**Clinical Pharmacology Supplemental BLA Review**

Division of Clinical Evaluation and Pharmacology/Toxicology
Office of Tissues and Advanced Therapy

| | |
|---|---|
| **BLA** | 125659/0/18 |
| **Product** | RYPLAZIM (plasminogen, human-tvmh) lyophilized powder for reconstitution, for intravenous use |
| **Sponsor** | Prometic Biopharmaceutics Inc. |
| **Indication** | Treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia) |
| **Date Received** | September 04, 2020 |
| **Reviewer** | Xiaofei Wang, Ph.D.<br>Clinical Pharmacologist, General Medicine Branch 2<br>Division of Clinical Evaluation and Pharmacology/Toxicology |
| **RPM** | Crystal Melendez |
| **Through** | Lei Xu, M.D., Ph.D.<br>Branch Chief<br>General Medicine Branch 2<br>Division of Clinical Evaluation and Pharmacology/Toxicology<br>Ilan Irony, M.D.<br>Deputy Director<br>Division of Clinical Evaluation and Pharmacology/Toxicology |

**Table of Contents**

# 1 EXECUTIVE SUMMARY

On September 04, 2020, Prometic Biotherapeutics, Inc. re-submitted its BLA125659 for Ryplazim (plasminogen, human-tvmh), seeking approval for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia). The recommended dose of Ryplazim is 6.6 mg/kg body weight administered by intravenous (IV) infusion every 2 to 4 days.

BLA 125659 was originally submitted on August 14, 2018, and received complete response due to chemistry, manufacturing and control (CMC) deficiencies.

Current re-submission includes responses to CMC deficiencies and updated results for the completed Phase 2/3 clinical study (Study 2002C011G) with additional subjects. Study 2002C011G is an open-label, single-arm, repeat-dose study evaluating the efficacy, pharmacokinetics (PK), and safety of replacement therapy with Ryplazim at the dose of 6.6 mg/kg in pediatric and adult subjects with plasminogen deficiency type 1. 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. The development of anti-plasminogen antibody did not affect clinical efficacy in study subjects.

The proposed dosing regimen of Ryplazim administered by IV infusion has demonstrated clinical efficacy with an acceptable safety profile; therefore, the proposed dosing regimen is acceptable. From clinical pharmacology standpoint, this reviewer recommends approval of the BLA.

# 2 INTRODUCTION/BACKGROUND

Plasminogen is a normal component of human blood that is synthesized in the liver and is involved in both intravascular and extravascular fibrinolysis, wound healing, cell migration, tissue remodeling, angiogenesis, and embryogenesis. Plasminogen is activated to plasmin by either tissue-type plasminogen activator (tPA) or urokinase-type plasminogen activator. Active plasmin is involved in the lysis of fibrin and extracellular matrix degradation.

Plasminogen deficiency type 1 (hypoplasminogenemia) is a rare (estimated prevalence of 1.6/million), chronic, genetic disease characterized by decreased plasminogen activity and plasminogen antigen levels, which cause abnormal extravascular accumulation or growth of fibrin rich, woody (ligneous) pseudomembranous lesions on mucous membranes that impair normal tissue and organ function.

Ryplazim is a plasma-derived, > 95% purity Glu-plasminogen that is the native circulating form of plasminogen in the blood. Ryplazim is supplied in a lyophilized powder for intravenous infusion.

The application is supported by two human clinical studies:

- a Phase 1, dose escalation, and pharmacokinetic study of Prometic plasminogen administered as intravenous infusion in adults and children with hypoplaminogenemia (study 2002C005G).
- a Phase 2/3, open-label, repeat-dose study of the pharmacokinetics, efficacy, and safety of Prometic plasminogen intravenous infusion in subjects with hypoplasminogenemia (Study 2002C011G)

The applicant submitted study report of both Studies 2002C005G and 2002C011G in the original submission. The clinical pharmacology review of the original submission included review of Phase 1 Study 2002C005G. In the current submission, the applicant provided updated report for Study 2002C011G with additional study subjects. The clinical pharmacology section of Study 2002C011G is evaluated in this review.

