Summary Basis for Regulatory Action

Date	**4 June 2021**
From	Alexey Khrenov, PhD, Review Committee Chair, OTAT/DPPT
BLA STN	**125659/0**
Applicant	**Prometic Biotherapeutics Inc.**
Submission Receipt Date	**14 August 2017**
PDUFA***Action Due Date**	**5 June 2021**
Proper Name	**plasminogen, human-tvmh**
Proprietary Name	**RYPLAZIM**
Indication	**Treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia)**

***** PDUFA = Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this BLA.

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Director, Office of Tissues and Advanced Therapies

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Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC, Product	Alexey Khrenov, PhD, OTAT/DPPT Ze Peng, PhD, OTAT/DPPT
• Facilities review	Priscilla M Pastrana, OCBQ/DMPQ Jie He, OCBQ/DMPQ
• Establishment Inspection Report	Eileen Liu, ORA/OBPO Linda Thai, ORA/OBPO
• QC, Test Methods, Product Quality	Ritu Agarwal, OCBQ/DBSQC Marie Anderson, OCBQ/DBSQC Salil Ghosh, OCBQ/DBSQC
Clinical • Clinical	Gavin Imperato, MD, PhD, OTAT/DCEPT Jasmine Gatti, MD, OTAT/DCEPT Lei Xu, MD, PhD, OTAT/DCEPT Ilan Irony, MD, OTAT/DCEPT
• Postmarketing safety epidemiological review (OBE/DE)	Bethany Baer, MD, OBE/DE Adamma Mba-Jonas, MD, MPH, OBE/DE
• BIMO	Haecin Chun, OCBQ/BMB
Statistical • Clinical data (OBE/DB) • Non-clinical data	Boris Zaslavsky, PhD, Dr.Sci., OBE/DB
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Theresa Chen, PhD, OTAT/DCEPT
Clinical Pharmacology	Xiaofei Wang, PhD, OTAT/DCEPT
Labeling • Promotional	Kristine Khuc, OCBQ/APLB

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1. Introduction

Biologics License Application (BLA) under STN 125659/0 was submitted by Prometic Biotherapeutics Inc. (Prometic) for plasminogen, human-tvmh, with the proprietary name RYPLAZIM. RYPLAZIM is indicated for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia). The active ingredient in RYPLAZIM is plasminogen purified from human plasma in compliance with 21 CFR 640.60.

RYPLAZIM is supplied in one dosage strength of 68.8 mg lyophilized plasminogen in a 50-mL single-dose glass vial. RYPLAZIM is reconstituted with 12.5 mL sterile Water for Injection (sWFI) for intravenous administration. RYPLAZIM contains no preservative.

This document summarizes the basis for approval of RYPLAZIM. A single-arm, open-label, 48-week Phase 2-3 clinical trial provides primary evidence of effectiveness and safety of RYPLAZIM for the treatment of plasminogen deficiency type 1 in adult and pediatric patients. Data from a Phase 1 trial, as well as patients treated through Expanded Access and Compassionate Use protocols contribute further to the safety and effectiveness database.

No patients who received RYPLAZIM died. One serious adverse event of possible worsening of gastrointestinal hemorrhage secondary to gastric ulcers was reported. No patients discontinued study participation or RYPLAZIM 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 and Compassionate Use programs.

The review team recommends traditional approval of this BLA with the Chemistry, Manufacturing, and Control Postmarketing Commitments (PMCs) described in Section11c “Recommendation for Postmarketing Activity.”

2. Background

Disease Background:

Plasminogen deficiency type 1 is a rare autosomal recessive disorder of homeostasis, caused by biallelic mutations in the *plasminogen* (*PLG*) gene, resulting in reductions in both the serum plasminogen antigen and activity level. Plasminogen is a normal component of human blood, and is cleaved to form plasmin, which is the main effector of fibrinolysis in human circulation. Patients with plasminogen deficiency type 1 experience substantial disease-related morbidity from ligneous lesions, which are thick, woody deposits that primarily 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.

Regulatory History

The BLA was submitted by Prometic Biotherapeutics Inc., which is a wholly-owned subsidiary of, and U.S. agent for Liminal Biosciences Inc. (Liminal; formerly Prometic Life Sciences Inc.), headquartered in Laval, Canada. Prometic Bioproduction Inc. is another Liminal subsidiary, also located in Laval, Canada, where the RYPLAZIM bulk drug substance is manufactured. The Prometic and Liminal entities operate essentially as parts of a single company.

RYPLAZIM was developed for the U.S. market under IND 16186. A BLA for RYPLAZIM was first submitted under STN 125647/0 as a rolling BLA. The final modules were submitted on 4 April 2017, and a "Refuse To File" (RTF) Letter was issued to Prometic on 1 June 2017 due to significant amount of information missing from the BLA.

