U.S. FOOD & DRUG ADMINISTRATION

Department of Health and Human Services
Public Health Service
Food and Drug Administration Center
for Biologics Evaluation and Research
Division of Epidemiology

Pharmacovigilance Original BLA Memorandum

From:	Bethany Baer, MD Medical Officer, Pharmacovigilance Branch (PVB), Division of Epidemiology (DE), Office of Biostatistics and Epidemiology (OBE), Center for Biologics Evaluation and Research (CBER)
To:	Crystal Melendez Regulatory Project Manager, Office of Tissues and Advanced Therapies (OTAT)
Through:	Adamma Mba-Jonas, MD, MPH Branch Chief, PVB, OBE, CBER
	Meghna Alimchandani, MD Deputy Director, Division of Epidemiology, OBE, CBER
Subject:	Review of Pharmacovigilance Plan
Applicant:	Prometic Biotherapeutics, Inc.
Product:	Ryplazim [Plasminogen (Human)]
Application Number:	BLA 125659/0/18
Proposed Indication:	Replacement therapy in adults and children with plasminogen deficiency
Submission Date:	Sep. 4, 2020
Action Due Date:	Jun. 5, 2021

1. Objective

The purpose of this review is to assess the adequacy of the Pharmacovigilance Plan based on the safety profile of Ryplazim [plasminogen (human)].

2. Product Information

- **Product description**
  Ryplazim is purified Glu-plasminogen derived from human plasma collected in North America. It is administered as an intravenous infusion. Its proposed indication is for the treatment of adults and children with clinical signs and symptoms associated with congenital plasminogen deficiency

- **Proposed formulation and dosing regimen**
  Ryplazim production involves the viral removal and inactivation steps of affinity chromatography, solvent/detergent treatment, and nanofiltration. Ryplazim is a lyophilized powder consisting of 68.8 mg of plasminogen to be reconstituted with 12.5 mL of water for infusion. After reconstitution, each 50 mL vial contains 5.5 mg/mL of plasminogen. The recommended dosage is 6.6 mg/kg body weight given every 2 to 4 days.

3. Pertinent Regulatory History

- Ryplazim was granted Orphan Drug Designation.
- Ryplazim was granted Rare Pediatric Disease status.
- Ryplazim was granted priority review.
- Ryplazim was initially submitted as an original BLA under BLA 125647 in April 2017. The submission received a Refuse to File letter in June 2017 as the submission was not sufficiently complete to enable a critical medical and technical review. The application was resubmitted for accelerated approval with additional information on Aug. 4, 2017. This second submission received a Clinical Response (CR) letter in April 2018.
- The BLA is now being resubmitted in response to the CR letter. The sponsor is applying for full approval rather than accelerated approval as the pivotal study is now complete.
- Ryplazim is currently not marketed in any country.

4. Materials Reviewed

Table 1: Materials Reviewed

Source	Subtype	Document Reviewed
Prometic Biotherapeutics	125659/0/18	Pharmacovigilance Plan, Version 3.0, dated Aug 11, 2020
Prometic Biotherapeutics	125659/0/18	Summary of Clinical Safety
Prometic Biotherapeutics	125659/0/18	Patient Narratives-Multiple Protocols
Prometic Biotherapeutics	125659/0/18	Ryplazim 2002C011G Final Clinical Study Report, dated July 29, 2020
Prometic Biotherapeutics	125659/0	Protocol 2002C011G Version 1 and Amendments, received Aug.14, 2017
Prometic Biotherapeutics	125659/0/18	Ryplazim Annotated Draft Labeling Text
Prometic Biotherapeutics	125569/0/20	Information Request Response, received Dec. 9, 2020
FDA	Memorandum	Division of Epidemiology Review of Pharmacovigilance Plan Version 2 by Bethany Baer, dated Mar. 1, 2018

5. Clinical Safety Database

The clinical program for Ryplazim consists of two uncontrolled open-label studies, four expanded access programs, an extended treatment protocol group, and compassionate use programs, as shown in Table 2 below.

