Data

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

Table 2 Patient Experience Data

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome Quality of Life (QOL) Assessment was evaluated in all subjects at multiple time points in Study 2002C011G.	6.1.11.2 Analyses of Secondary Endpoints
☐	Observer-reported outcome:	
☒	Clinician-reported outcome Clinical Global Impression-Global Improvement (CGI-I) scores were evaluated in all subjects at multiple time points in Study 2002C011G	6.1.11.2 Analyses of Secondary Endpoints
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Plasminogen Deficiency Type 1

Plasminogen deficiency type 1 (hypoplasminogenemia) is a rare (estimated prevalence as low as 1.6 per million; Schuster and Seregard, 2003) systemic condition that is associated with serious adverse clinical manifestations. Plasminogen deficiency type 1 is an autosomal recessive disorder, which is caused by genetic mutations (e.g., homozygous mutation, compound heterozygous mutation) that affect both alleles of the plasminogen gene (*PLG*) and is associated with a decrease in both the serum plasminogen antigen level and activity level. There is substantial heterogeneity (e.g.,

with regard to plasminogen activity level and disease manifestations) among patients with plasminogen deficiency type 1 due to the number of mutations and polymorphisms in *PLG* that cause the disease. Patients who have plasminogen deficiency type 1 usually survive into adulthood but generally experience substantial disease-related morbidity. As per Schuster et al. (Schuster et al., J Thromb Haemost. 2007; 5:2315–22): "Severe hypoplasminogenemia is associated with compromised extracellular fibrin clearance during wound healing, leading to pseudomembraneous (ligneous) lesions on affected mucous membranes (eye, middle ear, mouth, pharynx, duodenum, upper and lower respiratory tract and female genital tract). Ligneous conjunctivitis is by far the most common clinical manifestation". Ligneous conjunctivitis, which affects an estimated 80% of patients with type 1 plasminogen deficiency, is characterized by thick, woody deposits on the ocular conjunctiva that can result in blindness due to corneal involvement (which occurs in approximately 20-30% of patients) if left untreated. Extraocular lesions that are due to hypoplasminogenemia can result in life-threatening loss of function of the affected organ, depending on the anatomical location and severity of the lesion.

Plasminogen deficiency is a rare disease, with an estimated incidence of 1.6 per 1,000,000 individuals in the general population (Schuster et al., J Thromb Haemost. 2007; 5:2315–22). Precise prevalence data are unknown. Based on the reported incidence, the U.S. prevalence of the disease is estimated to be approximately 526 individuals. The disease primarily affects individuals aged from birth to 18 years, with the median age at first clinical manifestation reported as 9.54 months (Schuster et al., J Thromb Haemost. 2007; 5:2315–22).

Reviewer Comment: Plasminogen deficiency type 1 primarily affects pediatric patients.

Physiologic Function of Plasminogen

As per Mehta and Shapiro (Mehta and Shapiro, Haemophilia. 2008 Nov; 14(6):1261-8.): "Plasmin is a serine protease and is the predominant fibrinolytic enzyme in the human circulation. A considerable quantity of plasmin is also found in the extracellular matrix. The zymogen plasminogen circulates in blood and is converted to plasmin by the mammalian plasminogen activators tissue-plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA). The gene for plasminogen is located on chromosome 6, and the zymogen is predominantly produced by the liver. Native plasminogen is produced as two main forms, Glu- and Lys-plasminogen. Glu-plasminogen includes a glutamic acid at the N-terminus and has a half-life of 2.2 days. Alternatively, Lys-plasminogen (lysine residue at N-terminus) is also present in the circulation at a much lower concentration and has a shorter half-life of 0.8 day. Plasmin cleaves Glu-plasminogen to Lys-plasminogen, making it more prone to activation by the plasminogen activators and essentially creating a positive feedback loop.

Plasmin, once formed, is inactivated by its physiologic inhibitor α2-antiplasmin. Although unbound plasmin is rapidly inhibited by α2-antiplasmin, plasmin remains relatively protected when it sits on the lysine residues of the fibrin clot, with α2-antiplasmin's ability to inhibit plasmin having been decreased more than 100-fold. Although the role of plasmin in hemostasis is well defined, it also has other functions, including functioning as an integral component of wound-healing. A fibrin-rich extracellular matrix forms after cellular damage, with plasmin playing several roles in the degradation of this tissue. Plasmin directly degrades fibrin and other matrix glycoproteins, activates the matrix

metalloproteinases, and stimulates the release of transforming growth factor β, all functions representing critical steps in wound-healing.

Pathophysiology

There is heterogeneity in the magnitude of reduction in plasminogen activity level among patients with plasminogen deficiency type 1. In a case series of 50 patients with plasminogen deficiency type 1, the reported range of plasminogen activity was 4 - 51% (Tefs et al., Blood. 2006 Nov 1; 108(9):3021-6). Patients with plasminogen deficiency type 1 exhibit markedly impaired wound healing due to diminished intravascular and extravascular fibrinolysis that is a consequence of decreased functional activity of plasminogen. Ligneous conjunctivitis is caused when the physiologic deposition of fibrin in response to mechanical trauma to the conjunctival mucosa continues to build up due to decreased fibrinolysis caused by plasminogen deficiency.

Reviewer Comment: In the RYPLAZIM clinical development program, a quantitative correlation between plasminogen activity and clinical lesion burden was not established. However, those patients with plasminogen activity levels <5% at baseline appeared to have more severe clinical manifestations.

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

There are no approved therapies for treatment of plasminogen deficiency type 1. Surgical removal of ligneous lesions is performed, for example, in the case of lesions that are associated with pain or adverse effects on organ function. However, since surgery does not modify the underlying pathophysiology (i.e., plasminogen deficiency), surgical removal of ligneous lesions has a short-term effect due to virtually universal recurrence of lesions. From the literature, some surgically removed ligneous lesions can recur as soon as 48 hours post-removal, while others recur on the order of weeks to months. Investigational pharmacologic treatments, such as eyedrops containing plasminogen, fresh frozen plasma (FFP), antibiotics, and immunomodulatory agents, or intermittently administered systemic agents, such as IV FFP, have not demonstrated effectiveness as a treatment for ligneous conjunctivitis.

2.3 Safety and Efficacy of Pharmacologically Related Products

There are no pharmacologically related products that are currently available.

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

Single Patient Compassionate Use Protocol in Germany (2013)

A 22-month-old boy received Glu-plasminogen via IV infusion under a compassionate use protocol in Germany for treatment of plasminogen deficiency type 1. The baseline plasminogen activity level was < 2% (normal range: 75 -140%). When the child was 18 months old, he underwent repeated bronchoscopic laser removal of exophytic lesions within both mainstem bronchi that were causing substantial respiratory difficulty. The patient was noted to have viscous pulmonary secretions. At 20 months of age, the patient required cardiopulmonary support after experiencing cardiopulmonary arrest due to pulmonary obstruction that resulted in irreversible anoxic encephalopathy. One week afterward, the patient began receiving RYPLAZIM via IV infusion, first at a dose of 4

mg/kg, which was titrated upward to 6.5 mg/kg every 48 hours. After 6 weeks, the pulmonary lesions resolved sufficiently to relieve pulmonary obstruction as per chest X-ray and to improve oxygenation. Ligneous conjunctival lesions were also noted to have improved within this time frame. After lesion resolution, the child has been maintained on a dose of 6.6 mg/kg of RYPLAZIM every 48 hours, which kept the trough plasminogen activity level at ~30%. He has completed more than 4 years of maintenance therapy to prevent new lesions. When the dose frequency was reduced, the ligneous conjunctivitis recurred but rapidly resolved upon reinstitution of increased dosing frequency. No treatment-related adverse events were reported.

Phase 1 study (2002C005G) - Study Period: 12/2014 - 12/2015

This was an open-label, single-arm, dose-escalation study in which a single dose of RYPLAZIM IV was administered to adult and pediatric subjects with plasminogen deficiency type 1 and a baseline plasminogen activity level < 40%. The primary objective of the study was to assess pharmacokinetics (PK) to determine the dose of RYPLAZIM and the dosing interval that should be used for the Phase 2/3 study.

The study enrolled seven subjects at two clinical sites (i.e., U.S. and Norway). Two of the seven subjects were pediatric subjects age 13 and 15 years, and five were adults age 19 to 37 years. Five subjects were female. Five subjects received two infusions: one 2 mg/kg infusion, and one 6 mg/kg infusion. Two subjects received a single 6 mg/kg infusion.

- Cohort 1: 2 mg/kg; (n=5)
- Cohort 2: 6 mg/kg; (n=7)

RYPLAZIM was infused via slow infusion (10 minutes in duration) by syringe through a peripheral IV line. PK testing was performed by assessing plasminogen activity and antigen levels at baseline and at the following time points post-infusion: 5-15 minutes; and 1, 6, 24, 48, 72, 96, 120, 168, and 216 hours. Subjects received 30 days of safety follow-up, including assessment of D-dimer and immunogenicity.

PK Results:
No formal statistical analyses were performed by the applicant. In individual subjects, immediately (i.e., 5-15 minutes post-infusion time point for blood collection) after infusion the plasminogen activity increased by an absolute 77 - 132% over baseline after the 6 mg/kg dose. The plasminogen activity level for individual subjects never increased into the physiologic range (i.e., 70 – 130%) after the 2 mg/kg dose. The mean (± standard deviation) terminal half-life was 35.6 ± 17.6 hours and 35.7 ± 12.3 hours in Cohorts 1 (2 mg/kg dose) and 2 (6 mg/kg dose), respectively. The mean residence time (MRT) was 56.0 ± 30.7 hours and 52.6 ± 17.7 hours in Cohorts 1 (2 mg/kg) and 2 (6 mg/kg), respectively. The trough plasminogen activity decreased below an absolute value of 10% higher than baseline after 96 hours in most of the subjects who received a single IV dose of 6 mg/kg. Based on these findings, the applicant selected the regimen for the Phase 2/3 study (#2002C011G) – i.e., 6.6 mg/kg (comparable dose to 6 mg/kg administered in the Phase 1 study; see Section 6.1.2 for details) of RYPLAZIM with repeat dosing to be individualized based on a subject's baseline plasminogen activity levels and results of PK testing after a single IV dose. The applicant's rationale for the Phase 2/3 dosing is that the Phase 1 PK results demonstrated substantial inter-subject variability and appear to indicate that repeat doses of 6 mg/kg IV every 2 to 4 days

would be sufficient to maintain the absolute baseline-adjusted level plasminogen activity trough level above 10%. The target trough level was selected based on case reports in the literature for patients with ligneous conjunctivitis who had successful resolution of the ligneous lesions after receiving IV plasminogen when the plasminogen activity trough level was maintained higher than 10 - 20% above baseline.

Safety:
No SAEs or deaths were reported. No subjects developed anti-plasminogen antibodies. No changes in viral status were reported. The most common AE among Cohort 1 subjects was nasopharyngitis, and the most common AEs among Cohort 2 subjects were oropharyngeal pain, headache, dysmenorrhea, and skin lesion. No clinically significant hematology or serum chemistry laboratory test results were reported. Some of the subjects experienced transient hemoglobinuria and microalbuminuria. Four subjects in Cohort 2 had post-infusion D-dimer levels that were higher than 200 ng/mL which appears to be consistent with the lysis of fibrinous deposits.

Single-Patient Expanded Access Protocol (b) (6) April 2016
A 33-year-old male patient with plasminogen deficiency type 1 was administered RYPLAZIM under an expanded-access program. The patient's baseline plasminogen activity level was < 5%. The patient had systemic manifestations (i.e., chronic gingivitis, intermittent abdominal pain, dysphonia due to apparent impairment in vocal cord healing) due to plasminogen deficiency, starting at 9 months of age when he was diagnosed with ligneous conjunctivitis. He needed multiple surgeries to remove ligneous conjunctival lesions and obstructive nasopharyngeal pseudomembranes. The patient had experienced urinary tract obstruction and pain resulting from calcified pseudomembranes that had formed in the left renal collection system, and which recurred despite multiple ureteroscopy, laser ablation, and ureteral stent placement procedures and daily infusion of fresh frozen plasma (FFP). On baseline testing prior to RYPLAZIM infusion, the patient had chronic left ureteral obstruction and non-healing wounds (6 weeks in duration) on the dorsum and palm of the hand due to multiple surgical incisions that was performed to hand abscess that formed after minor cuts. He received IV infusion of RYPLAZIM at a dose of 6.6 mg/kg every 2 days and then later, every 3 – 7 days, which maintained plasminogen activity trough levels an absolute 10% above baseline. His surgical wounds healed, and renal obstruction resolved. Transient eye lesions were noted during long-term use, which resolved with continued study drug treatment. Total RYPALZIM exposure was approximately 194 weeks. No related adverse events were reported.