The current BLA, STN 125659/0, was submitted on 14 August 2017, which included an itemized response to the deficiencies outlined in the RTF Letter. The BLA was reviewed under the priority review schedule (8 months) of the PDUFA V program, as the indication for RYPLAZIM was granted Orphan Drug and Rare Pediatric Disease designations.

Substantive CMC deficiencies related to the validation of the manufacturing process, characterization of the bulk drug substance (BDS) and final drug product (FDP), specifications, facilities and equipment were identified during the review of the BLA and pre-license inspection (PLI) of the Prometic facility in Laval, Canada on 14-21 November 2017. As a result, a Complete Response Letter (CRL) was issued to Prometic on 9 April 2018. Prometic provided a complete response to the CRL on 4 September 2020 in an amendment under STN 125659/0.18. In response to an Information Request, Prometic submitted an amendment (STN 125659/0.19) containing a significant amount of new information regarding responses to Form 483 observations. On 6 November 2020 this amendment was classified as a Major Amendment, and the Action Due Date was changed to 5 June 2021.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Orphan Drug designation granted	5 March 2013
2. Pre-IND meeting	6 February 2014
3. IND submission	26 September 2014
4. Fast Track designation granted	7 June 2016
5. Pre-BLA meeting	5 October 2016
6. Rare Pediatric Disease designation granted	25 August 2017
7. BLA STN 125647/0 submission	4 April 2017
8. Refuse To File letter issued	5 June 2017
9. BLA STN 125659/0 submission	14 August 2017
10. BLA filed	12 October 2017
11. Mid-Cycle communication	14 December 2017
12. Late-Cycle meeting	8 March 2018
13. Complete Response Letter issued	9 April 2018
14. Response to Complete Response Letter	4 September 2020
15. Major Amendment	6 November 2020
16. Action Due Date	5 June 2021

3. Chemistry Manufacturing and Controls (CMC)

The review team concludes that the manufacturing process for RYPLAZIM is capable of yielding a product with consistent and acceptable quality attributes and recommends approval of the BLA.

a. Product Quality

RYPLAZIM - Structure, Function and Purity

The active ingredient in RYPLAZIM is plasminogen purified from human plasma, which acts as a replacement therapy for patients with plasminogen deficiency type 1. Plasminogen, the zymogen of plasmin, is synthesized in the liver and circulates in the blood.

The native form of plasminogen, Glu-plasminogen, contains 791 amino acids, 24 disulfide bridges with no free sulfhydryls, and five regions of internal sequence homology, known as kringles, between Lys 77 and Arg 560. Glu-plasminogen has a molecular weight of about 90 kDa and an isoelectric point (pI) of approximately 7, although differential glycosylation and/or removal of the N-terminal activation peptide can result in a pI range of 6-9. The protein has one N-linked and two O-linked glycosylation sites. Approximately 70% of the plasminogen in circulation contains only O-linked glycosylation, while the rest contains both N- and O-linked sugars.

Plasminogen is distributed throughout the body, and when the conditions are present for activation, the plasminogen zymogen is converted to the active enzyme, plasmin, by either tissue or urokinase plasminogen activator. Plasmin degrades fibrin clots and converts latent matrix metalloproteinases (pro-MMPs) into active MMPs, which further degrade extracellular matrix as part of the tissue healing/remodeling process.

RYPLAZIM is (b) (4) pure Glu-plasminogen. Product-related impurities include (b) (4) the product of (b) (4) while fully functional, is considered an impurity in RYPLAZIM, indicating the presence of (b) (4).

RYPLAZIM may also contain other plasma-derived proteins, including (b) (4)

(b) (4) chemical leachables and elemental impurities are potential process-related impurities, the levels of which are reduced and controlled during manufacture. The (b) (4) is unique to the RYPLAZIM process. However, studies provided by Prometic demonstrate that (b) (4)

Manufacturing process

The RYPLAZIM manufacturing process is outlined in Table 2. (b) (4)

(b) (4) producing the fully formulated BDS, which is (b) (4) before FDP manufacture.

FDP manufacture involves the (b) (4) of a (b) (4), which is packaged in (b) (4), sterile filtration, filling and lyophilization. The manufacture of the Intermediate and BDS are performed at Prometic Bioproduction Inc. in Laval, Canada; and the FDP is manufactured at (b) (4)

Table 2. RYPLAZIM manufacturing process

Intermediate Process	**Bulk Drug Substance (BDS) Process**	**Final Drug Product (FDP) Process**
(b) (4)	(b) (4)	(b) (4) ↓ **2.** Filtration (b) (4) ↓ **3.** Aseptic Filling and (b) (4) Stoppering ↓ **4.** Lyophilization (b) (4) Stoppering ↓ **5.** Oversealing ↓ **6.** 100% Visual Inspection ↓ **7.** Labeling and Packaging ↓ FDP