Table 2: Clinical Development Program Description

Study	No. of subjects	Description	Age range
2002C005G Phase 1 dose escalation, Completed	12 (7 unique subjects as 5 patients participated at both dose levels)	Single dose study for pharmacokinetic and safety data, open-label, single arm, US	Adolescent and adult
2002C011G Pivotal, Phase 2/3, Completed	15 (9 unique with 6 patients overlapping with study 2002C005G)	Repeat-dose study for efficacy and safety, open-label, single arm, US and Norway	Pediatric and adult
2002C013G Expanded Access, Ongoing	1	Single patient, repeat-dose, open-label, single arm	Adult
2002C016G Expanded Access, Completed	1	Single patient, repeat-dose, open-label, single arm	Pediatric
2002C017G Expanded Access, Completed	1	Single patient, repeat-dose, open-label, single arm	Pediatric
2002C019G Expanded Access, Ongoing	1	Single patient, repeat-dose, open-label, single arm	Pediatric
2002C018G Extended Treatment Protocol, Ongoing	10 (8 from study 2002C011G, 1 from Study 2002C016G, 1 from 2002C017G), no unique patients	Repeat-dose, open-label, single arm	Pediatric and adult
Compassionate use, 10 patients ongoing, 4 patients completed	14 (5 from study 2002C011G, 9 unique patients)	Repeat-dose, open-label, single arm, patients from Norway, UK, Canada, Germany, and Israel	Pediatric and adult

There was a total of 29 unique patients who received at least one dose of Ryplazim in the clinical development program. The age range was 11 months to 42 years, and the

exposure duration was 1 day to 214 weeks. All of the patients had plasminogen deficiency. There were 28 unique patients (17 pediatric and 11 adult) who received repeated doses of Ryplazim. Twenty-three subjects (79%) received over one year of repeated doses of Ryplazim. Half of the recipients were female. There were 15 adult subjects (20-42 years of age) and 8 pediatric subjects (0-16 years of age) in the phase 1 and 2/3 studies. All of the subjects in the phase 1 and 2/3 studies were White, and the baseline plasminogen activity levels for most subjects were ≤30%. The most common adverse events (AEs) classified by the Investigator as at least possibly related to the study drug in the Phase 2/3 pivotal study were nausea, fatigue, and headache, each of which occurred in 3/15 (20%) patients. There were no cases of hypersensitivity reactions in the studies.

There were 8 treatment emergent serious adverse events (TESAEs) in 7 subjects during the clinical development program. One patient had a tympanomastoidectomy and ossiculoplasty. The other events were pneumonia, ileus, neutropenia (2 events), acute pyelonephritis, and a peptic ulcer hemorrhage. The ulcer hemorrhage was the only TESAE felt by the investigator or sponsor to be at least possibly related to the study drug. The ulcer patient had a recent history of bleeding gastric ulcers 35 days prior to treatment. The patient developed a serious gastrointestinal bleed following the second dose of Ryplazim.

Additionally, there was a patient in the pivotal trial who had a set of severe, but not serious, adverse events consisting of nausea, chest discomfort, fatigue, arthralgia, back pain, dizziness, paresthesia, and flushing. This 39-year-old female had a urinary tract infection at the same time as the symptoms and is the same patient who had the pyelonephritis TESAE described above. These events occurred after the patient's 20th and 21st infusions with Ryplazim. The investigator felt the symptoms were possibly related to Ryplazim. The patient temporarily stopped receiving Ryplazim and then restarted 12 days later at a slower infusion rate. She then tolerated the drug well except for one episode of "feeling sick" prior to her 22nd dose. She returned to her regular infusion rate and tolerated it well.

There were 3 (20%) subjects in pivotal trial 2002C011G who developed anti-plasminogen antibodies. None of these patients had a clinically meaningful reduced response nor a decrease in plasminogen activity.

There were no cases of clinically significant bleeding related to fibrinolysis in the phase 1-3 clinical trials. There was a patient with a recent history of bleeding peptic ulcers who was treated with Ryplazim for compassionate use and developed a gastrointestinal hemorrhage, as discussed above.

In Study 2002C011G, there were 5/15 (33%) of subjects who had AEs associated with bleeding, which were not considered to be clinically significant. There were 21 bleeding-associated TEAEs in these 5 patients and all were mild. Eighteen (85.7%) of these events had a short duration. There were 10/15 subjects who had occult blood in the post-baseline urinalysis in the pivotal study. Study 2002C005G also found that there

were 4 subjects in each of the two study cohorts who had blood in the urine. Additionally, there was one subject with epistaxis in the expanded access program, and one subject with blood in the stool in the treatment protocol 2002C018G.