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

- The studies were conducted under IND 16186.
- RYPLAZIM was granted Fast Track, and Orphan Drug designations for the treatment of plasminogen deficiency type 1 (hypoplasminogenemia).
- A pre-BLA meeting was held on 10/5/2016.
- Original BLA was submitted on 8/14/2017.
- Complete Response Letter was issued on 4/08/2018 due to Chemistry, Manufacturing and Control (CMC) deficiencies.
- Response to Complete Response Letter: 9/4/2020

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The Clinical module of the BLA submission was sufficient in quality for the Clinical Reviewer to complete the clinical review without any major amendments for additional clinical information.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Studies 2002C005G and 2002C011G were conducted under an IND16186, in accordance with the regulations that are specified in 21 CFR 312, and were compliant with GCP (Good Clinical Practice), including informed consent/assent for all study subjects and ethical treatment of study subjects.

Since the Phase 2/3 study (2002C011G) that serves as the primary source of evidence of effectiveness and safety to support the BLA, was conducted at only a single domestic clinical site (i.e., Indianapolis, IN), the Division of Inspections and Surveillance (DIS) conducted a routine bioresearch monitoring (BIMO) inspection of the single U.S. clinical investigator, during the review of the original BLA submission in 2017. There were no a priori concerns with safety or scientific misconduct regarding the U.S. site prior to the inspection. The DIS inspection of the U.S. clinical investigator did not reveal any substantive findings.

3.3 Financial Disclosures

The applicant has adequately disclosed financial interests/arrangements with clinical investigators for the studies #2002C011G and #2002C005G), as recommended in the FDA guidance for industry *Financial Disclosure by Clinical Investigators*. The Clinical Reviewer did not identify any financial conflicts of interest for study investigators based on the disclosed information provided in the BLA (Table 3 and Table 4).

Table 3 Financial Disclosure for Study 2002C011G

Covered clinical study (name and/or number): 2002C011G
Was a list of clinical investigators provided? X☐ Yes ☐ No (Request list from applicant)
Total number of investigators identified: 2
Number of investigators who are sponsor employees (including both full-time and part-time employees): _____
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____ Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☐ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? ☐ Yes ☐ No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): _____ Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

Table 4 Financial Disclosure for Study 2002C005G

Covered clinical study (name and/or number): 2002C005G		
Was a list of clinical investigators provided:	Yes X	No (Request list from applicant)
Total number of investigators identified: 1		
Number of investigators who are sponsor employees (including both full-time and part- time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes	No (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes	No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes	No (Request explanation from applicant)

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

4.1 Chemistry, Manufacturing, and Controls

RYPLAZIM is a lyophilized preparation of purified, human plasma donor-derived plasminogen. The human source plasma is collected from healthy North American (U.S. and Canadian) donors at registered plasma sites that meet FDA and Health Canada requirements for testing human blood donors for evidence of infection due to communicable disease agents. Plasma pools must test negative for HIV, HCV, HBV, and HAV, and must have a level of human parvovirus B19 DNA ≤ 10_4 IU/mL to meet the lot release criteria for manufacture of RYPLAZIM. RYPLAZIM is intended to be

reconstituted, passed through a syringe disc filter, and administered by IV infusion. Each vial contains 68.8 mg of plasminogen. After reconstitution with 12.5 mL of Sterile Water for Injection, the solution is comprised of an active ingredient – Glu-plasminogen (human) -- and inactive ingredients (i.e., sodium citrate, sodium chloride, glycine, and sucrose). Reconstituted RYPLAZIM does not contain any preservatives and is comprised of 5.5 mg/mL Glu-plasminogen in (b) (4) sodium citrate, (b) (4) sodium chloride, (b) (4) glycine, and (b) (4) sucrose.

There were major CMC deficiencies in the original BLA submission, including: inadequate process control and validation, insufficient studies to support process development, the potency assay is not suitable for its intended purpose, inadequate qualification of critical manufacturing equipment, inadequate characterization and control of product aggregation, and insufficient justification for most of the specifications for the Drug Substance Intermediate, Bulk Drug Substance (BDS), and Final Drug Product (FDP). The applicant tried to address all these issues in the current resubmission. See CMC Reviewer's memo for complete details.

4.2 Assay Validation

Description of the plasminogen activity assay (as per the BLA submission):
(b) (4) validated the measurement of total plasminogen (PLG) antigen in human citrated plasma using (b) (4) quantitative (b) (4)

This human plasminogen antigen assay is for the quantitative determination of the total levels of human plasminogen in clinical (b) (4) plasma samples. This assay is a (b) (4)

This report described the successful validation of an (b) (4) method to quantify human plasminogen antigen in human plasma. The inter-assay precision, intra-assay precision, accuracy, lower quantification limit, analytical sensitivity and analytical specificity of this test were deemed acceptable. The laboratory director reviewed the validation study and determined the performance characteristics of this test to be acceptable.

Please refer to the Chemistry, Manufacturing, and Control Reviewer's memo for additional details.

4.3 Nonclinical Pharmacology/Toxicology

See Pharmacology/Toxicology Reviewer's memo for details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

RYPLAZIM is intended to achieve at least partial restoration of the physiologic serum plasminogen activity level in patients with plasminogen deficiency type 1.

4.4.2 Human Pharmacodynamics (PD)

Decreased plasminogen levels causes formation of fibrin-rich, ligneous pseudomembranous lesions on mucous membranes that can impair normal tissue and organ function. Replacement therapy increases the plasma level of plasminogen enabling a temporary correction of the plasminogen deficiency and reduction or resolution of extravascular fibrinous lesions.

4.4.3 Human Pharmacokinetics (PK)

Study #2002C005G
See PK data in Section 2.4.

Study #2002C011G
The PK profiles of RYPLAZIM were similar in pediatric and adult populations. With the treatment of RYPLAZIM at 6.6 mg/kg every 2 to 4 days, the plasminogen trough activity levels were generally above the target levels (≥ absolute 10% above baseline) in both pediatric and adult populations. See Clinical Pharmacology review for details.

4.5 Statistical

Due to the limited sample size, the applicant performed descriptive statistical analyses. See Statistical Reviewer's memo for details.

4.6 Pharmacovigilance

The pharmacovigilance plan submitted by the applicant is summarized in the BLA as follows:

The applicant is committed to securing standardized systems for the routine pharmacovigilance (PV) practice to monitor and report adverse events associated with the use of RYPLAZIM. Routine PV objectives include the following:

1. Comprehensive and timely post-marketing surveillance assessment by qualified personnel of spontaneously reported events, including expedited reporting of qualifying events in compliance with worldwide regulatory requirements;

2. Regular surveillance of the scientific literature for reports of adverse events;

3. Preparation of Annual Safety Summaries in accordance with applicable regulatory guidelines.

4. Preparation and submission of Periodic Benefit-Risk Evaluation Reports (PBRER)/ PSURs in accordance with applicable regulatory requirements.

Applicant's routine pharmacovigilance (PV) actions include:

1. Monitoring of adverse events and serious adverse reactions from the ProMetic post-marketing safety database;

2. Reconciliation of such reactions with the FDA's Adverse Event Reporting System (FAERS), as applicable;

3. Routine pharmacovigilance of foreign reports; and

4. Expedited reporting to the FDA of any serious adverse reactions occurring in the United States and serious unexpected adverse reactions occurring outside the United States, within 15 days after receipt of the unsolicited or solicited information.

5. Evaluation and notification of potential new safety signals. When a safety signal is identified, further assessment and characterization of the safety signal is conducted, including the evaluation of individual case reports and aggregate data analysis, as appropriate.

6. Continuity in receiving and reporting new safety information to the regulatory authorities worldwide.

7. Preparation of responses to regulatory queries regarding safety issues.

8. Additional activities, as appropriate:

    a. Update the Company Core Datasheet (CCDS)/Safety Database with new safety information;

    b. Product label revision with new safety information (in cooperation with regulatory authorities);

    c. Informational letters to the treating physicians and pharmacists.

See Epidemiology review for details.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

Data from the following sources (i.e., two clinical studies and expanded access programs) contributes to the Clinical Review of the BLA:

- The primary evidence of effectiveness and safety comes from a completed Phase 2/3 study (2002C011G) in which IV Plasminogen (Human) was administered to 15 adult and pediatric subjects.

- Supportive safety/efficacy data comes from a treatment protocol, US single patient expanded access and non-US single patient compassionate use protocols.

- A completed Phase 1 study (2002C005G), which was conducted in 7 adult and pediatric subjects, served as the basis for determination of the dosing regimen for the Phase 2/3 study.

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

- Study 2002C005G Main Study Report
- Study 2002C011G Main Study Report
- Study 2002C011G M5 Datasets (adam xpt files, sdtm xpt files)

5.3 List of Studies/Clinical Trials

A total of 29 subjects received at least one dose of RYPLAZIM via IV infusion and 28 unique subjects (17 pediatric and 11 adult) received repeated doses of RYPLAZIM. Total repeat-dose treatment exposure ranged from 4 to 214 weeks across the subject population (6 to 214 weeks for pediatric subjects and 4 to 194 weeks for adult subjects). RYPLAZIM treatment is ongoing in 22 subjects, as of the data cut-off date of January 1, 2020.

- Phase 1, dose-escalating study 2002C005G (n = 7)

- Phase 2/3 study 2002C011G (n = 15, including 6 subjects who completed Study 2002C0005G and 9 new subjects)

- US single patient Expanded Access Protocols (EAPs): (b) (6) (n = 4)

- Treatment Protocol 2002C018G (n = 10, including 8 patients who completed Study 2002C011G, 2 patients who completed EAPs (b) (6) and (b) (6)

- Non-US Compassionate use (n = 14, including 5 patients who completed Study 2002C011G (Norway [n = 3], United Kingdom [n = 1], and Canada [n = 1]) and 9 patients in Germany [n = 5], United Kingdom [n = 3], and Israel [n = 1]).

5.4 Consultations

5.4.1 Advisory Committee Meeting

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

5.4.2 External Consults/Collaborations

No consultations were obtained in the evaluation of the BLA application.

5.5 Literature Reviewed

The Clinical Reviewer reviewed the literature references provided by the applicant in the BLA, as well as manuscripts that were identified in PubMed database searches for single keywords or combinations of the following keywords: plasminogen, type 1 plasminogen deficiency, hypoplasminogenemia, Glu-plasminogen, Lys-plasminogen, ligneous conjunctivitis, and clinical trial.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study 2002C011G

Study Title: 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)

Primary:

- To evaluate the efficacy of plasminogen replacement therapy on clinically evident or visible signs and symptoms of hypoplasminogenemia during the 48 weeks of dosing in Segments 2 and 3.

- To achieve an increase of individual plasminogen activity trough levels by at least an absolute 10% (i.e., 10 U/dL) above baseline in adult and pediatric subjects with hypoplasminogenemia during the 12 weeks of plasminogen replacement therapy in Segment 2.

Reviewer Comment: The clinical review focuses on the clinical efficacy through Week 48. Please see Clinical Pharmacology review for the PK assessments. Of note, the assessment of plasminogen activity trough level at Week 12 was intended to be used as a surrogate endpoint for accelerated approval in the original BLA submission.

Secondary:

- 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 pharmacokinetics (PK) and immunogenicity during the 48 weeks of dosing.

6.1.2 Design Overview

This was an open-label, single-arm, study to assess the safety and efficacy of RYPLAZIM intravenous administered to adult and pediatric subjects with plasminogen deficiency type 1. The primary objectives included assessment of PK outcomes (i.e., baseline-adjusted plasminogen activity trough level) and the correlation with clinical outcomes (i.e., ligneous lesion resolution) at 12 weeks (interim analysis) and clinical outcomes (ligneous lesion resolution and durability of effect) at 48 weeks. The study was conducted in the following Segments:

- Segment 1: subjects received a single dose of 6.6 mg/kg of RYPLAZIM on study Day -4. The PK data collected for each subject after this initial dose was used to determine the dosing interval for individual subjects.