## 3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

- The pharmacokinetic profiles of Ryplazim were similar in adult and pediatric subjects. After the first dose of Ryplazim, absolute plasminogen activity level achieved physiological range (70 – 130%): 117.5 ± 27.1% in both subject populations.
- After 12 weeks of treatment with Ryplazim at the dose of 6.6 mg/kg every 2 to 4 days, mean exposure (AUClast) of baseline-adjusted plasminogen activity levels increased by approximately 1.4- to 1.6-fold comparing to the levels after the first dose in pediatric and adult subjects, respectively. Mean clearance and volume of distribution at steady-state decreased to approximately 64% and 77% of that after the first dose of Ryplazim in both subject populations.
- 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., ≥ absolute 10% above baseline) for at least 3 measurements for all 15 subjects.
- Between Week 12 to Week 48, plasminogen activity levels generally remained above target levels despite of decreased dosing frequency in most subjects.

## 4 CLINICAL PHARMACOLOGY LABELING COMMENTS

The clinical pharmacology reviewer has reviewed the package insert for BLA 125659/0/18 and finds it acceptable pending the following revisions shown below.

**Reviewer's Comment:**
1. Per FDA Guidance for Industry – Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (December 2016), *the CLINICAL PHARMACOLOGY section of the labeling must contain the following subsections:*
*12.1 Mechanism of Action*
*12.2 Pharmacodynamics*
*12.3 Pharmacokinetics*

Please include a pharmacodynamic subsection in your labeling.

2. Please remove references from label.
3. Please provide actual trough concentrations data in adults and children as a function of weeks in a tabulated form.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

~~RYPLAZIM is a plasma-derived human plasminogen that increases plasminogen levels. Plasminogen is a normal component of human blood and is involved in both intravascular and extravascular fibrinolysis, wound healing, cell migration, tissue remodeling, angiogenesis and embryogenesis.[4,5] Plasminogen is activated to plasmin by either tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA). Active plasmin is involved in the lysis of fibrin and extracellular matrix degradation.[6]~~

~~Congenital plasminogen deficiency is a disease characterized by decreased plasminogen levels, which cause formation of fibrinous deposits on mucous membranes that impair normal tissue and organ function.[7,8,9,10] The most common clinical manifestations are ligneous conjunctivitis and ligneous gingivitis.[9] RYPLAZIM increases plasminogen levels over the effective dosing period and treats the clinical manifestations of the disease. Lesion improvement or resolution was documented across the range of clinical manifestations, both visible (external) and non-visible (internal). Administration of RYPLAZIM over an extended period has shown to prevent recurrence of lesions *[see Clinical Studies (14)]*~~

**Reviewer's Comment:**
We recommend the following MOA:

Plasminogen deficiency type 1 is characterized by decreased plasminogen levels. Treatment with RYPLAZIM temporarily increases plasminogen levels in blood.

### 12.2 Pharmacokinetics

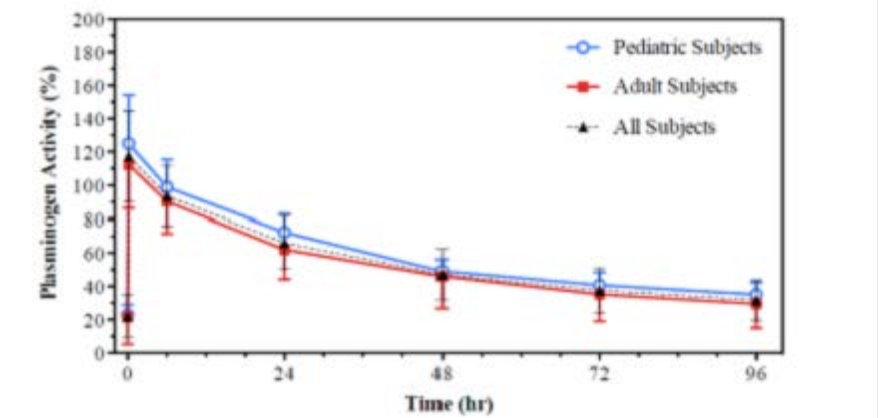
The pharmacokinetics of RYPLAZIM were assessed via measurements of plasminogen activity (chromogenic assay) in plasma. Plasminogen activity is a measurement of functional plasminogen levels and is therefore the most accurate and specific method to quantify active Plasminogen (Human) Intravenous concentration in subject's plasma. Plasminogen was measured as both absolute and baseline-adjusted levels.