Of note, the study protocol defined an AE as "any untoward medical occurrence (whether or not considered to have a causal relationship to IMP [investigational medicinal product]) in a study subject administered an IMP. Therefore, an AE can be any unfavorable and unintended sign (including clinically significant laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP. However, signs and observations that are associated with clinical improvement (such as discharge of blood clots in urine), as judged by the investigator, will not be reported as AEs."[1] When ligneous lesions on mucus membranes resolve, hematuria and epistaxis can occur as part of the clinical effect of the plasminogen. The study protocol included a rule to stop the treatment if a subject had an uncontrolled bleeding event requiring hospitalization. The sponsor states that there were no cases of clinically significant bleeding related to fibrinolysis or lesion resolution observed in the plasminogen-treated patients in the clinical trials. There was the one case of the peptic ulcer hemorrhage in the compassionate use program.

Reviewer comment: The definition of an adverse event in the study protocol is not ideal since it excludes episodes of bleeding from being reported as AEs. As a result, the true rate of mild epistaxis and hematuria in the study is not known. The 10/15 subjects in the pivotal trial with occult blood by urinalysis indicate the level of mild bleeding was high. This issue was discussed with the clinical reviewer, and it was noted that there were no serious bleeding episodes in the pivotal study.

There were four cases of elevated D-dimer levels during Study 2002C005G. As D-dimer can be the result of fibrinolysis, these elevated levels could be due to lysis of the lesions associated with plasminogen deficiency. In Study 2002C011G, there were 8 subjects with abnormal post-baseline D-dimer values with 3 of those reaching clinically significant increases in D-dimer levels. All of the three subjects had a heavy disease burden with lesions that showed clinically significant improvement at the time of the increase in D-dimer levels.

Reviewer comment: The Division of Epidemiology (DE) agrees with the applicant's assessment that the D-dimer increases were consistent with Ryplazim's mechanism of action, i.e. the fibrinolysis of the ligneous lesions.

The clinical trials did not study drug interactions, use in pregnancy, use in lactation, or use in geriatric (>65 years old) patients. There was one subject in the clinical trials who became pregnant and continued treatment with Ryplazim. A healthy infant was delivered, but the mother had post-partum hemorrhage consistent with uterine atony. She was treated with methylergonovine and prostaglandin. The patient continued treatment with Ryplazim.

[1] Protocol 2002C011G Version 1 and Amendments, p. 46.

6. Summary of Prior Marketed Experience

Not applicable. The product has not been previously approved in any other countries.

7. Applicant's Pharmacovigilance Plan

The applicant's PVP Version 3 includes important risks and areas of missing information outlined in Tables 3-5 below.

Table 3: Applicant's Pharmacovigilance Plan for Important Identified Risks

Important Identified Risk	Planned Pharmacovigilance Activity
Bleeding related to fibrinolysis and lesion resolution	Labeling through the package insert Routine pharmacovigilance, including expedited reporting of qualifying spontaneous events, as applicable, periodic and annual reviews and safety discussion within the PBRER/PSURs, as appropriate. A toll-free call center telephone line will be set up and maintained to provide information and manage the receipt of Individual Case Safety Reports (ICSRs)

Table 4: Applicant's Pharmacovigilance Plan for Important Potential Risks

Important Potential Risks	Planned pharmacovigilance activity
• Hypersensitivity reactions • Transmittable infectious agents • Neutralizing antibodies • Tissue sloughing related to lesion resolution	Information on the symptoms associated with the important potential risks are included in the product label (see Warnings and Precautions) Clinically significant events will be monitored by routine pharmacovigilance measures including expedited reporting of qualifying spontaneous events, periodic reviews and safety discussions within the PBRER/PSUR, as appropriate A toll-free call center telephone line will be set up and maintained to provide information and manage the receipt of ICSRs

Of note, the PVP states that PBRERs/PSURs will be submitted quarterly for the first year following approval and at a frequency to be agreed upon with FDA thereafter.