- Segment 2: subjects received a dose of 6.6 mg/kg every 2 to 4 days for 12 weeks. Subjects receive RYPLAZIM at the study site every 4 weeks, with interim dosing (i.e., in between the study visits spaced 4 weeks apart) to be performed by study personnel either at the study site or an ancillary site. For subjects

enrolled at the U.S. study site, RYPLAZIM could be administered by a home health nurse at the subject's home, by the subject themselves, or by a caregiver or family member of the subject.

- Segment 3: subjects received RYPLAZIM for an additional 36 weeks. The dose for Segment 3 is 6.6 mg/kg with the frequency of dosing to be based on data collected in Segment 2, with modification to the dosing regimen to be also based on ongoing assessment of clinical response and plasminogen activity trough levels. In the event of lack of clinical effect, the target plasminogen activity trough level would be a minimum of 45%, to be achieved by increase in dosing frequency.

The pre-specified data analysis plan is as follows:

- 12-week Interim Analysis (submitted in the original BLA): After 10 subjects completed Segment 2 of the study and were evaluable for the primary PK endpoint.

- 48-week Primary Efficacy Analysis: The analysis of the primary efficacy endpoint (i.e., clinical response of ligneous to therapy) after all subjects have completed the Week 48 visit (submitted in the current submission).

- Final Analysis: To be conducted when all subjects have completed the final safety visit.

6.1.3 Population

The study eligibility criteria call for enrollment of male or female subjects, age 2 – 80 years, who have plasminogen deficiency type 1 due to mutation(s) in the *PLG* gene, confirmed by genetic testing, with a baseline plasminogen activity level < 45% and a documented history of typical lesions and symptoms. Subjects were excluded from enrollment if they had received plasminogen (eyedrops or IV infusion), fresh lyophilized plasma (FFP) within 2 weeks of screening due to the potential for these agents to affect plasminogen activity levels.

6.1.4 Study Treatments or Agents Mandated by the Protocol

RYPLAZIM was administered at a dose of 6.6 mg/kg every 2 to 4 days via intravenous infusion via a peripheral vein (e.g., antecubital or dorsum of hand) over 10 to 30 minutes using a syringe with a filter.

The dosing frequency was adjusted depending on lesion response and treatment-emergent adverse events (TEAEs). The dosing frequency was adjusted in seven subjects at Site 01 (US) by the Investigator at the request of the Applicant due to a national shortage of Sterile Water for Injection, USP (SWFI).

Treatment duration ranged from 48 to 124 weeks, with long-term duration dependent on the availability of Treatment Protocol 2002C018G. The majority of the subjects (9/15, 60%) received at least 108 weeks of RYPLAZIM. All 3 subjects from Norway received 48-64 weeks of RYPLAZIM per protocol.

Most doses of RYPLAZIM were administered at home, and most subjects had at least one minor dosing deviation. Missed or reduced infusions were transient in nature and did not appear to negatively impact the outcome of the study.

A total of 5 subjects (1 pediatric and 4 adult) had 16 major protocol deviations, 11 of which occurred at the Norway site. A total of 14 subjects (5 pediatric and 9 adult) had minor dosing deviations, such as reconstituted using multiple lots of RYPLAZIM, missing lot numbers, or other dosing information due to compliance issues, change in infusion time window, and missed or reduced infusions. A total of 4 subjects (1 pediatric and 3 adult) had minor efficacy deviations, the majority of which occurred at the Norway site. The most common efficacy deviation was missing lesion photographs, which were used to complement the treatment response in conjunction with the Investigator's clinical assessment. The missing photographs did not alter the efficacy outcome of the study. The remaining protocol deviations were minor and predominantly related to errors related to laboratory/vital signs testing procedures. None of these minor protocol deviations negatively impacted the efficacy, PK, or safety outcomes of the study.

Subject (b) (6) (33-year-old White not Hispanic/Latino female in Norway) became pregnant during the study and remained in the study per Investigator, Medical Monitor and applicant agreement assessing risk versus benefit. Of note, she entered the study with a history of infertility (fibrin pseudomembranes in uterus) due to her underlying disease.

Reviewer Comment: Of the 2 study sites, the US site had more experience with RYPLAZIM since the Phase 1 study (Study 2002C005G) was conducted there. Of note, none of the major protocol deviations negatively impacted the PK, efficacy, or safety outcomes of the study.

6.1.5 Directions for Use

Treatment Compliance
RYPLAZIM administration is recorded by the person who performed a given administration (study personnel or home nurse, subjects themselves, or subjects' caregivers). Subjects document receipt of RYPLAZIM and return the used vials for accountability and also document administrations in a study diary.

6.1.6 Sites and Centers

Study Sites and Principal Investigators:

1. Indiana Hemophilia and Thrombosis Center, Indianapolis, Indiana, United States of America (US); PI: Amy Dana Shapiro, MD
2. Oslo University Hospital, Oslo, Norway; PI: Dr. Per Morten Sandset

6.1.7 Surveillance/Monitoring

Assessments During the Study Period:

<u>Clinical and PK Assessments</u>

Segment 2

- clinical assessments: Performed at Weeks 1, 4, 8, and 12,

- blood samples:
  - collected every 2 weeks prior to RYPLAZIM infusion for assessment of plasminogen activity trough levels.
  - At Week 12, blood samples for PK assessment were collected at the following time points: between 5 and 15 minutes post-infusion, and at Hours 6, 24, 48, 72, and 96.

Segment 3:

- Clinical assessments are performed every 12 weeks
- blood samples for assessment of plasminogen activity trough levels are collected at every study visit (i.e., 12 weeks apart) prior to infusion.

Reviewer Comment: Subjects continued to receive RYPLAZIM after Week 48 in Segment 3. In addition, 8 subjects continued to receive RYPLAZIM in the Treatment Protocol. See Appendix 1 for details.

All subjects were clinically evaluated by the investigator or designee for the clinical manifestations of plasminogen deficiency type 1. The types and timing of clinical assessments depended on each subject's disease presentation and included,

- Clinical assessment and/or photographs
- Functionality tests (e.g., spirometry)
- Imaging of non-visible lesions (e.g., ureteral, oropharyngeal and bronchial) based on the investigator's discretion.

Subject Diary

In Segments 2 and 3, subjects are instructed to use a study diary to record clinical symptoms, RYPLAZIM administration, the use of concomitant medications, and the occurrence of adverse events.

Safety Monitoring

Assessment of safety is performed at the following time points: Baseline, every 4 weeks during Segment 2, every 12 weeks during Segment 3, and at the final visit. The following safety information is collected: 1) treatment-emergent AEs (TEAEs); 2) clinical laboratory testing (hematology, chemistry, coagulation/fibrinolysis parameters, and urinalysis) results; 3) vital signs (blood pressure, heart rate, respiratory rate, and temperature); 4) physical examination findings; 5) immunogenicity (development of anti-plasminogen antibodies); and 6) virologic status testing.

Study Stopping Rules:

Administration of RYPLAZIM to an individual subject will be suspended and a safety review would be conducted if a subject experienced any of the following: anaphylaxis, clinically significant AE, development of neutralizing antibodies, or thrombotic or bleeding events that require hospitalization.

Safety Monitoring Committee (SMC):

An SMC comprised of the sponsor's medical monitor and an independent medical monitor performing ongoing oversight of the study on a periodic and ad hoc basis.

6.1.8 Endpoints and Criteria for Study Success

Primary (Clinical)

The primary efficacy endpoint is the overall rate of 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 (responder rate) is defined as 50% of subjects with visible or other measurable non-visible lesions demonstrating at least a 50% improvement in lesion number/size or functionality impact from baseline.

Clinical Assessment of Visible Lesions

Clinical evaluation by the investigator or designee was pre-specified as the method to assess the primary efficacy endpoint and was used to assess ligneous lesions. All subjects were clinically evaluated by the investigator or designee for the clinical manifestations of plasminogen deficiency type 1 at the specified time points. A 1-mm scale was included in the digital photography to determine the size (length and width) of visible lesions. Visible lesions that had both length and width as measured by the 1 mm scale were referred to as "measurable lesions" and visible lesions that were too small to be measured using the 1-mm scale (i.e., length and/or width could not have been measured) were referred to as "non-measurable lesions." For non-measurable lesions, the investigator or designee assessed each lesion qualitatively as either resolved, improved, unchanged, or worsened. Of these assessments, only lesions assessed as resolved were included in the calculation of overall clinical success as it represented 100% improvement. This approach was taken to ensure that all lesions included in the calculation of overall clinical success improved by at least 50% as described in the definition of overall clinical success.

Functionality Testing

Spirometry was performed in subjects who had respiratory tract involvement of plasminogen deficiency type 1. Spirometry measurements included forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), peak expiratory flow, and FEV1/FVC ratio. If applicable, these tests were performed at Screening and Baseline (before the first dose of RYPLAZIM), and every 4 weeks thereafter. However, no testing beyond Baseline was warranted if the subject's lung function was within normal limits at Screening and/or Baseline. Spirometry was not repeated at Baseline if Screening was within 21 days of Baseline.

Assessment of Non-visible Lesions

Non-visible lesions (e.g., ureteral, oropharyngeal, and bronchial) were qualitatively evaluated as appropriate via imaging studies, such as computed tomography (CT) scans, x-ray, or other suitable imaging techniques at the Investigator's discretion. For example, if lung involvement was suspected, lesions were to be monitored via chest x-ray/CT scan obtained at Screening (unless already available within the past 6 months) and at the Week 12 visit, and at other time points if warranted. The investigator or designee assessed each non-visible lesion qualitatively as either resolved, improved, unchanged, or worsened. Of these assessments, only resolved was included in the calculation of overall clinical success as it represented 100% improvement. This approach was taken to ensure that all lesions included in the calculation of overall clinical success improved by at least 50% as described in the definition of overall clinical success.

Reviewer Comment: We consider the single-arm, open-label Phase 2/3 study an adequate and well-controlled study. Based on the natural history of this rare condition, and phenotypic heterogeneity, sustained significant improvement (e.g., >50% in lesion size/number) or resolution of disease-associated ligneous lesions is highly unlikely to have occurred spontaneously; additionally, the lack of appearance of new lesions over the 48-week study period is highly unlikely to have occurred by chance alone given the pathophysiology of the condition.

Primary (PK)
The primary PK endpoint is the number and percentage of responders (i.e., a subject who achieves the target plasminogen activity trough level -- a minimum of an absolute 10% (10 U/dL) baseline-adjusted level -- for at least 3 assessed time points during the12 weeks epoch of Segment 2. Primary endpoint success (performance criterion) was defined in the protocol as a minimum of 80% of evaluable subjects (i.e., at least 8/10 subjects) achieving the target trough level for at least 3 assessed time points during the 12 weeks of Segment 2.

Secondary Efficacy Endpoints

- 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
- Clinical Global Impression-Global Improvement (CGI-I) scores at 12 and 48 weeks
- Quality of life scores at 12 and 48 weeks.

Visible Lesions (clinical and photographic evaluation):
Visible lesions are defined as lesions that can be imaged and analyzed using digital photography. Visible lesion size is calculated from photographs of the lesions that are taken by study staff, using a scale to measure the length and width of each lesion that was included in the photographs. Visible lesions for which length and width could be measured are characterized as “measurable lesions,” and visible lesions for which either length and/or width could not be measured are characterized as “non-measurable lesions.”

Non-Visible Lesions (imaging testing and functional assessment):
Non-visible lesions are defined as lesions that may be measured directly or indirectly by imaging studies (e.g., CT scan, MRI, ultrasonography) or functional assessments (e.g., spirometry, audiography, oximetry).

Reviewer Comment: Only one subject had lesion that required functional assessment by spirometry.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The Efficacy Population Week 48-Segment 3 included all 15 enrolled subjects who completed the Week 48 visit at the time. The Efficacy Population Week 48-Segment 3 was used for evaluating all primary and secondary clinical efficacy endpoints.

The PK population included all subjects who had completed Segment 2 dosing and had provided at least 3 blood samples to measure plasminogen activity trough levels. PK Population was used for all PK analyses.

The safety population included any subject who received at least 1 dose of study drug and provided safety data for at least one non-screening visit. Safety analysis was based on the Safety Population.