Controls of manufacturing process

The control strategy for the manufacture of RYPLAZIM is composed of a combination of process and product quality controls at different process steps and intermediates. Prometic identified Critical Quality Attributes (CQAs) in a risk assessment exercise and used the CQAs to establish a control scheme that includes Critical Process Parameters (CPPs) and In-Process Controls (IPCs). The acceptable ranges for the IPCs and CPPs are statistically justified and reasonable. The IPCs and CPPs allow adequate control over the performance of the manufacturing process steps and ensure the quality of their outputs. To further improve process control, both Proven Acceptable Ranges and narrower Process Control Ranges were established for the CPPs. Similarly, Prometic set both Alert and Action limits for the IPCs.

The control strategy also includes lot release testing of the (b) (4) FDP for microbial contaminants, identity, purity, and strength. The RYPLAZIM FDP is

released based on two orthogonal assays for product strength - plasminogen content by (b) (4) and total protein content by (b) (4) as well as a potency (activity) method, Plasminogen activity by (b) (4) In the absence of a publicly recognized standard for plasminogen activity, Prometic established an in-house reference material to maintain product consistency. Complete specifications for the RYPLAZIM Intermediate, BDS ad FDP are shown in Tables 3, 4, and 5, respectively.

Table 3. Specification for the RYPLAZIM Intermediate

Parameter monitored	Test Method	Acceptance criteria
(b) (4)		

Table 4. Specification for the RYPLAZIM BDS

Parameter monitored	Test Method	Acceptance criteria
(b) (4)		

Parameter monitored	Test Method	Acceptance criteria
(b) (4)		

Table 5. Specification for the RYPLAZIM FDP

Parameter monitored	Test Method	Acceptance criteria
pH	pH Measurement (b) (4)	(b) (4)
Appearance	Visual Inspection (b) (4)	
Appearance – Particulates	(b) (4)	Essentially free of visible particulates
((b) (4)		
(b) (4)		
(b) (4)		
Particulate Matter (b) (4)	(b) (4)	
Particulate Matter (b) (4))	(b) (4)	(b) (4)
		(b) (4)
Reconstitution /Dissolution Time	Visual inspection and timer	NMT 10 minutes
(b) (4)		
Total Plasminogen	(b) (4)	
(b) (4)		
Total Proteins	(b) (4)	
Plasminogen Activity	(b) (4)	
(b) (4)		
Sterility	(b) (4)	No growth
Endotoxin	(b) (4)	
Sucrose Concentration	(b) (4)	
Glycine Concentration	(b) (4)	
Plasminogen purity	(b) (4)	
(b) (4)	(b) (4)	
	(b) (4)	

Evaluation of safety regarding adventitious agents

For non-viral adventitious agents, such as bacteria, fungi, and mycoplasma, the potential of contamination of these agents is well controlled through the use of validated cleaning/ sanitization procedures, e.g., the use of (b) (4) solutions, and in-process filtration steps, including (b) (4) sterile filtration. The final product of RYPLAZIM is further ensured to be free of non-viral adventitious agents by testing for Sterility and Endotoxins. Prometic manufactures RYPLAZIM according to Current Good Manufacturing Practice (cGMP) regulations.

To minimize the risk of transmissible spongiform encephalopathy (TSE) agents, Prometic uses only Source Plasma collected from FDA-licensed plasma collection centers. Donors who are at risk for TSE are excluded from plasma donation, as specified in the current FDA guidance regarding donation collection in the U.S.

All plasma donations, (b) (4) , and (b) (4) pools are tested for viral markers in compliance with FDA requirements. Other than Source Plasma, no raw materials of human or animal origin are used in the manufacture of RYPLAZIM. No excipients of human or animal origin are used in the formulation of RYPLAZIM drug product. Thus, the potential risk of contamination by adventitious viruses or TSE agents is minimized.

Additionally, the potential of viral contamination of RYPLAZIM is mitigated by two dedicated and orthogonal viral clearance steps: Solvent/Detergent (S/D) treatment (b) (4) and nanofiltration (b) (4) 20-nm filter in tandem). The plasminogen affinity chromatography step in the manufacturing process also contributes to viral removal. Prometic has evaluated these steps in down-scale studies. The enveloped viruses selected in the studies include human immunodeficiency virus type 1 (HIV-1); pseudorabies virus (PRV, model virus for enveloped DNA viruses including hepatitis B virus (HBV)); and bovine viral diarrhea virus (BVDV, model virus for enveloped RNA viruses). The non-enveloped viruses selected in the studies include hepatitis A virus (HAV); encephalomyocarditis virus (EMCV, model virus for HAV); reovirus type 3 (Reo-3); and porcine parvovirus (PPV, model virus for human parvovirus B19 (B19V)). These viruses resemble viruses which may contaminate the production of RYPLAZIM and represent a wide range of physico-chemical properties in the testing of the ability of the manufacturing process to eliminate viruses. As shown in Table 6, down-scale studies on the relevant steps resulted in the following total log reduction factors, in parentheses, for these viruses: HIV-1 (≥ 17.2), PRV (≥ 13.(b) (4) BVDV (≥ 11.8), HAV (≥ 10.(b) (4) EMCV (≥ 11.2), Reo-3 (≥ 7.1), and PPV (≥ 9.7). These results are sufficient to support the effectiveness of viral clearance in the proposed commercial manufacturing process.