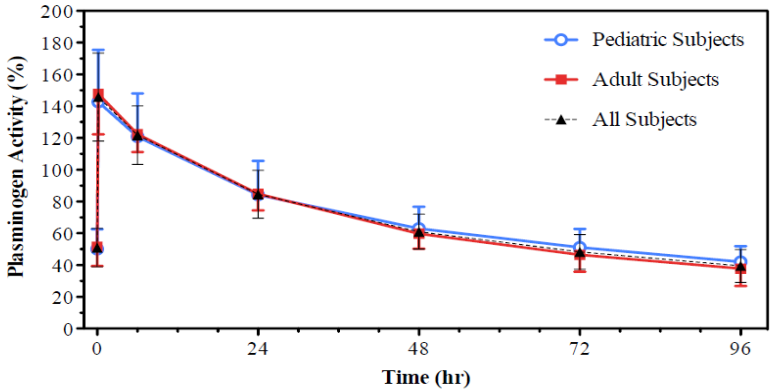
In RYPLAZIM Trial 2, pharmacokinetic analyses were conducted in 15 subjects (6 pediatric and 9 adults) who completed at least 12 weeks of RYPLAZIM 6.6 mg/kg administered every second, third or fourth day and had sufficient plasma samples. Full pharmacokinetic profiles of plasminogen were measured over 96 hours after the first and Week 12 infusions and trough levels of plasminogen were measured at baseline and at Weeks 2, 4, 6, 8, 10, and 12.

Mean absolute plasminogen activity in adult and pediatric subjects reached physiological levels (70% to 130%) immediately after the first infusion that were sustained for approximately 24 hours and remained an absolute 10% above baseline 72 hours after dosing (Figure 1 [top panel]). After 12 weeks, mean absolute plasminogen activity in adult and pediatric subjects reached physiological levels (70% to 130%) immediately after dosing, were sustained for approximately 24 hours and continued to maintain an absolute 10% above baseline 96 hours after dosing (Figure 1 [bottom panel]).

**Reviewer's Comment:**
The PK profiles are clearly described in text and Table 3. Please delete Figure 1 to minimize redundancy.

**Figure 1: Mean (± Standard Deviation) Absolute Plasminogen Activity Levels in Adult and Pediatric Subjects After the First Infusion (Top) and 12 Weeks (Bottom) of RYPLAZIM**




Although some inter-subject variability was observed, PK parameters for baseline-adjusted plasminogen activity levels were generally similar between adult and pediatric subjects.

**Reviewer's Comment:**
Please note the assay method.
The numbers in Table 3 was updated to keep one digit after the decimal.

**Table 3: Pharmacokinetic Parameters of Mean (± Standard Deviation) Baseline-Adjusted [a] Plasminogen Activity Levels in Adult and Pediatric Subjects After the First Dose and 12 Weeks RYPLAZIM**

| PK Parameter | Adult (N = 9) | | Pediatric (N = 6) | | Combined (N = 15) | |
|---|---|---|---|---|---|---|
| | First Dose | Week 12 | First Dose | Week 12 | First Dose | Week 12 |
| $AUC_{Last}$ (hr*%) | 2860.9 (700.7) | 4665.6 (762.1) | 3367.6 (852.8) | 4641.6 (1393.4) | 3063.6 (778.7) | 4656.0 (1012.7) |
| $AUC_{INF}$ (hr*%) | 3317.3 (915.7) | 5676.0 (1186.6) | 4038.5 (1104.2) | 5815.5 (1863.5) | 3605.8 (1023.9) | 5731.8 (1431.7) |
| CL (mL/h/kg) | 1.5 (0.5) | 0.9 (0.2) | 1.3 (0.4) | 0.9 (0.3) | 1.44 (0.5) | 0.92 (0.3) |
| $C_{max}$ (%) | 91 (17.5) | 127 (17.4) | 102 (31.1) | 120 (31.6) | 95 (23.5) | 125 (23.3) |
| Half-life (hr) | 32.4 (13.1) | 38.5 (7.1) | 36.3 (10.0) | 40.3 (5.0) | 34.0 (11.7) | 39.2 (6.2) |
| $MRT_{LAST}$ (hr) | 29.7 (3.7) | 33.0 (1.6) | 31.8 (2.0) | 34.2 (1.5) | 30.6 (3.2) | 33.5 (1.6) |