All analyses were conducted per the statistical analysis plan (SAP), as well as its supplement, developed for the study.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The protocol planned for 15 subjects to be enrolled in the study. A total of 15 subjects (6 pediatric and 9 adult) were enrolled in the study and included in the efficacy, PK and safety data analysis populations. Of the 15 subjects in the efficacy population, 11 subjects in the combined population (3 pediatric and 8 adult) had any lesions at baseline.

6.1.10.1.1 Demographics

Table 1 summarizes the demographics of the subjects enrolled in the Phase 2/3 study. Six of the 15 subjects also participated in the Phase 1 study. Table 5 lists the demographics of each subject.

Table 5 Demographics and Baseline Characteristics of Each Subject

Subject ID	Age (years)	Gender	Race	Ethnicity	Weight (kg)
(b) (6) (Adult)	39	F	White	NHL	79.2
(Adult)	35	M	White	NHL	96.4
(Pediatric)	16	F	White	NHL	69.4
(Adult)	24	F	White	NHL	67.7
(Adult)	20	M	White	NHL	67.4
(Adult)	37	F	White	NHL	66.3
(Adult)	24	F	White	NHL	68.7
(Pediatric)	5	F	White	NHL	19.6
(Pediatric)	16	F	White	HL	87.6
(Pediatric)	11	F	White	NHL	29.9
(Pediatric)	6	M	White	NHL	22.3
Pediatric)	4	F	White	NHL	16.2
(Adult)	33	M	White	NHL	96.0
(Adult)	33	F	White	NHL	68.0
(Adult)	42	F	White	NHL	50.4

NHL: Non-Hispanic or Latino, HL: Hispanic or Latino
Source: BLA 125659 submission.

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 histories of drug hypersensitivity comprised 3 pediatric subjects (b) (6)) and 6 adult subjects (b) (6)

Subject Histories of Plasminogen Deficiency Type 1

All 15 enrolled subjects had a least 1 prior symptom and/or lesion associated with plasminogen deficiency type 1. Prior symptoms and/or lesions occurred on the eyes, ears, nose, mouth (gingiva, tonsils, and vocal cords), airways/lungs, gastrointestinal tract, kidney, urethra, ovaries, cervix, uterus, and vagina and on the skin (delayed wound healing and palmar/plantar warts).

Fourteen of 15 subjects (93.3%; (b) (6) had past symptoms and/or lesions of the eyes.

Eleven of 15 subjects (73.3%; (b) (6)) had multisystem disease.

Fourteen of 15 subjects (93.3%) had past symptoms and/or lesions that started in childhood, unknown in one subject.

Eleven of 15 subjects (73.3%) had past symptoms and/or lesions > 2 years duration.

Nine of 15 subjects (60.0%) had past symptoms and/or lesions > 5 years duration.

Eight of 15 subjects (53.3%) had past symptoms and/or lesions > 10 years duration.

Five of 15 subjects (33.3%) had past symptoms and/or lesions > 20 years duration.

Range (years) of past symptoms and/or lesions: 11 months to 42 years.

Prior treatments of past symptoms/lesions of plasminogen deficiency type 1 comprised surgical and medical procedures (including bronchoscopy and laryngoscopy), eye drops, and systemic medications.

Fourteen of 15 subjects (93.3%) had at least 1 prior surgical and/or medical procedure (b) (6)).

Ten of 15 subjects (66.7%) had multiple surgical and/or medical procedures (Listing 16.2.6.3) ((b) (6)

One subject (b) (6)) underwent 20 eye surgeries, 43 bronchoscopies and laryngoscopies, and 1 surgery each on the trachea, cervix, nasal passage, and uterus to remove pseudomembranous lesions.

One subject (b) (6)) underwent cryotherapy for a left eye lesion.

The baseline plasminogen activity and plasminogen levels are listed in Table 6.

Table 6 Screening and Baseline Plasminogen Activity and Plasminogen Levels

Subject ID		Plasminogen Activity [a] (%)		Plasminogen Antigen [b] (mg/dL)	
		Screening	Baseline [c]	Screening	Baseline [c]
(b) (6)	(Adult)	26	29 (Day 0)	3.4	3.8 (Day 0)
	(Adult)	29	43 (Day 0)	4.4	5.4 (Day 0)
	(Pediatric)	30	28 (Day 0)	5.5	5.6 (Day 0)
	(Adult)	32	28 (Day 0)	9.6	13.4 (Day 0)
	(Adult)	18	22 (Day 0)	2.5	2.1 (Day 0)
	(Adult)	< 5	< 5 (Day 0)	< 0.5	< 0.5 (Day 0)
	(Adult)	26	31 (Day -4)	3.8	5.2 (Day -4)
	(Pediatric)	23	22 (Day -4)	4.1	3.4 (Day -4)
	(Pediatric)	24	20 (Day -4)	3.7	4.8 (Day -4)
	(Pediatric)	18	17 (Day -4)	3.5	3.5 (Day -4)
	(Pediatric)	36	29 (Day -4)	11.5	5.5 (Day -4)
	(Pediatric)	17	18 (Day -4)	6.5	3.7 (Day -4)
	(Adult)	< 5	< 5 (Day -4)	< 0.5	< 0.5 (Day -4)
	(Adult)	15	15 (Day -4)	2.7	4.0 (Day -4)
	(Adult)	4	< 5 (Day -4)	< 0.5	< 0.5 (Day -4)

ID = Identification Number; Site 01 = US; Site 02 = Norway;
a Plasminogen activity normal range is 70% to 130%, as determined by the laboratory.
b Plasminogen antigen normal range is 6-20 mg/dL, as determined by the laboratory.
c Baseline is Day -4 for subjects starting study drug treatment in Segment 1 and Day 0 for subjects starting study drug treatment in Segment 2.
Source: Reproduced from BLA 125659 original submission.

Nine subjects had 32 visible (external) lesions (defined as lesions that could be imaged and analyzed with digital photography) and 10 subjects had 15 non-visible (internal) lesions at baseline, with 4 subjects having no lesions. Of the 32 visible lesions, 9 were measurable (i.e., both length and width as measured by a 1-mm scale) and 23 were non-measurable (too small to measure using the 1-mm scale). Of the 15 baseline non-visible lesions, 12 were assessed during the study; the remaining 3 lesions were not assessed due to location of the lesions. Visible lesions were located on the eyes and gingiva, with eye lesions being the most common; manifestations of abnormal wound healing were acne, palmar/plantar warts, scars/wounds, and fluctuating tumors (cysts). Non-visible lesions were located on the naris, bronchus, abdomen, kidney, colon, uterus, cervix, and vagina. One subject ((b) (6) had a clinically significant spirometry finding at baseline (FEV_1 of 1.57 L, 47% of predicted normal) associated with a bronchus lesion (
Table 7 Listing of Clinical Manifestations of Plasminogen Deficiency Type 1 at Baseline

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Table 7 Listing of Clinical Manifestations of Plasminogen Deficiency Type 1 at Baseline

Subject ID	Lesion Type	Lesion Site	Lesion Size	Post-Baseline Assessment
(b) (6) (Adult)	Vis ble	Left eye	10 mm × 2 mm	Yes
	Vis ble	Right eye	10 mm × 2 mm	Yes
	Non-vis ble	Cervix	Present	No
(Adult)	Vis ble	Left eye	15 mm × 5 mm	Yes
(Pediatric)	None	---	---	---
(Adult)	Vis ble	Upper gingiva	Non-measurable	Yes
	Non-vis ble	Bronchus	Present	Yes
(Adult)	None	---	---	---
(Adult)	Vis ble	Left eye	Non-measurable	Yes
	Vis ble	Right eye	Non-measurable	Yes
	Vis ble	Gums, lower left canine	Non-measurable	Yes
	Vis ble	Gums, lower left first bicuspid	Non-measurable	Yes
	Vis ble	Gums, lower right canine	Non-measurable	Yes
	Vis ble	Gums, upper right first bicuspid	Non-measurable	Yes
	Vis ble	Gums, upper right second bicuspid	Non-measurable	Yes
	Non-vis ble	Nasal, right nare at inferior turbinate	Present	Yes
	Non-vis ble	Bronchus	Present	Yes
	Non-vis ble	Renal	Present	Yes
(Adult)	Non-vis ble	Cervix	Present	Yes
(Pediatric)	Vis ble	Right eye, lower lid	10 mm × 5 mm	Yes
	Vis ble	Right eye, upper lid	15 mm × 5 mm	Yes
	Non-vis ble	Vagina	Present	Yes
(Pediatric)	Non-vis ble	Colon	Present	Yes
	Non-vis ble	Vagina	Present	Yes
(Pediatric)	Vis ble	Left eye	5 mm × 3 mm	Yes
	Non-vis ble	Colon	Present	No[b]
(Pediatric)	None	---	---	---
(Pediatric)	None	---	---	---
(Adult)	Vis ble	Left eye	4 mm × 4 mm	Yes
	Vis ble	Right eye	4 mm × 4 mm	Yes
	Vis ble	Lower gingiva	Non-measurable	Yes
	Vis ble	Upper gingiva	Non-measurable	Yes
	Vis ble	Acne on back	Non-measurable	Yes
	Vis ble	Multiple wounds/scars, hands	Non-measurable	Yes
	Vis ble	Palmar warts, both hands	Non-measurable	Yes
	Vis ble	Plantar warts, both feet	Non-measurable	Yes
	Non-vis ble	Bronchus	Present	Yes
(Adult)	Vis ble	Left eye	4 mm × 3 mm	Yes
	Vis ble	Scar, right shoulder	Non-measurable	Yes
	Vis ble	Scar, right underarm	Non-measurable	Yes
	Non-vis ble	Uterus	Present	Yes
(Adult)	Vis ble	Left eye	Non-measurable	Yes
	Vis ble	Right eye	Non-measurable	Yes
	Vis ble	Lower gingiva	Non-measurable	Yes
	Vis ble	Upper gingiva	Non-measurable	Yes
	Vis ble	Fluctuating tumors (cysts), wrists	Non-measurable	Yes
	Vis ble	Palmar warts, both hands	Non-measurable	Yes
	Vis ble	Plantar warts, both feet	Non-measurable	Yes
	Non-vis ble	Bronchus	Present	Yes
	Non-vis ble	Abdomen	Present	No
	Non-vis ble	Uterus	Present	Yes

Source: BLA 125659 submission

Genetic Profiles of Plasminogen Deficiency
Fourteen of the 15 subjects had genetic testing (Subject (b) (6) did not consent to genetic testing). Ten of the 14 subjects (71.4%) had a heterozygous missense variant (C.112A>G, p.Lys38Glu) in exon 2 of *PLG*, and 2 of 14 subjects (14.3%) had a homozygous missense variant (C.2T>C, p.Met1Thr) in the start codon of *PLG*. Subjects (b) (6) and Subjects (b) (6) are siblings. Some genetic testing was completed under Study 2002C005G.

6.1.10.1.3 Subject Disposition

Table 9 summarizes subject disposition. All subjects completed the primary efficacy assessment at 48-week.

Table 8 Summary of Subject Disposition

Parameter	Pediatrics	Adults	Total
Subjects enrolled	9	6	15
Screen failures	0	0	0
Completed study	8	5	13
Discontinued study	1	1	2
Withdrawal by subject	0	1	1
Investigator's discretion	1	0	1

Source: BLA 125659 submission

Reviewer Comment: No subject withdrew throughout the 48 weeks of treatment period when the primary clinical efficacy endpoint was assessed. The discontinuation of the two subjects occurred during after completing the primary efficacy assessment at Week 48.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

a. The overall rate of 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 defined as 50% of subjects with visible or other measurable non-visible lesions demonstrating at least a 50% improvement in lesion number/size or functionality impact from baseline.)

Eleven subjects had lesions at baseline (Table 9). Five subjects (all adult) had respiratory tract involvement due to plasminogen deficiency type 1. Of these subjects, only 1 (Subject (b) (6)) had a clinically significant spirometry finding at baseline (FEV_1/FVC ratio of 0.46).

Table 9 Summary of Data Analysis Populations

Data Analysis Population	Adults	Pediatrics	Total Subjects
Efficacy Population (Week 48-Segment 3)	9	6	15
Subjects with any lesions at baseline	9	2	11
Subjects with visible lesions	7	2	9
Subjects with non-visible lesions	7	3	10
Subjects who had abnormal organ functionality at baseline	1	0	1

Source: Modified from BLA 125659 original submission.