Table 6. Total virus reduction factors (log_{10}) for inactivation/removal of various viruses achieved by the manufacturing process of RYPLAZIM

Manufacturing step	HIV-1 (Env.)	PRV (Env.)	BVDV (Env.)	HAV (Non-Env.)	EMCV (Non-Env.)	Reo-3 (Non-Env.)	PPV (Non-Env.)
(b) (4) affinity chromatography	≥ 5.2	ND	ND	3[(b) (4)]	3.6	ND	2[(b) (4)]
Solvent/detergent treatment	≥ 6.1	≥ 6.5	≥ 5.8	NA	NA	NA	NA
Nanofiltration	≥ 5.9	≥ 6.5	≥ 6.0	≥ 7.1	≥ 7.6*	≥ 7.1	≥ 7.0
Total virus reduction factors (log_{10})	≥ 17.2	≥ 13[(b) (4)]	≥ 11.8	≥ 10[(b) (4)]	≥ 11.2	≥ 7.1	≥ 9.7

Env.: enveloped virus; Non-Env.: Non-enveloped virus; ND: not done; NA: not applicable; *: the result generated from the (b) (4) .

Control of aggregation

Plasminogen has an intrinsic propensity to form aggregates, which occurs by way of hydrophobic interactions between intact plasminogen monomers, and is readily reversible. The propagation and/or reversal of aggregates depends on variables such as (b) (4) . Prometic also verified the effect of various stress factors, including (b) (4) in RYPLAZIM.

Prometic developed an aggregate control strategy using (b) (4) analytical techniques: (b) (4) The combination of (b) (4) is employed to monitor and control particles of various sizes, and each technique is used to quantitate or monitor the aggregates present in the (b) (4) (b) (4) reconstituted FDP. Specifically, (b) (4) is used to quantitate the amount of (b) (4) within (b) (4) FDP. (b) (4) is used to monitor the (b) (4) in the (b) (4) FDP. (b) (4) is used to determine the (b) (4)

Aggregation is measured at the following stages, mostly by all (b) (4) methods: (b) (4) and FDP (b) (4)). Prometic developed statistically justified acceptance criteria for all in-process control and release tests.

Process validation

Prometic conducted process development and validation studies which informed process development and optimization. Process Performance Qualification (PPQ) studies at commercial scale took place during the manufacturing of the Intermediate (b) (4) BDS (b) (4) and FDP (b) (4). The campaign was performed in May-September 2019. In general, the results of the PPQ 2 campaign were acceptable. The study results demonstrated consistent process performance.

Stability
The Intermediate is stored (b) (4) proven acceptable range of (b) (4) for a maximum of (b) (4) until (b) (4) to manufacture (b) (4).

The BDS is stored at (b) (4) for a maximum of (b) (4). Stability data for BDS have been collected under (b) (4) storage conditions (b) (4) to support the claim of a (b) (4) shelf life when the BDS is stored at (b) (4).

The FDP is stored at 2°C to 25°C for a maximum of 24 months. Stability data were collected under refrigerated (5°C ± 3°C), room temperature (25°C (b) (4) and accelerated stability (b) (4)) storage conditions.

Issues identified during review
In the first review cycle, substantive CMC deficiencies related to the validation of the manufacturing process, characterization of the BDS and FDP, specifications, facilities and equipment were discovered during the review of the BLA, and pre-license inspection (PLI) of the Prometic facility in Laval, Canada on 14-21 November 2017. These issues were not resolved in the first review cycle and resulted in the issuance of a CRL to Prometic on 9 April 2018.

The following substantive CMC issues were included in the CRL: (i) generally inadequate control strategies for the development of the product and validation of the manufacturing process, (ii) lack of a control strategy for protein aggregation, (iii) lack of validated hold times and process times, (iv) deficient analytical methods, (v) improperly justified specifications for the Intermediate, BDS and FDP, (vi) deficient shipping validation studies, (vii) not fully established stability of the Intermediate, BDS and FDP, and (viii) unresolved issues from the prelicensure inspection (PLI). Due to these multiple significant issues, the PPQ campaign originally performed was deemed inadequate, and the manufacturing process was not considered validated. These deficiencies are now resolved with the new data provided in Prometic's response to the CRL submitted on 4 September 2020. Prometic performed a large number of development and comparability studies, and significantly improved the manufacturing process. The improved process was successfully validated in the new PPQ campaign.

