Application Type	Original Application – Resubmission to Complete Response
STN	125659/0/18
CBER Received Date	September 04, 2020
PDUFA Goal Date	June 05, 2021
Division / Office	OTAT
Committee Chair	Alexey Khrenov, Ph.D.
Clinical Reviewer(s)	Gavin H Imperato, M.D.
Project Manager	Crystal Melendez, M.T., R.N., B.S.N.
Priority Review	No
Reviewer Name(s)	Boris Zaslavsky, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Renée C. Rees, Ph.D. Team Leader, OBE/DB
	Boguang Zhen, Ph.D. Branch Chief, OBE/DB
Applicant	ProMetic BioTherapeutics, Inc.
Established Name	Plasminogen (Human)
(Proposed) Trade Name	RYPLAZIM™
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	A (b) (4)
Dosage Form(s) and Route(s) of Administration	For intravenous use through a syringe disc filter after reconstitution
Dosing Regimen	6.6 mg/kg body weight given every two to four days pharmacokinetic profile, and/or the patient's clinical condition.
Indication(s) and Intended Population(s)	Replacement therapy in adults and children with congenital plasminogen deficiency.

1. EXECUTIVE SUMMARY

This submission is intended to provide additional support of RYPLAZIM, also known as Plasminogen (Human), for a proposed indication of replacement therapy in adults and children with congenital plasminogen deficiency (hypoplasminogenemia).

The original BLA was submitted under the Accelerated Approval pathway on August 4, 2017. An interim analysis of the ongoing Study 2002C011G was the basis for the statistical efficacy review in the original submission. The primary efficacy endpoint was overall clinical success, defined as 50% of subjects with visible lesions achieving at least a 50% improvement at 48 weeks in an average lesion size in subjects with lesions or functionality impact from baseline. Of the 14 subjects enrolled in the study at the time of the interim analysis, 10 subjects (6 adult and 4 pediatric) were evaluable for the PK surrogate and efficacy endpoints. Efficacy was achieved in all 10 subjects (100%; 95% CI: 0.7411, 1).

The FDA issued a Complete Response letter on April 9, 2018 with chemistry, manufacturing, and controls (CMC) deficiencies. In addition to the response to the CMC deficiencies, amendment BLA 125659/0/18 provides new clinical data for the now completed study 2002C011G.

Of the 15 subjects enrolled in the completed study with a mean (SD) age of 23.0 (13.05) years (range: 4 to 42 years), 13 subjects completed the study, and 11 subjects (6 adult and 5 pediatric) were evaluable for the primary clinical endpoint. Efficacy was achieved in all 11 subjects (100%; 95% CI: 0.7616, 1).

Three subjects (20.0%) had a total of four treatment-emergent serious adverse events (TESAEs), all of which were judged by the investigator as not related to the study drug. No deaths occurred.

The efficacy and safety results appear to demonstrate that RYPLAZIM is tolerated in subjects with hypoplasminogenemia.

2. INTRODUCTION

The program of clinical studies in subjects with hypoplasminogenemia concluded with the completion of the phase 3 Study 2002C011G; Details of my review for this study can be seen in my statistical memo, dated April 4, 2018, for BLA 125659/0. Amendment 125659/0/18 provides the clinical data for the now completed study 2002C011G. It includes data for a pediatric subject (b) (6) that was not included in the previous BLA submission BLA 125659/0.

3. STATISTICAL EVALUATION

The primary objectives were to evaluate the effect of RYPLAZIM on the clinical manifestations of congenital plasminogen deficiency after 48 weeks of treatment (primary efficacy endpoint). Of the 15 subjects screened, 15 subjects were

enrolled. Of the 15 enrolled subjects, 13 subjects completed the study. Subject (b) (6) was discontinued by the Investigator, and Subject (b) (6) decided to withdraw from the study. Both subjects had non-compliance issues with the study protocol but discontinued the study after week 48. At entry into the study, subjects were from 4 to 42 years old. Four (26.7%) subjects were male and 11(73.3%) female, with an overall mean (SD) age of 23.0 (13.05) years. Nine subjects (60.0%) were > 17 year of age. All subjects were White.

According to the study protocol, the evaluable population for the primary clinical endpoint subjects had at least 1 lesion at the baseline. Subjects (b) (6) had no lesions at baseline. Eleven (11) subjects (6 adult and 5 pediatric) were evaluable and completed 48 weeks of treatment. Efficacy was achieved in all 11 subjects (100%; 95% CI: 0.7616, 1) as all subjects with any lesion at baseline had at least 50% of their lesions resolved with a percentage of total lesions resolved of 100%. All lesions responded to RYPLAZIM by week 48. This included complete resolution of 25 of 32 (78.12%) visible lesions and 9 of 12 (75%) assessable non-visible lesions.

The Safety population was defined as a set of subjects who received at least one dose of RYPLAZIM and provided safety data for at least one non-screening (non-first) visit. All 15 enrolled subjects were included for safety evaluation. There were no deaths. Three subjects (20.0%) had a total of four TESAEs, all of which were judged by the Investigator as not related to the study drug: Subject (b) (6) (5-year-old female) had two TESAEs; Subject (b) (6) (4-year-old female) had one TESAE; Subject (b) (6) (42-year-old female) had one TESAE.

4. CONCLUSIONS

An overall clinical success of 100% was achieved in both pediatric and adult subjects. Of 15 subjects in the Safety Analysis set, three subjects developed TESAE to RYPLAZIM. No deaths occurred during the study. The results of the study appear to demonstrate that Ryplazim was tolerated in subjects with hypoplasminogenemia.