The primary efficacy endpoint was achieved in both pediatric and adult subjects. All subjects with any lesion at baseline had at least 50% improvement in the number/size of their lesions, or the functionality of the lesions (Table 11 and Table 12).

Table 11 Status of Visible and Assessable Non-Visible Lesions During the 48-Week Study Period

Lesion Category	Lesions at Baseline	Lesions Assessed at Week 48	% of Lesions Improved at Week 48	% of Lesions Resolved at Week 48
Adult Visible Lesions	29	29	24.1% (7/29)	75.9% (22/29)
Pediatric Visible Lesions	3	3	0% (0/3)	100% (3/3)
Adult Assessable Non-Visible Lesions	11 [a]	9	22.2% (2/9)	77.8% (7/9)
Pediatric Assessable Non-Visible Lesions	4 [b]	3	33.3% (1/3)	66.7% (2/3)

Source: Table created with data provided in the BLA 125659 original submission.
[a] Two baseline lesions were not assessed at Week 48.
[b] One baseline lesion requiring invasive procedural assessment was not assessed at Week 48.

Status of Visible Lesions at 48 Weeks:

Of the 32 visible lesions at baseline, 25 (78.1%) resolved and 7 (21.9%) improved by Week 48. These lesions mainly located in the eyes (ligneous conjunctivitis), nose, gingiva (ligneous gingivitis), gums, palmar and plantar warts.

- Of the 3 visible lesions at baseline for pediatric subjects, all 3 (100%) resolved by Week 48 with all lesions (3/3, 100%) responding by Week 4.

- Of the 29 visible lesions at baseline for adult subjects, 22 (75.9%) resolved and the remaining 7 (24.1%) improved by Week 48.

Status of Assessable Non-Visible Lesions at 48 Weeks:

Of the 12 assessable non-visible lesions at baseline for pediatric and adult subjects combined, 9 (75.0%) resolved and the remaining 3 (25.0%) improved by Week 48.

Status of Visible Lesions at Week 48 by Pediatric and Adult Subjects:

Of the 9 pediatric and adult subjects with visible lesions at baseline, 7 (77.8%) had complete resolution of lesions and the remaining 2 (22.2%) had improved lesions by Week 48.

- Of the 2 pediatric subjects with visible lesions at baseline, both (100%) had complete resolution of lesions by Week 48.
- Of the 7 adult subjects with visible lesions at baseline, 5 (71.4%) had complete resolution of lesions and the remaining 2 (28.6%) had improved lesions by Week 48.

Functional Assessment:

One subject with severe respiratory tract involvement had a >75% improvement in lung function at the Week 12 assessment. A response was first observed at Week 4. Further respiratory assessments were not made.

Recurrent or New Lesions:

No recurrent lesions nor new lesions appeared in any subject through Week 48, including those subjects with no lesions at baseline.

Table 12 Primary Efficacy Endpoint – Overall Clinical Success at Week 48

Subject Population	Overall Clinical Success (%) Based on All Lesions (Number of Subjects)	Overall Clinical Success (%) Based on Visible Lesions (Number of Subjects)	Overall Clinical Success (%) Based on Measurable Lesions (Number of Subjects)
Pediatric	100% (3/3)	100% (2/2)	100% (2/2)
Adult	100% (8/8)	86% (6/7)	100% (4/4)
Combined	100% (11/11)	89% (8/9)	100% (6/6)

Source: Modified from BLA 125659 original submission.

Reviewer Comment: U.S. subjects had the option of continuing with RYPLAZIM through a treatment protocol after completing the Phase 2/3 study. A total of 12 subjects enrolled in the protocol, including 8 subjects who completed the Phase 2/3 study. Lesion response for internal and external lesions after Week 48 through the last day of treatment was generally maintained or improved in both pediatric and adult subjects despite reductions in dosing frequency in many subjects. One subject ((b) (6) developed a new visible lesion on the left eye while on an every-5-day dosing, lesion resolved after changed to every-2-day dosing. There were no recurrent or new lesions in other subjects (See Appendix 1 for more detailed information).

Six patients between 11 months and 3 years of age received repeated administration of RYPLZIM through EAPs or Compassionate Use. All showed lesion improvement without any serious adverse reactions being report (see Appendix 2 for details).

Effect of RYPLAZIM cessation: A total of 4 subjects had a 30-day post final visit. Of these subjects, lesion response worsened for two subjects ((b) (6) Both

subjects had a heavy lesion burden at baseline and baseline plasminogen activity levels < 5%. Lesions continued to show a complete response with no new lesion through the 30-day post final visit in the other two subjects. The baseline plasminogen activity levels were 15% and 45%, respectively.

b. Th primary PK endpoint: The number and percentage of responders (i.e., a subject who achieves the target plasminogen activity trough level -- a minimum of an absolute 10% (10 U/dL) baseline-adjusted level -- for at least 3 assessed time points during the12 weeks epoch of Segment 2

All 15 subjects achieved their target plasminogen activity trough levels (i.e., ≥ absolute 10% above baseline) for at least 3 measurements during the 12 weeks of plasminogen replacement therapy in Segment 2. Please refer to the clinical pharmacology review for additional details.

6.1.11.2 Analyses of Secondary Endpoints

"Overall clinical success at week 12" was achieved as 73% of subjects with visible and assessable non-visible lesions at baseline had >50% improvement after 12 weeks of study drug treatment with RYPLAZIM.

- Clinical Global Impression-Global Improvement (CGI-I) scores
  - CGI-I Scale is a 7-point scale (1 = very much improved, 7 = very much worse) that is completed by the clinical investigator and is designed to document the clinician's perception of the change in the subject's clinical condition compared to baseline.
  - subjects were rated as very much improved (CGI-I score 1)
  - 2 subjects were much improved (CGI-I score 2)

- Quality of Life (QOL) Assessment
  - The quality of life assessment consisted of a 10-point scale (0 = non-functioning, 10 = normal), adapted from a scale developed by the American Chronic Pain Association, that is completed by the subject and is designed to capture the subject's perception of their quality of life.
  - 9 subjects had a score of 10 (normal) at baseline, and 13 had a score of 10 at Week 48.
  - QOL score were improved or maintained in all but 1 subject (93.3%) through Week 48.

Reviewer Comment: The secondary endpoints seem to support the primary endpoints. However, both secondary endpoints are subject to bias in the single arm, open label study. In addition, there is also a ceiling effect for the QOL endpoint, as subjects who were 10 at baseline had no room to improve.

6.1.11.3 Subpopulation Analyses

All data were presented descriptively for the combined subject population and also for adult and pediatric populations separately. No formal subpopulation analyses were performed due to small sample size.

6.1.11.4 Dropouts and/or Discontinuations

There were no dropouts during Week 48 study period.

6.1.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.1.12 Safety Analyses

6.1.12.1 Methods

6.1.12.2 Overview of Adverse Events

There were no deaths, and no subject had a treatment emergent adverse event (TEAE) that resulted in discontinuation of RYPLAZIM (Table 13).

Table 13 Overview of Treatment-Emergent Adverse Events, Safety Population

	Adult (N = 9)	Pediatric (N = 6)	Total (N = 15)
At least 1 TEAE	9 (100%)	6 (100%)	15 (100%)
At least 1 Severe TEAE	2 (22.2%)	4 (66.7%)	6 (40.0%)
At least 1 TEAE related to RYPLAZIM	4 (44.4%)	1 (16.7%)	5 (33.3%)
At least 1 TESAE	1 (11.1%)	2 (33.3%)	3 (20.0%)
At least 1 TESAE related to RYPLAZIM	0	0	0
At least 1 TEAE leading to study discontinuation	0	0	0
At least 1 TESAE leading to study discontinuation	0	0	0
At least 1 TEAE leading to death	0	0	0

TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.
Source: BLA125659 Study Report

Adverse reactions that occurs in 10% or more of subjects are listed in Table 14Table .

Table 14 Adverse Reactions (≥10%) of Study Subjects

Adverse Reactions	**Pediatric (N = 6)**	**Adult (N = 9)**	**Total (N = 15)**
Nausea	0	3 (33%)	3 (20%)
Fatigue	0	3 (33%)	3 (20%)
Headache	0	3 (33%)	3 (20%)
Abdominal pain	0	2 (22%)	2 (13%)
Abdominal pain lower	0	2 (22%)	2 (13%)
Constipation	0	2 (22%)	2 (13%)
Dry mouth	1 (17%)	1 (11%)	2 (13%)
Gastric dilatation	0	2 (22%)	2 (13%)
Dizziness	0	2 (22%)	2 (13%)
Arthralgia	0	2 (22%)	2 (13%)
Back pain	0	2 (22%)	2 (13%)
Pain in extremity	0	2 (22%)	2 (13%)
Vaginal hemorrhage	0	2 (22%)	2 (13%)

Source: BLA 125659 Study Report

Reviewer Comment: ARs seem to be more frequent in adult subjects; however, interpretation of data is limited due to 1) the small number of subjects in both adults and pediatric subjects and 2) under-reporting of symptoms in pediatric subjects.

Mild clinically-evident bleeding (vaginal bleeding, hematuria, oozing from ocular and cutaneous lesions) are likely a consequence of plasminogen's physiologic effects (lysis of ligneous lesions), which is supported by similar reports in the literature of patients with plasminogen deficiency type 1 who exhibited mild bleeding as ligneous lesions began resolving after treatment with IV Lys-plasminogen.

6.1.12.3 Deaths

There were no deaths.

6.1.12.4 Nonfatal Serious Adverse Events

Three subjects (20.0%) had a total of 4 serious adverse events, all of which were judged by the Investigator as not related to RYPLAZIM.

Subject (b) (6) **(5-year-old White not Hispanic/Latino female in the US) had** surgical procedures (ear operation [tympanomastoidectomy] and ossiculoplasty) to treat a right tympanic membrane perforation and conductive hearing loss after receiving approximately 105 weeks of RYPLAZIM treatment.

Subject (b) (6) **(4-year-old White not Hispanic/Latino female in the US) had a** severe pneumonia after receiving approximately 82 weeks of RYPLAZIM treatment.

Subject (b) (6) **(42-year-old White not Hispanic/Latino female in Norway) had a** severe ileus after receiving approximately 48 weeks of RYPLAZIM treatment.

Reviewer Comment: The reviewer agrees that these SAEs likely are unrelated to RYPLAZIM.

6.1.12.5 Adverse Events of Special Interest (AESI)
Patients with plasminogen deficiency type 1 may bleed from active mucosal disease-related lesions during RYPLAZIM therapy. Two adult subjects experienced vaginal hemorrhage, one adult experienced hematuria and one adult experienced hemoptysis. None of them were considered serious.

6.1.12.6 Clinical Test Results

Elevated D-dimer levels were observed in 3 subjects (b) (6) following RYPLAZIM treatment, all of whom had the lowest baseline plasminogen activity (< 5%) and highest baseline lesion burden (≥ 8 lesions). These elevations are consistent with reports in the literature regarding D-dimer elevation in patients with ligneous lesions immediately post-infusion of Lys-plasminogen. Since there were no clinical adverse events (e.g., thrombotic events) that accompanied the rise in D-dimer levels in these three subjects, and there was a strong temporal correlation between the elevations in D-dimer and infusion of, the elevated D-dimer levels appear to be reflective of physiologic effect (i.e., lysis of fibrinous lesions) of RYPLAZIM.

6.1.12.7 Dropouts and/or Discontinuations

There were no dropouts in the first 48 weeks of the study. Two subjects discontinued after 48 weeks.

6.1.13 Study Summary and Conclusions

Efficacy
The clinical data from study 2002C011G provide primary evidence of effectiveness of RYPLAZIM administered via IV infusion every 2-4 days in patients with type 1 plasminogen deficiency. The study was not concurrently controlled, but it was adequate to investigate efficacy outcomes for the rare condition of type 1 plasminogen deficiency, which has a well-defined natural history that is characterized by the formation of ligneous lesions that are notoriously difficult to resolve and recur despite surgical removal. All 11 subjects, including 3 pediatric subjects, who had lesions at baseline had at least 50% improvement in the number/size of their lesions after 48 weeks of treatment with RYPLAZIM. One subject with pulmonary lesions had abnormal spirometry at baseline which normalized after 12 weeks of treatment. There were no recurrent or new external lesions in any subject through Week 48.