| | | | | | | |
|---|---|---|---|---|---|---|
| $V_{SS}$ (mL/kg) | 62.8 (11.2) | 47.2 (5.6) | 64.1 (12.9) | 52.5 (15.2) | 63.3 (11.4) | 49.3 (10.4) |
| $T_{1/2}$ (hr) | 32.4 (13.1) | 38.5 (7.1) | 36.3 (10.0) | 40.3 (5.0) | 34.0 (11.7) | 39.2 (6.2) |

$AUC_{LAST}$ = area under the time-concentration curve, from time 0 to the last measured time point; $AUC_{INF}$ = extrapolated area under the time-concentration curve, from time 0 to infinity; CL = clearance; $C_{max}$ = peak concentration; MRT = mean residence time; $V_{SS}$ = steady-state volume of distribution; $T_{1/2}$ = half-life

[a] Baseline-adjusted plasminogen activity levels were calculated by subtracting the baseline (pre-infusion) value from each subsequent time-point.

## 5 RECOMMENDATIONS

Based on the pharmacokinetic (PK) results of Study 2002C005G and Study 2002C011G, the clinical pharmacology reviewer recommends approval for this BLA, provided that satisfactory agreement is reached between the applicant and the FDA regarding the language in Section 12 of the package insert. Please refer to section 4 for detailed Labeling Recommendations.

## 6 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 (Study No. 2002C011G).

**Objectives:**

***Primary Objective***

- To evaluate the efficacy of plasminogen replacement therapy on clinically evident or visible symptoms of hypoplasminogenemia/congenital plasminogen deficiency 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 pediatric and adult subjects with hypoplasminogenemia/congenital plasminogen deficiency during the 12 weeks of plasminogen replacement therapy in Segment 2.

***Secondary Objectives***

- To evaluate the efficacy of plasminogen replacement therapy on clinically evident or visible symptoms of hypoplaminogenemia/ congenital plasminogen deficiency during the 12 weeks of plasminogen replacement therapy in Segment 2.
- To evaluate the safety and tolerability of plasminogen replacement therapy during the 48 weeks of dosing.
- To evaluate the effect of plasminogen replacement therapy on trough plasminogen levels and immunogenicity during the 48 weeks of dosing.

### 6.1 Study Design

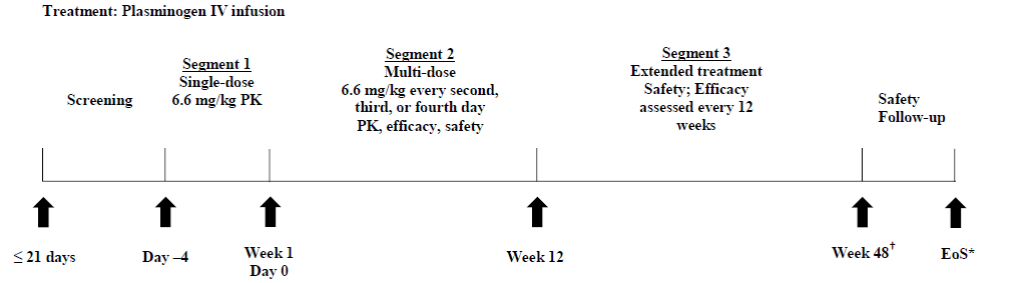
This was a phase 2/3, open-label, single-arm, repeat-dose study evaluating the efficacy PK, and safety of replacement therapy with the study drug, Ryplazim, in pediatric and adult subjects with congenital plasminogen deficiency.

As shown in Figure 1, the study consisted a screening period and 3 study drug treatment segments. Subjects received 6.6 mg/kg of Ryplazim every 2 to 4 days for all treatment segments. PK profiles of plasma plasminogen activity and plasminogen antigen were obtained after the first dose of Ryplazim (Week1) and after 12 weeks of Ryplazim treatment (Week 12), and baseline-adjusted PK parameters were derived using non-compartmental analysis.