Prometic conducted comparability studies and confirmed that the material manufactured using the improved process is comparable to that used in the clinical trials. The data provided demonstrate major improvements in process consistency, and the results obtained are within the ranges established for the materials manufactured by the earlier versions of the manufacturing process.

Reasons for the postmarketing commitments to support approval

PMC # 1
At this time, the number of BDS and FDP batches manufactured using the current commercial process is limited, which is inadequate to assess process variability and establish appropriate specification acceptance criteria in a statistically sound manner. Prometic tried to justify the acceptance criteria of specifications based on values calculated using data from batches manufactured prior to process improvement, which is

not appropriate. To address this concern, Prometic established alert limits based on the variability observed in the batches manufactured using the current process (PPQ 2 and later batches). Prometic has also committed to review additional commercial manufacturing data and revise the acceptance criteria when the amount of data sufficient for statistical analysis are acquired (see section 11.c. below).

PMC # 2
Prometic did not perform in-use stability studies using the PPQ 2 batches, and only resubmitted the previous data to support the 3-hour stability of reconstituted FDP. No new in-use stability data were generated using the most recent tests and specification acceptance criteria. Due to the nature of the studies, the original in-use stability studies were much less affected by the poor intermediate precision of the analytical methods; new studies are confirmatory in nature and should not delay approval. Prometic proposed to perform these studies post-approval, which is acceptable, and has agreed to a postmarketing commitment to this effect (see section 11.c. below).

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the plasminogen drug substance and drug product were found to be adequate for their intended use.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of RYPLAZIM are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Table 7. Manufacturing Facilities Table for RYPLAZIM

Name/address	FEI number	DUNS number	Inspection/ waiver	Results/ Justification
Drug Product Manufacturing and Labeling (b) (4)	(b) (4)		Waiver	ORA (b) (4) NAI

Drug Substance Manufacturing *Drug Substance and Drug Product* Testing Prometic Bioproduction Inc. 531 des Praires BLVD Building (b) (4) Laval, Quebec Canada H7V1B7	3010550055	202985149	Pre-License Inspection	CBER PLI November 2017 OAI OBPO PLI May 2021 NAI
Drug Product Testing (b) (4)	(b) (4)		Waiver	CDER (b) (4) VAI
Drug Product Testing (b) (4)	(b) (4)		Waiver	CDER (b) (4) NAI

CBER conducted a pre-license inspection (PLI) of Prometic Bioproduction Inc. from November 14 - 21, 2017 for the Drug Substance manufacturing and testing and Drug Product testing. At the end of the inspection, CBER issued a Form FDA 483 with 12 observations. The inspection was classified as OAI. The firm responded to the observations on December 12 ,2017, January 12, 2018, January 22, 2018, February 12, 2018, March 13, 2018 and September 04, 2020 and the corrective actions were reviewed and found to be adequate pending verification.

ORA conducted a second PLI of Prometic Bioproduction Inc. from May 17 - 24, 2021 for the Drug Substance manufacturing. The inspection was classified as NAI. No issues were identified.

ORA conducted a surveillance inspection for the (b) (4) The inspection was classified as NAI. No issues were identified.

CDER conducted a surveillance inspection of (b) (4). The inspection was classified as VAI. All inspectional 483 observations were resolved.

CDER conducted a surveillance inspection of (b) (4). The inspection was classified as NAI. No issues were identified.

e. Container/Closure System

The drug product is filled into 50mL (b) (4) clear borosilicate glass vial with 20mm opening (b) (4)), stoppered with 20mm elastomeric bromobutyl grey rubber stopper (b) (4) and sealed with a 20mm aluminum seal with a flip-off finish plastic cap (b) (4)). The container closure integrity testing was conducted by (b) (4) , employing the (b) (4) test method and (b) (4) test method; all acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

The nonclinical testing program for RYPLAZIM consisted of in vivo studies in healthy, immune-competent rats which evaluated: 1) the pharmacokinetic profile following a single intravenous administration of RYPLAZIM and 2) the toxicology profile following daily intravenous administration of RYPLAZIM for five consecutive days. The plasma half-life in rats ranged from 3.7 to 7.1 hours (plasma half-life in humans is approximately (b) (4) days). No adverse findings were observed at the highest dose level administered (21.8 mg/kg/day). Although plasminogen knockout mice exist, in vivo pharmacology studies were not performed by the Applicant due to the potential for development of cross-species anti-human antibodies. The Applicant instead provided data from the scientific literature review to support the physiological role of RYPLAZIM in the treatment of congenital plasminogen deficiency. Safety pharmacology, developmental and reproductive toxicology (DART), and genotoxicity studies with RYPLAZIM were not conducted; the review team considered these studies unlikely to be informative. Limited single-dose and repeat-dose studies in healthy rats evaluating the toxicity of various resins and processing reagents used in the manufacturing process of RYPLAZIM were conducted. Data generated from these studies, as well from in vitro genotoxicity studies, did not reveal any safety concerns.