Reviewer Comment: The efficacy outcomes indicated above would not be expected by chance alone, given what is known about the natural history of plasminogen deficiency type 1. These clinical outcomes are consistent with the hypothesized physiological effect of plasminogen administration to subjects with plasminogen deficiency type 1.

Safety
No subjects died during the study period, and no serious adverse events (SAEs) were reported. No subjects discontinued study participation due to the occurrence of an adverse event (AE). Two subjects experienced severe AEs that were classified by the PI as possibly related to Plasminogen (Human): Immediately after receiving Dose #20, one subject experienced transient nausea, fatigue, arthralgia, back pain, dizziness,

paresthesia, and flushing, which resolved after administration was temporarily paused and did not recur when treatment was re-initiated five days later. One subject experienced transient back pain 3 days after receiving Plasminogen (Human). The most common adverse reactions (>10%) experienced by all evaluable subjects during the 48-week study period were: abdominal pain, bloating, nausea, fatigue, extremity pain, hemorrhage, constipation, dry mouth, headache, dizziness, arthralgia, and back pain.

7. INTEGRATED OVERVIEW OF EFFICACY

An Integrated Summary of Efficacy (i.e., an analysis using pooled of data from subjects enrolled in studies 2002C005G and 2002C011G) was not performed, since subjects in study 2002C005G received only a single dose of IV RYPLAZIM for assessing PK, while subjects in study 2002C011G received dosing of RYPLAZIM every 2 to 4 days for 48 weeks for the primary efficacy analysis. Data from EAPs and Compassionate Use support efficacy of RYPLAZIM in improving lesions; however, due to lack of consistent outcome measures between clinical studies and EAP/Compassionate Use protocols, it is challenging to integrate efficacy.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The Integrated Overview of Safety is based on pooled data from subjects and patients treated with intravenous infusion of RYPLAZIM. The data were assembled from available clinical trial results, as well as data from Expanded Access and compassionate use.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

29 unique subjects/patients have been treated with RYPLAZIM as part of clinical trials, expanded access, and compassionate use. These programs are follows:

- A completed Phase 1 study (2002C005G), which was conducted in 7 adult and pediatric subjects, served as the basis for dosing for the Phase 2/3 study.
- A completed Phase 2/3 study (2002C011G) which provides primary evidence of effectiveness and safety in which IV Plasminogen (Human) was administered to 15 adult and pediatric subjects. 9 of these subjects were unique.
- Expanded Access and Compassionate Use Protocols: Supportive safety/efficacy data comes from US FDA's single patient expanded access protocols (b) (6)), a treatment protocol (b) (6)) for subjects who completed studies 2002C011G, (b) (6) and non-US single patient compassionate use protocols. 13 of these subjects were unique.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Table 15 summarizes the duration of treatments for these patients in different programs.

Table 15 Overall Repeat-Dose Exposure of RYPLAZIM

Programs	N	Male/ Female	Pediatric/ Adult	Age Range at the Start of Treatment	Treatment Exposure
Study 2002C011G [a]	15	4/11	6/9	4-42years	48-124 weeks[a]
Single-patient EAP	4	3/1	3/1	16 months-33 years	6-194 weeks
Compassionate use	9	7/2	8/1	11 months-38 years	4-214 weeks
Total	28	14/14	17/11	11 months-43 years	4-214 weeks

Source: BLA 12659 resubmission

8.2.3 Categorization of Adverse Events

Adverse events (AEs) were coded using MedDRA Version 19.1.

The Safety Population included all subjects who received RyPLAZIM regardless of follow-up status.

All AEs analyzed in the safety database were TEAEs, which refer to AEs with an onset date and time equal to or after RYPLAZIM treatments.

TEAEs were considered related (i.e., adverse reactions) if they were possibly or probably related based on temporal sequence between administration and the event, a biologically plausible relationship, or the lack of an alternative explanation for the event.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

The safety monitoring of patients in EAP, Compassionate use may not be as stringent or consistent as subjects in clinical trials. Some detailed information may lack in patients treated under EAP or Compassionate use.

8.4 Safety Results

8.4.1 Deaths

There were no deaths.

8.4.2 Nonfatal Serious Adverse Events

Three subjects had a total of 4 serious adverse events in Study 2002C011G. See Section 6.1.12.4 for details. In addition, the following SAEs were reported:

- Gastrointestinal (GI) hemorrhage: A 14 year-old male patient received RYPLAZIM for ligneous conjunctivitis, tracheobronchial, pharyngeal, and small intestine ligneous lesions via Compassionate use program in Israel. Severe hemorrhage was observed from the gastrostomy tube 2 days after the second dose. The patient was transfused with 2 packs of blood and 4 packs of FFP. Endoscopy showed multiple ulcers with one actively bleeding near the pylorus. The ulcer was coagulated, and the bleeding stopped. Follow-up endoscopy 7 days later showed no active bleeding. Sucralfate was added to esomeprazole for treatment of the peptic ulcer disease. A follow-up endoscopy was performed, and no ulcers were observed. Given the mechanism of action of plasminogen in

fibrinolysis, it is possible that RYPLAZIM played a role in either prolonging or worsening the active bleeding.

- Fever and neutropenia: 17 month-old female patient received RYPLAZIM via EAP (EAP (b) (6) . The patient was admitted to the hospital due to persistent fever and a down-trending absolute neutrophil count (ANC) of 320 cells/µL 2 months after starting RYPLAZIM. Empiric broad spectrum antibiotics were started. During the hospital stay the blood cultures stayed negative. The ANC nadired at 220 cells/µL and the ANC showed an up-trending. The patient was discharged on (b) (6) . Follow-up information received from the site showed the ANC at 101 cells/µL and 515 cells/µL 2 weeks later. This event was assessed as not related to RYPLAZIM but more likely due to the patient's underlying illness with the suppression of the bone marrow.

- Pyelonephritis: A 39 year-old female subject received RYPLAZIM in Study 2002C011G and then in the Treatment Protocol. The subject experienced the serious TEAE of pyelonephritis, which was considered as not related.

Reviewer Comment: Due to limited information on these SAEs, it is a little difficult to assess the relatedness. The reviewer agrees with applicant's assessments.

8.4.3 Study Dropouts/Discontinuations

Two subjects discontinued the Phase 2/3 study. Please see Table 8 for details.

8.4.4 Common Adverse Events

Table 16 summarizes the adverse reactions occurred in ≥ 10% of subjects who received repeated RYPLAZIM. Of the 29 unique subjects/patients treated with RYPLAZIM across all clinical programs, 10 were excluded from the pooled safety analysis as follows: 9 patients who received RYPLAZIM through single patient expanded access or Compassionate use were not included in the population for the determination of Adverse Reaction frequency. These patients were excluded as the monitoring and adverse event collection may not be as rigorous as subjects in clinical trials or patients in the Treatment protocols. Additionally, one subject who received only one dose in Study 2002C005G was also excluded.

Table 16 Adverse Reactions Reported in ≥ 10% of Patients with Plasminogen Deficiency Type 1

Adverse Reactions	Number of Patients (%) (N = 19)
Abdominal pain	3 (16%)
Gastric dilatation (bloating/feel bloated)	3 (16%)
Nausea	3 (16%)
Fatigue	3 (16%)
Pain in extremity	3 (16%)
Hemorrhage*	3 (16%)
Constipation	2 (11%)
Dry mouth	2 (11%)
Headache	2 (11%)
Dizziness	2 (11%)
Arthralgia	2 (11%)
Back pain	2 (11%)

*2 subjects had vaginal hemorrhage, 1 subject had hemoptysis and hematuria.
Source: Reproduced from RYPLAZIM package insert.

8.4.5 Clinical Test Results

Most patients in EAP and Compassionate Use programs had plasminogen level assessed prior to RYPLAZIM treatment. They were abnormal. Increase in plasminogen levels were observed after treatment.

See Sections 6.1.12.6 for clinical test results of Study 2002C011G.

8.4.6 Systemic Adverse Events

In Study 2002C011G, one of 15 subjects (6.7%) in had a TEAE associated with a change in BP; no subject had a TEAE associated with clinically significant changes in heart rate or respiratory rate. Six subjects (40.0%) had TEAEs of mild pyrexia that either resolved on the same day or within a few days; these events occurred at different times throughout the study, were not serious, and considered by the Investigator as not related to RYPLAZIM.

8.4.7 Local Reactogenicity

Not applicable.

8.4.8 Adverse Events of Special Interest

The SAE of GI hemorrhage suggest that RYPLAZIM can worsen active bleeding not related to disease lesions.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Two doses were assessed in Study 2002C005G. Both were administered as single administration. There is not clear relationship between dose and adverse events.

8.5.2 Time Dependency for Adverse Events

There is insufficient information to assess this.

8.5.8 Immunogenicity

In Study 2002C011G, three subjects (20%) developed anti-plasminogen antibodies following RYPLAZIM treatment. Comparison of pharmacokinetic (PK) parameters and /or trough activity levels for those positive samples with the parameters assessed either at baseline or for negative samples suggest these antibodies are not neutralizing antibodies (inhibitors) to plasminogen.

Reviewer Comment: None of the three subjects who developed anti-plasminogen antibodies had a clinically meaningful reduced response to RYPLAZIM. There was no decrease in plasminogen activity in these subjects based on a comparison of anti-plasminogen positive blood samples with anti-plasminogen negative blood samples. Taken together, data from these three subjects suggests that anti-plasminogen antibodies are not neutralizing *in vivo*, and do not interfere with the clinical effect of RYPAZIM.

8.6 Safety Conclusions

The most frequent adverse reactions (incidence ≥ 10%) observed in clinical studies and EAP / Compassionate Use include abdominal pain (16%), bloating (16%), nausea (16%), fatigue (16%), extremity pain (16%), hemorrhage (16%), constipation (11%), dry mouth (11%), headache (11%), dizziness (11%), arthralgia (11%), and back pain (11%). No subjects discontinued study participation due to adverse reactions. There were no deaths. One patient had serious AR of possible worsening of GI hemorrhage caused by gastric ulcer.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

One subject became pregnant during the study period and continued to receive RYPLAZIM after consultation with her physician. The subject delivered a baby who weighed 3.2 kg and measured 48 cm in length and who appeared to have no health issues. Labor was induced using oxytocin and the subject experienced post-partum hemorrhage (total estimated volume of hemorrhage = 1.3 L) that required treatment with methylergonovine and prostaglandin. The data from this single subject are insufficient to assess whether the RYPLAZIM can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

9.1.2 Use During Lactation

RYPLAZIM was not studied in breast-feeding mothers.

9.1.3 Pediatric Use and PREA Considerations

The safety and efficacy of RYPLAZIM has been established in pediatric patients. Use of RYPLAZIM is supported by the two clinical trials, expanded access and compassionate use programs that included 17 pediatric patients age 11 months to 16 years. See Appendices for the narratives of these patients.

Reviewer Comment: Twenty seven of the 28 patients who received repeated administrations of RYPLAZIM had onset of symptoms associated with plasminogen deficiency type 1 during childhood. So, this disease primarily affects pediatric patients.

RYPLAZIM is not subject to PREA, since the product received Orphan Drug designation.

9.1.4 Immunocompromised Patients

RYPLAZIM was not studied in immunocompromised subjects.

9.1.5 Geriatric Use

RYPLAZIM was not studied in geriatric subjects.

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

Not applicable.

10. CONCLUSIONS

The clinical information presented in the BLA supports the conclusion that RYPLAZIM administered via IV infusion is a safe and effective treatment for plasminogen deficiency type 1 in pediatric and adult patients.

The primary evidence of effectiveness is based on significant improvements in clinically meaningful efficacy outcomes observed in Study 2002C011G, an adequate and well-controlled study, for pediatric and adults with plasminogen deficiency type 1.

Study 2002C011G enrolled 15 subjects, including 6 pediatric subjects (4-16 years). All subjects received RYPLAZIM at a dose of 6.6 mg/kg administered every 2 to 4 days for 48 weeks or longer. Ten subjects, including 3 pediatric subjects, had lesions at baseline. At week 48, All subjects with any lesion at baseline had at least 50% improvement in the number or size of their lesions. There were no recurrent or new external lesions in any subject through Week 48. In addition, 6 pediatric subjects (11 months to 3 years of age) received repeat administrations of RYPLAZIM without any serious ARs.