Table 5: Applicant's Pharmacovigilance Plan for Areas of Missing Information

Area of Missing Information	Planned pharmacovigilance activity
• Drug interactions • Pregnancy • Lactation • Geriatric Use	Information on use during pregnancy, lactation, for geriatric patients, and the possibility of drug interactions are included in the product label All important risks will continue to be monitored through routine pharmacovigilance measures, including expedited reporting of qualifying spontaneous events, periodic and annual reviews and safety discussions within the PBRER/PSURs, as appropriate A toll-free call center telephone line will be set up and maintained to provide information and manage the receipt of ICSRs

8. Analysis of Applicant's Pharmacovigilance Plan

Versions 1 and 2 of Ryplazim's Pharmacovigilance Plan (PVP) have previously been reviewed. The sponsor modified the plan appropriately based on DE feedback and new information emerging from the clinical trials. The plan now reflects the important identified and potential risks as well as the areas of missing information. The applicant has proposed labeling which provides information on the risks. Specific safety issues from the plan are discussed below. Since plasminogen deficiency is a very rare disease (estimated to have a prevalence of 1.6 per one million people), the subject pool is small. Therefore, there is limited data for all of these identified risks.

Safety Issues identified in the Pharmacovigilance Plan:

- Bleeding Related to Fibrinolysis and Lesion Resolution: Due to the action of Ryplazim to break down fibrin, there may be bleeding from mucosal lesions during treatment. There were no cases of serious bleeding during the clinical trials, but there was one case in a patient receiving Ryplazim on a compassionate use basis. There were also cases of epistaxis and hematuria that could be the result of the breakdown of mucosal lesions when exposed to the plasminogen activity. In addition to causing bleeding from pre-existing lesions, it is possible that a patient could have bleeding due to fibrinolysis in areas where there is not a known pre-existing lesion. This risk is now classified as an important identified risk.
- Hypersensitivity reactions: Allergic hypersensitivity reactions are possible with all products that introduce new proteins into a patient. The immune response to the protein can include urticaria, fever, wheezing, edema, and hypotension, along with other symptoms. There were no cases of hypersensitivity reactions in the clinical trials.
- Transmittable Infectious Agents: As Ryplazim is from human plasma, there is a risk of transmitting infectious agents like hepatitis B or C virus or HIV. This risk is greatly reduced by screening plasma donors for known viruses, removing viruses during processing of the product, and inactivating viruses during

production. There were no known cases of transmission of infectious agents seen during the clinical trials.

- Neutralizing Antibodies: There is potential for neutralizing antibodies to form against any protein introduced into patients. There were 3/15 (20%) subjects who tested positive for anti-plasminogen antibodies in the clinical trials. Since there is no commercially available test for anti-plasminogen antibodies, the applicant developed a diagnostic test for this product. The proposed product label includes information on contacting the sponsor if neutralizing antibody testing is needed.
- Tissue Sloughing Related to Lesion Resolution: Similar to bleeding discussed above, there can be tissue sloughing when a mucosal lesion is degraded by the Ryplazim. This would be especially significant if there are large lesions in the airway. To address this risk, the proposed package insert Warnings and Precautions section includes the statement that personnel trained in airway management and appropriate equipment should be available when initiating treatment in patients with large mucosal lesions in the tracheobronchial tree. During the clinical trials, there were no clinically significant cases of tissue sloughing reported.

It is noted that the sponsor plans to submit periodic safety reports quarterly for the first year and then discuss the frequency with the FDA. The Code of Federal Regulations (CFR) Title 21, Sec. 600.80 requires that periodic adverse experience reports be submitted at quarterly intervals for the first 3 years of licensure. If the sponsor would like to submit the periodic adverse event report in a different format (PSUR or PBRER) or at a different frequency, then a waiver request would need to be approved.

9. Recommended Pharmacovigilance Actions

- DE agrees with the pharmacovigilance activities proposed by the applicant in the Pharmacovigilance Plan, Version 3.0, along with adverse event reporting as required under 21CFR600.80. Please note that 21CFR600.80 requires that periodic adverse experience reports be submitted at quarterly intervals for the first 3 years of licensure. If the sponsor would like to submit the periodic adverse event report in a different format (PSUR or PBRER) or at a different frequency, then a waiver request would need to be submitted and approved.
- The reviewed safety data do not substantiate a need for a Risk Evaluation and Mitigations Strategy (REMS), a separate safety postmarketing requirement (PMR) study, or a separate safety postmarketing commitment (PMC) study at this time.