5. Clinical Pharmacology

Treatment with RYPLAZIM temporarily increases plasminogen levels in blood in patients with plasminogen deficiency type 1.

The pharmacokinetics of RYPLAZIM was evaluated in two clinical studies:

- a Phase 1, dose escalation, and pharmacokinetic study of RYPLAZIM administered as intravenous infusion in adults and children with hypoplasminogenemia (Study 2002C005G),

- a Phase 2-3, open-label, repeat-dose study of the pharmacokinetics, efficacy, and safety of RYPLAZIM intravenous infusion in patients with hypoplasminogenemia (Study 2002C011G)

The pharmacokinetic samples were analyzed for both plasminogen activity and antigen levels. PK parameters were estimated by noncompartmental analysis using baseline-adjusted plasminogen activity and antigen levels. Plasminogen activity levels were measured using a chromogenic assay, where assay calibration curve was performed with a (b) (4) with an assigned value of (b) (4) plasminogen. Plasminogen activity in measured samples was reported as percentage (%) of normal. Plasminogen antigen levels was measured using an (b) (4)

The results of the Phase 1 study (Study 2002C005G) showed that RYPLAZIM, when administered at a single IV dose of 6.0 mg/kg, increased plasminogen activity to physiological levels in adolescent and adult patients without any safety concerns. Dosing intervals were adjusted to achieve absolute plasminogen activity trough levels at least 10% above baseline levels.

In the Phase 2-3 study (Study 2002C011G), pediatric and adult patients with plasminogen deficiency type 1 received 6.6 mg/kg of RYPLAZIM every 2 to 4 days. After the first dose of RYPLAZIM, absolute plasminogen activity level was 117.5 ± 27.1%, which reached the physiological range (70-130%), in adult and pediatric patients. After 12 weeks of treatment with RYPLAZIM at the dose of 6.6 mg/kg every 2 to 4 days (steady-state), mean exposure (AUClast) of baseline-adjusted plasminogen activity levels increased by approximately 1.4- to 1.6-fold, compared to the levels after the first dose in pediatric and adult patients. Mean clearance and volume of distribution at steady-state decreased to approximately 64% and 77% of that after the first dose of RYPLAZIM, respectively, in both pediatric and adult populations. The clearance of RYPLAZIM was similar between adult and pediatric populations.

The plasminogen activity trough levels were also monitored. During the first 12 weeks of treatment with RYPLAZIM at 6.6 mg/kg every 2 to 4 days, plasminogen activity trough levels achieved target plasminogen activity trough levels (i.e., ≥ an absolute 10% improvement from baseline in activity) for at least three measurements for all 15 patients. This was an applicant-defined PK target. Between Week 12 to Week 48, plasminogen activity levels generally remained above target levels despite decreased dosing frequency in most patients.

Available data indicated that the development of anti-plasminogen antibodies did not affect clinical efficacy in study patients.

6. Clinical/Statistical

a. Clinical Program

The RYPLAZIM clinical development program consisted of 29 unique patients who received at least one dose of RYPLAZIM by IV infusion and 28 unique patients (17

pediatric and 11 adult) who received repeated doses of RYPLAZIM by IV infusion. Total repeat-dose treatment exposure ranged from 4 to 214 weeks across the patient population (6 to 214 weeks for pediatric patients and 4 to 194 weeks for adult patients). RYPLAZIM treatment is ongoing in 22 patients, as of the data cut-off date of January 1, 2020.

RYPLAZIM Clinical Development Programs include the following:

- Study 2002C005G (Phase 1), serving as the basis for dosing for Study 2002C011G (n = 7),
- Study 2002C011G (n = 15, including 6 patients who completed the Phase 1 study and 9 new patients),
- U.S. single-patient Expanded Access (n = 4),
- Expanded Access Treatment Protocol (n = 10, including 8 patients who completed Study 2002C011G, and 2 patients who received RYPLAZIM under single-patient Expanded Access),
- Non-US Compassionate Use protocols (n = 14).

Phase 2-3 Study (Study 2002C011G)

This was an open-label, single-arm, repeat-dose study of PK , safety and efficacy of RYPLAZIM administered to adult and pediatric patients with plasminogen deficiency type 1. The study enrolled 15 patients, including 6 pediatric patients (4-16 years). All patients received RYPLAZIM at a dose of 6.6 mg/kg administered every 2 to 4 days for 48 weeks or longer.