The study had an overall clinical success of 100%, meaning that all subjects with any lesions at baseline (n=11) had at least 50% of their lesions resolved with a median time to resolution of 8 weeks.

Reviewer Comment: The implied control across the RYPLAZIM clinical development programs is actually external – i.e. the natural course of the disease in the absence of any form of plasminogen replacement therapy. Therefore, it is understood that it is highly unlikely that disease associated ligneous lesions would resolve spontaneously for a prolonged period of time in the absence of RYPLAZIM.

The effectiveness of RYPLAZIM was supported by data from EAPs and Compassionate Use. In addition to the 6 pediatric subjects enrolled in the Phase 2/3 study (4-16 years), 6 pediatric patients (age 11 months to 3 years) received repeat administrations of RYPLAZIM through these programs showed improvement in lesions.

The safety database included 29 subjects from clinical trials and EAPs and Compassionate Use. RYPLAZIM was well-tolerated, with a favorable safety profile. The potential serious risks with IV infusion of RYPLAZIM include bleeding, tissue sloughing, hypersensitivity reaction, transmission of infectious disease agents and neutralizing antibodies. These risks can be mitigated by adequate risk mitigation information in the PI and Patient Information Sheet, and routine pharmacovigilance plan.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

Risk-benefit considerations for RYPLAZIM are summarized in Table 17.

Table 17 Risk-Benefit Assessment: Evidence and Conclusions

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The primary clinical manifestations are the formation of ligneous lesions that are a result of a decreased capacity for fibrinolysis due to plasminogen deficiency. • Ligneous lesion can result in serious (e.g., blindness due to corneal involvement in patients with ligneous conjunctivitis, severe pain due to conjunctival and uterine lesions) and life-threatening (e.g., respiratory failure due to tracheobronchial obstruction, renal insufficiency due to genitourinary tract obstruction) clinical conditions.	• Plasminogen deficiency type 1 is a serious and life-threatening condition, based on the clinical manifestations of patients with this condition.
Unmet Medical Need	• There are no approved therapeutics for treatment of patients with plasminogen deficiency type 1. • Surgical removal of ligneous lesions results in only temporary relief for patients, since there is near universal recurrence of the lesions within weeks to months. • Due to the lack of approved therapies, the condition is associated with significant morbidity.	• There is an unmet medical need for medical therapy for patients who have plasminogen deficiency type 1.
Clinical Benefit	• The primary evidence of efficacy comes from a single Phase 2/3 clinical trial, in which 15 subjects who were 4 to 42 years of age received IV infusion of RYPLAZIM at a dose of 6.6 mg/kg administered every 2 to 4 days for 48 weeks. There were 6 pediatric subjects (4-16 years). Efficacy was established on the basis of overall rate of clinical success at 48 Weeks. Overall rate of clinical success is defined as 50% of patients with visible or other measurable non-visible lesions achieving at least 50% improvement in lesion number/size. All subjects with any lesion at baseline had at least 50% improvement in the number or size of their lesions. There were no recurrent or new external lesions in any subject through Week 48. • Based on the natural history, sustained significant improvement or resolution of disease-associated ligneous lesions is highly unlikely to have occurred spontaneously; additionally, the lack of appearance of new lesions over the 48-week study period is highly unlikely to have occurred by chance alone given the pathophysiology of the condition. • 6 pediatric subjects (age 11 months to 3 years) received repeat administrations of RYPLAZIM via expanded access / Compassionate Use with clinical benefit.	• The clinical data collected after 48 weeks of treatment with RYPLAZIM provide substantial evidence of a clinical benefit regarding resolution of ligneous lesions due to plasminogen deficiency type 1.
Risk	• The most common adverse reactions included: abdominal pain, gastric dilatation, nausea, fatigue, pain in extremity, hemorrhage, constipation, dry mouth, headache, dizziness, arthralgia, and back pain. • Some subjects experienced mild bleeding at the site of resolving ligneous lesions, which appears to be consistent with the expected physiologic consequence of lesion resolution due to increased fibrinolysis. RYPLAZIM can worsen active bleeding. • Potential risks include transmission of infectious disease agents, tissue sloughing, hypersensitivity reactions, which have not been observed in clinical development.	• The available evidence indicates that IV infusion of RYPLAZIM is associated with a relatively low level of risk.
Risk Management	The risk management plan consists of • Routine pharmacovigilance plan. • Adequate information provided in Prescribing Information (PI) and Patient Information Sheet.	• Risks can be mitigated through routine medical management and adequate PI without requiring other regulatory measures such as REMS, or PMR.

11.2 Risk-Benefit Summary and Assessment

The overall risk-benefit of administering IV RYPLAZIM to patients with plasminogen deficiency type 1 is sufficiently favorable, given that RYPLAZIM appears to have been generally safe, with compelling evidence of clinical benefit regarding resolution of ligneous lesions that are difficult to treat, and there is an unmet medical need for treatment of plasminogen deficiency type 1 in the absence of any FDA-approved therapies.

11.3 Discussion of Regulatory Options

The regulatory options include a decision as to whether to approve the BLA.

11.4 Recommendations on Regulatory Actions

Based on analyses of the clinical safety and efficacy data contained in the BLA submission, the Clinical Reviewer considers the benefit/risk favorable in support of traditional approval of RYPLAZIM for the treatment of plasminogen deficiency type 1 in pediatric and adult patients.

11.5 Labeling Review and Recommendations

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

The overall content of the PI suitably conveys known information regarding safety and efficacy results of RYPLAZIM demonstrated in clinical trials, and from the expanded access program.

The overall content of the PI contains adequate warnings for medical practitioners, as well as for caregivers, considering RYPLAZIM for treatment of plasminogen deficiency type 1.

11.6 Recommendations on Postmarketing Actions

Based on the review of the safety data submitted in the BLA, the Applicant's proposed postmarketing risk mitigation plans, including adequate risk mitigation information in the PI and Patient Information Sheet, and routine pharmacovigilance plan, are acceptable.

The available data do not suggest a safety concern that would warrant either a Risk Evaluation and Mitigation Strategy (REMS) or a safety related PMR clinical study.

APPENDICES

Appendix 1 – Narratives of baseline, treatment and outcome of 15 subjects of Study 2002C011G

Subject (b) (6): female, 41 years-old, symptoms started at 8 months of age; had 2 visible/measurable lesions on her left and right eyes, each measuring 10 mm × 2 mm, a non-visible lesion on her cervix with dysmenorrhea and painful intercourse; a plasminogen activity level of 29% at screening and was enrolled in Study 2002C011G; received RYPLZIM at a dose of 6.6 mg/kg administered every 3-4 days for at least 96 weeks and every 7 days thereafter for a total of 186 weeks (120 week in Study 2002C011G and the rest in Treatment Protocol 2002C018G); Her plasminogen activity trough levels exceeded the target of ≥ absolute 10% above baseline; her lesions resolved after 4 weeks of treatment in Study 2002C011G; no new or recurrent lesions; Reported 23 TEAEs, including a severe TEAE of pyelonephritis, none of the TEAEs were considered related.

Subject (b) (6): male, 35 years-old, developed ligneous conjunctivitis on both eyelids and was diagnosed with plasminogen deficiency type 1 at approximately 9 months of age; had 9 conjunctival surgeries; 1 visible/measurable lesion on his left eye, measuring 15 mm × 5 mm; a plasminogen activity level of 43% at screening and was enrolled in Study 2002C011G; received RYPLAZIM at a dose of 6.6 mg/kg administered every 2-3 days for at least 48 weeks, and every 4-7 days thereafter for a total of 117 weeks; plasminogen activity trough levels exceeded the target of ≥ absolute 10% above baseline; lesions resolved after 4 weeks of treatment in Study 2002C011G; no new or recurrent lesions; No TEAEs reported; discontinued the study 2002C011G due to Investigator's discretion (subject non-compliance), 30 days after the last dose.

Subject (b) (6): female, 16 years-old, symptoms developed ligneous conjunctivitis at about 2 year of age and was diagnosed at 3 years of age; received, heparin, FFP, plasminogen drop for ligneous conjunctivitis and ear lesions, which were resolved; no visible or non-visible lesion and a plasminogen activity level of 28% at screening and was enrolled in Study 2002C011G; received RYPLZIM at a dose of 6.6 mg/kg administered every 4 days for 48 weeks, and every 7 days thereafter for a total of 86 weeks; Her plasminogen activity trough levels exceeded the target of ≥ absolute 10% above baseline; no new lesions; Reported 26 TEAEs, none were considered related.

Subject (b) (6) female, 24 years-old, symptoms of ligneous conjunctivitis started during infancy and was diagnosed at about 17 months of age, additional lesions noted on the nares, gingiva, tonsils, vocal cords, cervix, ovaries, urethra, and lungs, tried FFP, heparin, laser removal of cervical lesions; had 1 visible lesion on her upper gingiva, 1 non-visible lesion in her bronchus with a percent predicted normal FEV1 of 115% and a plasminogen activity level of 28% at screening and was enrolled in Study 2002C011G; received RYPLZIM at a dose of 6.6 mg/kg administered every 3-4 days for 189 weeks (including 123 weeks in Study 2002C011G, and 66 weeks via Compassionate use in United Kingdom; Her plasminogen activity trough levels exceeded the target of ≥ absolute 10% above baseline; her lesions resolved after 4 weeks of treatment in Study 2002C011G; no new or recurrent lesions; Reported 37 TEAEs, none of the TEAEs were considered related.

Subject (b) (6): male, 37 years-old, symptoms of ligneous conjunctivitis in both eyes started around 2 years of age and was diagnosed at about 5 years of age, no lesion and a plasminogen activity level of 22% at screening and was enrolled in Study 2002C011G; received RYPLZIM at a dose of 6.6 mg/kg administered every 3-4 days for 123 weeks in Study 2002C011G, and every 7 days for 60 weeks via Compassionate use in Canada (total treatment duration: 183 weeks); plasminogen activity trough levels exceeded the target of ≥ absolute 10% above baseline; no new or recurrent lesions; Reported 7 TEAEs, none of the TEAEs were considered related.

Subject (b) (6): female, 37 years-old, symptoms of ligneous conjunctivitis started around 2 years of age and was diagnosed at about 14 years of age, had 18 eye surgeries to remove lesions; had 7 visible/non-measurable lesions on left and right eyes, lower gingiva and upper gingiva and nonvisible lesions on bronchus, nasal area and renal area, a percent predicted normal FEV1 of 46.7%, and plasminogen activity level of <5% at screening and was enrolled in Study 2002C011G; received RYPLZIM at a dose of 6.6 mg/kg administered every 2-4 days for 190 weeks (124 weeks in Study 2002C011G, and 66 weeks in the Treatment Protocol); plasminogen activity trough levels exceeded the target of ≥ absolute 10% above baseline; the eye and gingival lesions resolved at Week 4 and the bronchial lesion resolved with normal FEV1 at Week 12, no new or recurrent lesions; Reported 4 TEAEs, none of the TEAEs were considered related.

Subject (b) (6): female, 22 years-old, diagnosed at about 10.5 years of age with no lesions, had cervical bleeding and pain later; 1 non-visible lesion on cervix and plasminogen activity level of 31% at screening and was enrolled in Study 2002C011G; received RYPLZIM at a dose of 6.6 mg/kg administered every 3-4 days for 96 weeks and then every 7 days for 93 weeks for a total 189 weeks (120 weeks in Study 2002C011G, and 69 weeks in the Treatment Protocol); plasminogen activity trough levels exceeded the target of ≥ absolute 10% above baseline; cervical lesion resolved at Week 24, no new or recurrent lesions; Reported 7 TEAEs, none of the TEAEs were considered related.

Subject (b) (6): female, 5 years-old, developed ligneous conjunctivitis at 4 years and diagnosed at about 5 years of age, had 3 eye surgeries to remove lesions; 2 visible/measurable lesions on lower/ upper lids of the right eye, measuring 10 mm×5 mm and 15 mm ×5 mm, respectively and plasminogen activity level of 22% at screening and was enrolled in Study 2002C011G; received RYPLZIM at a dose of 6.6 mg/kg administered every 3 days for 96 weeks and then every 4 days afterwards for a total of 184 weeks in Study 2002C011G, and the Treatment Protocol; plasminogen activity trough levels exceeded the target of ≥ absolute 10% above baseline; resolved 1 eye lesion at Week 8 and 1 eye lesion at Week 24 and improvement in the vaginal lesion at Week 48, no new or recurrent lesions; Reported 17 TEAEs, including 2 severe TEAEs, none of the TEAEs were considered related.