The study was divided into three segments:
Segment 1: Day -4 to Day 0;
Segment 2: Day 0 to Week 12; and
Segment 3: Week 12 to Week 48.

The primary objectives included:

- Evaluating 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,
- Achieving an increase of individual plasminogen activity trough levels by at least an absolute 10% above baseline in adult and pediatric patients with hypoplasminogenemia during the 12 weeks of plasminogen replacement therapy in Segment 2.

Primary Clinical Efficacy Endpoint

The primary efficacy endpoint was 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) was defined as 50% of patients with visible or other measurable non-visible lesions demonstrating at least a 50% improvement in lesion number/size or functionality impact from baseline. The formation of ligneous lesions is a direct result of abnormally low plasminogen activity levels. The primary efficacy endpoint is clinically meaningful as it assesses the clinical manifestation of disease, which impacts how a patient feels and functions, to a greater or lesser extent depending on the organ system affected.

Eleven patients, including 3 pediatric patients, had lesions (32 external lesions and 12 internal lesions), at baseline. At Week 48, all 11 patients with any lesion at baseline had at least 50% improvement in the number or size of their lesions. Twenty-five of the 32 (78%) external lesions, and 9 of the 12 (75%) internal lesions were resolved. There were no recurrent or new lesions in any patient through Week 48. The study had an overall clinical success of 100%, meaning that all 11 patients with any lesions at baseline had at least 50% of their lesions resolved, with a median time to resolution of 8 weeks. There was no inferential hypothesis testing.

Based on the natural history of this rare condition, and phenotypic heterogeneity, sustained substantial improvement (i.e., > 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 or recurrent lesions over the 48-week study period is highly unlikely to have occurred by chance alone given the pathophysiology of the condition. Therefore, we consider the single-arm, open-label, Phase 2-3 study to be an adequate and well-controlled study.

Primary PK Endpoint

The primary PK endpoint was the number and percentage of responders (i.e., a patient who achieved 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 the 12 weeks epoch of Segment 2. Primary endpoint success (performance criterion) was defined in the protocol as a minimum of 80% of evaluable patients (i.e., at least 8/10 patients) achieving the target trough level for at least 3 assessed time points during the 12 weeks of Segment 2.

All 15 patients 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. See Clinical Pharmacology Section for details.

Expanded Access and Compassionate Use

The effectiveness of RYPLAZIM was supported by data from Expanded Access and Compassionate Use. In addition to the 6 pediatric patients (4-16 years) in Study 2002C011G, 6 pediatric patients (age 11 months to 3 years) who received repeat administrations of RYPLAZIM through Expanded Access and Compassionate Use programs showed improvement in lesions.

Efficacy Conclusion

The clinical information presented in the BLA supports the conclusion that RYPLAZIM administered via IV infusion every 2 to 4 days is an effective treatment for plasminogen deficiency type 1 in pediatric and adult patients. Patients treated with RYPLAZIM at the recommended dose of 6.6 mg/kg administered every 2 to 4 days showed substantial improvement or complete resolution of ligneous lesions, and absence of recurrent or new ligneous lesions. These effects reduce pain and discomfort, and reduce the likelihood of serious and life-threatening complications of the disease. The primary evidence of effectiveness is based on substantial improvements in clinically meaningful efficacy outcomes observed at Week 48 in Study 2002C011G, an adequate and well-controlled study (external control), for pediatric and adult patients with plasminogen deficiency type 1. Additional data from Expanded Access and Compassionate Use support the Phase 2-3 efficacy results. Thus, the primary evidence of effectiveness from the Phase 2-3 adequate and well-controlled study, combined with confirmatory evidence of effectiveness from the Expanded Access and Compassionate Use information, meet the regulatory requirement for substantial evidence of effectiveness of RYPLAZIM for the treatment of plasminogen deficiency type 1.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

One bioresearch monitoring (BIMO) inspection of a clinical study site was conducted for Protocol 2002C011G in support of this Biologics License Application (BLA). Results from the inspection did not reveal substantive issues that impact the data submitted in the BLA.

c. Pediatrics

Plasminogen deficiency is a rare disease, with an estimated incidence of 1.6 per 1,000,000 individuals in the general population. While most patients with plasminogen deficiency type 1 survive into adulthood, severe clinical manifestations have been described in the pediatric population including respiratory failure and hydrocephalus. In the RYPLAZIM clinical development program, 27 of the 28 patients who received repeated administrations of RYPLAZIM had onset of clinical manifestations due to plasminogen deficiency type 1 during childhood.

The Pediatric Research Equity Act (PREA) requirement is not applicable to RYPLAZIM for the treatment of plasminogen deficiency type 1 because RYPLAZIM was granted orphan designation for the indication. Both pediatric and adult patients were enrolled into RYPLAZIM clinical trials and were treated in Expanded Access and Compassionate Use programs.

d. Other Special Populations

RYPLAZIM was not studied in geriatric patients.

7. Safety and Pharmacovigilance

Safety

The safety database consists of 29 patients 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. There were 17 pediatric patients and 12 adults, ranging from 11 months to 42 years of age. Fifteen patients were female. Twenty-eight patients were Caucasian, and one patient was Asian.

No patients died. There was one serious adverse event of possible worsening of gastrointestinal hemorrhage secondary to gastric ulcers. No patients discontinued study participation or treatment due to the occurrence of an adverse event. The most frequent adverse reactions (incidence ≥10%) were abdominal pain, gastric dilatation, nausea, fatigue, pain in extremity, hemorrhage, constipation, dry mouth, headache, dizziness, joint pain, 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 studies or in Expanded Access or Compassionate Use programs.

These risks of RYPLAZIM administration can be mitigated by routine medical management, appropriate labeling of Prescribing Information (PI), Patient Information Sheet and the postmarketing pharmacovigilance plan proposed by the Applicant.

Postmarketing Pharmacovigilance

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 Postmarketing Requirement (PMR) clinical study.

8. Labeling

The proposed proprietary name, RYPLAZIM, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on September 8, 2017 and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on November 6, 2017.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed PI, Patient Information Sheet, and package and container labels, on June 3, 2021, and found them acceptable from a promotional and comprehension perspective.

9. Advisory Committee Meeting

No advisory committee was sought, with the following rationale. The new molecular entity provision (NME) does not apply to RYPLAZIM because it is not a new molecule, but a non-modified endogenous protein found in the absolute majority of the human population. The proposed indication for RYPLAZIM is a replacement therapy for treatment of patients with type 1 plasminogen deficiency, and the mechanism of action and function of plasminogen in RYPLAZIM is the same as that of endogenous plasminogen present in the blood. Review of the data in the RYPLAZIM clinical studies did not reveal unexpected safety or efficacy issues. Review of information submitted in the BLA for RYPLAZIM did not raise controversial issues or pose unanswered scientific questions, which would have benefited from Advisory Committee discussion and recommendations. This application did not raise significant public health questions on the role of RYPLAZIM in the diagnosis, cure, mitigation, treatment, or prevention of diseases.

10. Other Relevant Regulatory Issues

The submission was granted priority review, and a rare pediatric disease priority review voucher.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The review team recommends traditional approval of RYPLAZIM for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia).

b. Benefit/Risk Assessment

The benefit of RYPLAZIM is the improvement and even resolution of ligneous lesions, and prevention of ligneous lesion formation or recurrence. This leads to prevention of complications associated with the ligneous lesions such as visual impairment, blindness, respiratory failure, hydrocephalus, abnormal wound healing, and infertility.

Some patients experienced bleeding at the site of resolving ligneous lesions, which is consistent with RYPLAZIM's mechanism of action. RYPLAZIM may worsen active bleeding. Potential risks include transmission of infectious disease agents, tissue sloughing, and hypersensitivity reactions, which have not been observed in patients treated with RYPLAZIM. IV infusion of RYPLAZIM is associated with a relatively low level of risk.

There is an unmet medical need for treatment of plasminogen deficiency type 1, a serious, lifelong condition. The benefits described above are substantial and potentially life-changing for these patients. The observed risks were relatively mild. Serious risks are likely to be rare and can be mitigated by adequate PI and Patient Information Sheet, and routine pharmacovigilance plan. Therefore, the overall benefit-risk profile of RYPLAZIM is favorable for patients with plasminogen deficiency type 1.

c. Recommendation for Postmarketing Activities

Prometic committed to the following PMCs:

PMC # 1

Prometic Biotherapeutics Inc. (Prometic) commits to revise the acceptance criteria of the specifications for RYPLAZIM Intermediate, Bulk Drug Substance (BDS) and Final Drug Product (FDP) by analyzing the data generated from the manufacture of [redacted] batches of RYPLAZIM using the current commercial process. Prometic commits to perform an interim statistical re-assessment of all the alert limits in the current commercial process by analyzing the data from the manufacture of all commercial batches up to 31 May 2022, and submit the interim study report as a *Changes-Being-Effected Supplement* by 31 July 2022. Prometic commits to submit the Final Study Report as a *Prior Approval Supplement* by 30 September 2023**.**

Final Study Report Submission: 30 September 2023

PMC #2

Prometic commits to perform in-use stability studies to confirm the stability of the reconstituted RYPLAZIM FDP under real-world use conditions. The RYPLAZIM FDP batches used in the studies should be manufactured by the current commercial process that meet the acceptance criteria of the current FDP specification. Prometic commits to submit the final study report as Postmarketing Commitment – Final Study Report by 31 May 2022.

Final Study Report Submission: 31 May 2022