Subject (b) (6) female, 16 years-old, developed ligneous conjunctivitis and diagnosed at about 8 years of age, later ligneous vaginitis; 2 non-visible lesions on her colon and vagina, and plasminogen activity level of 20% at screening and was enrolled in Study 2002C011G; received RYPLZIM at a dose of 6.6 mg/kg administered every 3-4 days for a total of 184 weeks (112 weeks in Study 2002C011G, and 72 weeks in the Treatment Protocol); plasminogen activity trough levels exceeded the target of ≥ absolute 10% above baseline; resolved the colon and vaginal lesions at Week 12, no new or recurrent

lesions; Reported 57 TEAEs, no serious TEAEs, none of the TEAEs were considered related.

Subject (b) (6): female, 11 years-old, developed ligneous conjunctivitis and diagnosed at 5 years of age; 1 visible/measurable lesion on her left eye, measuring 5 mm × 3 mm, 1 non-visible lesion on her colon and plasminogen activity level of 17% at screening and was enrolled in Study 2002C011G; received RYPLZIM at a dose of 6.6 mg/kg administered every 3-4 days for108 weeks in Study 2002C011G, then every 5 days for 67 weeks in the Treatment Protocol; plasminogen activity trough levels exceeded the target of ≥ absolute 10% above baseline; resolved eye lesion, colon lesion not assessed due to the invasiveness of the procedure and need for anesthesia, no new or recurrent lesions; Reported 45 TEAEs, no serious TEAEs, none of the TEAEs were considered related.

Subject (b) (6): male, 6 years-old, developed ligneous conjunctivitis and diagnosed at 4.5 years of age; no lesions and plasminogen activity level of 29% at screening and was enrolled in Study 2002C011G; received RYPLZIM at a dose of 6.6 mg/kg administered every 2-5 days for 96 weeks in Study 2002C011G, then every 7-10 days for 67 weeks in the Treatment Protocol; plasminogen activity trough levels exceeded the target of ≥ absolute 10% above baseline; developed a new visible non-measurable lesion on the left eye on prior to the Week 60 assessment while on an every-5-day dosing, lesion resolved after changed to every-2-day dosing; Reported 29 TEAEs, no serious TEAEs, none of the TEAEs were considered related.

Subject (b) (6): female, 4 years-old, developed ligneous conjunctivitis and diagnosed at 5 months of age, had multiple procedures; no lesions and plasminogen activity level of 18% at screening and was enrolled in Study 2002C011G; received RYPLZIM at a dose of 6.6 mg/kg administered every 3-4 days for 84 weeks in Study 2002C011G, then every 5 days for 4 weeks in Study 2002C011G and for 66 weeks in the Treatment Protocol; plasminogen activity trough levels exceeded the target of ≥ absolute 10% above baseline; no new or recurrent lesion; Reported 28 TEAEs, including one serious TEAE of pneumonia, none of the TEAEs were considered related.

Subject (b) (6): male, 33 years-old, diagnosed at 22 years of age, unknown onset of symptoms, had ligneous conjunctivitis in both eyes, lesions in gingival lesions, nose lesion, skin lesions, airway and palmar/plantar; 8 visible lesions (2 measurable lesions on his left and right eyes, each measuring 4 mm × 4 mm, and 6 non-measurable lesions on his lower/upper gingiva, acne on, multiple wounds/scars on both hands, palmar warts, and plantar warts), 1 non-visible lesion on the bronchus and plasminogen activity level of <5% at screening and was enrolled in Study 2002C011G; received RYPLZIM at a dose of 6.6 mg/kg administered every 2-3 days for 48 weeks in Study 2002C011G, then for 114 weeks through compassionate use in Norway; plasminogen activity trough levels exceeded the target of ≥ absolute 10% above baseline; resolved bronchial lesion at Week 4, eye lesions at Week 8, and gingival lesions and plantar warts at Week 48, and improved acne, wounds/scars, and palmar warts through Week 48; when RYPLAZIM was stopped for 29 days for the post treatment safety visit, many of his lesions worsened, the eye lesions showed a complete response and skin manifestations demonstrated improvement after restarting; reported 19 TEAEs, 7 TEAEs were considered related.

Subject (b) (6): female, 33 years-old, ligneous conjunctivitis developed about 1 year old and diagnosed at 18 years of age; 3 visible lesions including 1 measurable lesion on left eye, measuring 4 mm × 3 mm, and 2 non-measurable lesions (scars) on her right shoulder, 1 non-visible lesion on her uterus, and plasminogen activity level of 15% at screening and was enrolled in Study 2002C011G; received RYPLZIM at a dose of 6.6 mg/kg administered every 2-4 days for 64 weeks in Study 2002C011G, then intermittently (every 7 or 14 days and stopped for 3 weeks twice) for 99 weeks through compassionate use in Norway; plasminogen activity trough levels exceeded the target of ≥ absolute 10% baseline; resolved eye and non-visible uterine lesions at Week 12 and the non-measurable scars at Week; became pregnant and delivered a healthy baby girl while remaining on treatment; reported 65 TEAEs, 58 TEAEs were considered related.

Subject (b) (6) female, 42 years-old, developed ligneous conjunctivitis, gingivitis, and oral lesions during infancy and diagnosed at 31 years of age; 7 visible/non-measurable lesions on her left/right eyes, lower/upper gingiva, fluctuating tumors on both wrists, palmar wart, and plantar warts, 3 non-visible lesions on her bronchus, abdomen, and uterus and plasminogen activity level of <5% at screening and was enrolled in Study 2002C011G; received RYPLZIM at a dose of 6.6 mg/kg administered every 2-3 days for 56 weeks in Study 2002C011G, then for 111 weeks through compassionate use in Norway; plasminogen activity trough levels exceeded the target of ≥ absolute 10% above baseline; resolved bronchial lesion by Week 4, the uterine lesion by Week 8, eye lesions by Week 12 and the fluctuating tumors by Week 36; reported 88 TEAEs, 70 TEAEs were considered related; 1 serious TEAE, not related.

Appendix 2 – Narratives of baseline, treatment and outcome of patients who received repeated RYPLAZIM via treatment protocol, EAP or Compassionate use

Expanded Access Protocol (b) (6) with Continued Treatment in Treatment Protocol 2002C018G [Patient (b) (6)

Female, 17 months-old, developed ligneous conjunctivitis and diagnosed at 3 weeks of age, had multiple procedures for surgical removal of the conjunctival lesions, improved with plasminogen concentrate ophthalmologic drops, but exacerbated after respiratory infection, later developed airway obstruction due to deposits in the right mainstem bronchus; tried FFP without much improvement, via EAP, received RYPLZIM at a dose of 6.6 mg/kg administered every day for 5 days followed by every 2-3 days for 138 weeks via EAP, and for 12 weeks in the Treatment Protocol; plasminogen activity trough levels increased from 12% to 108%; airway lesions improved after 10 days of RYPLAZIN treatment, no recurrence of airway lesions. No safety concerns noted.

Expanded Access Protocol (b) (6) with Continued Treatment in Treatment Protocol 2002C018G [Patient (b) (6)]

Male, 16 months-old, diagnosed at 7 months of age, symptoms included ligneous conjunctivitis in both eyes, recurrent pneumonia and asthma likely due to tracheobronchial involvement; due to airway obstruction and hypoxemia secondary to ligneous lesions in both main bronchi, received RYPLZIM via EAP at a dose of 6.6 mg/kg administered every day initially followed by every 2-3 days for 25 weeks, and then every 4 days for 62 weeks in the Treatment Protocol; showed improvement in in respiratory function and no recurrence of eye lesions post-surgery. No safety concerns were noted in this patient.

Expanded Access Protocol (b) (6)

Male, 3-years old, ligneous conjunctivitis started at 6-7 weeks old and diagnosed at 2-3 years of age, FFP and plasminogen eye drop was used with some improvement; due to identification of airway lesions, received RYPLZIM via EAP at a dose of 6.6 mg/kg administered every day initially followed by every 2-3 days for 6 weeks; improvement in lesions was observed, no safety concerns were noted in this patient.

Compassionate Use: Treatment of a 17 Year-Old Male in Germany

Male, 17 years-old, symptoms included ligneous conjunctivitis, gingivitis, respiratory distress and hearing loss baseline plasminogen activity level <10%; received RYPLZIM via Compassionate use at a dose of 6.6 mg/kg administered every day initially followed by 1-3 times a week for 188 weeks, respiratory function improved. No safety concerns were noted in this patient.

Compassionate Use: Treatment of a 38 Year-Old Male in Germany

38 year-old male with heterozygous mutation of *PLG* and a heterozygotes defect of factor V, had a history of poor chronic wound healing, frequent upper respiratory tract infections and suffered from recurrent bronchitis, baseline plasminogen activity was 45%; received RYPLZIM via Compassionate use to improve wound healing at a dose of 6.6 mg/kg administered 3 time a week for 4 weeks, improvement in symptoms of chronic

bronchitis, no report of improvement in wound healing; no safety concerns were noted in this patient.

Compassionate Use: Treatment of a 11 Month-Old Female in Germany

Female, 11 months-old, baseline plasminogen activity was 27%, received RYPLZIM via Compassionate use due to ligneous conjunctivitis, VP shunt malfunction with persistent hydrocephalus and ascites, and failure to thrive at a dose of 6.6 mg/kg administered 1-5 days per week for 66 weeks, ligneous conjunctivitis and ascites improved. No safety concerns were noted in this patient.

Compassionate Use: Treatment of a 5 Year-Old Male in Germany

Male, 5 years-old, plasminogen activity trough levels during FFP administration ranged from 15%-40%, received RYPLZIM via Compassionate use due to ligneous conjunctivitis, gingival hyperplasia, and central line associated thrombosis extending into the right atrium, at a dose of 6.6 mg/kg administered every 3 days for 7 weeks, ligneous conjunctivitis and gingival hyperplasia improved. No safety concerns were noted in this patient.

Compassionate Use: Treatment of a 14 Year-Old Male in United Kingdom

Male, 14 years-old, had severe ligneous conjunctivitis, baseline plasminogen activity level 12%, received RYPLZIM via Compassionate use due to ligneous conjunctivitis, at a dose of 6.6 mg/kg administered twice a week, ligneous conjunctivitis resolved, on RYPLAZIM for 177 weeks. No safety concerns were noted in this patient.

Compassionate Use: Treatment of a 6 Year-Old Female in United Kingdom

Female, 6 years-old, had ligneous conjunctivitis, baseline plasminogen activity level 27%, received RYPLZIM via Compassionate use due to ligneous conjunctivitis, at a dose of 6.6 mg/kg administered twice a week to every 28 days, ligneous conjunctivitis resolved, lesion recurred when dosed every 35 days, on RYPLAZIM for 170 weeks. No safety concerns were noted in this patient.

Compassionate Use: Treatment of a 3 Year-Old Male in United Kingdom

Male, 3 years-old, had severe ligneous conjunctivitis, baseline plasminogen activity level 12%, received RYPLZIM via Compassionate use due to ligneous conjunctivitis, at a dose of 6.6 mg/kg administered twice a week and then every 7 days, ligneous conjunctivitis improved, on RYPLAZIM for 12 weeks. No safety concerns were noted in this patient.

Compassionate Use: Treatment of a 14 Year-Old Male in Israel

Male, 14 years-old, had ligneous conjunctivitis, tracheobronchial, pharyngeal, and small intestine ligneous lesions, baseline plasminogen activity level unknown, history of peptic ulcer bleeding treated with esomeprazole about 1 month before initiating RYPLZIM, received RYPLZIM via Compassionate use, at a dose of 6.6 mg/kg administered every 2 days for two doses, experienced GI bleeding 2 days after the second dose, stopped RYPLAZIM for 16 days, restarted at the same dose twice a week for 22 weeks, no

change of lesion, experienced a serious AE of GI bleeding 2 days after the second dose of RYPLAZIM, found to have peptic ulcer, considering the mechanism of action of plasminogen in fibrinolysis, it is possible that the plasminogen played a role in either prolonging or worsening the active bleeding