Blood samples were obtained for PK analysis at baseline (pre-dose), and at 5-15 minutes, 6 hours, 24 hours, 48 hours, 72 hours, and 96 hours post-dose. Both plasma plasminogen activity and antigen levels were measured using validated chromogenic assay and (b) (4) assay, respectively.

A total of 15 subjects (6 pediatric aged 4 to 16 years and 9 adult aged 19 to 42 years) with congenital plasminogen deficiency enrolled in the study and had PK assessment.

**Figure 1. Study Schema (Study 2202C011G)**




EoS = End of Study (visit); IV = intravenous; PK = pharmacokinetic(s); US = United States.
†Week 48 = Efficacy evaluations for the primary endpoint performed at Week 48 for both Norway and US subjects
*EoS = A Safety Follow-up visit was required 30 days after the last dose of study drug, with the exception of US subjects that entered into Treatment Protocol 2002C018G where treatment was not withheld for this 30 day visit.

*Source: Applicant. Study Report # 2002C011G.*

## 6.2 Results

A total of 15 subjects (6 pediatric aged 4 to 16 years and 9 adult aged 19 to 42 years) with congenital plasminogen deficiency enrolled in the study and had PK assessment. Six subjects (5 adult and 1 pediatric) had documented individual PK profiles due to their participation in the Phase 1 study (Study 2002C005G), where they received a single dose of Ryplazim at 6 mg/kg. Nine subjects (4 adult and 5 pediatric) received their first dose of Ryplazim in this Phase 2/3 Study 2002C011G.

### 6.2.1 Pharmacokinetics

**Plasminogen Activity**

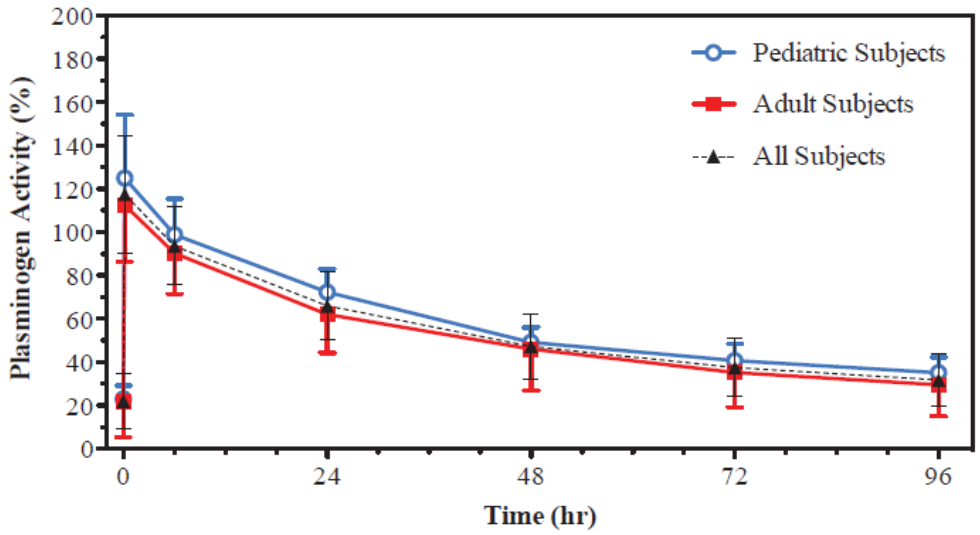
Plasminogen activity is a measurement of functional plasminogen levels using the (b) (4) The plasminogen in a plasma sample is (b) (4) The quantity of the plasminogen-(b) (4) is determined by the (b) (4) in the test sample. As illustrated in Figure 2 and Figure 3, plasminogen activity levels were measured up to 96 hours after the first dose of Ryplazim and after 12 weeks of Ryplazim for PK assessment. Adult and pediatric subjects had similar plasminogen activity PK profiles. At baseline, mean (± SD) plasminogen activity was 21.1 ± 10.8% (20.3 ± 13.7% in adult subjects and 22.3 ± 5.1% in pediatric subjects). After 12 weeks of repeated doses of Ryplazim, trough plasminogen activity levels reached 51.0 ± 12.0% (51.7 ± 12.3% in in adult subjects and 50.0 ± 12.6% in pediatric subjects).

After first dose of Ryplazim, absolute plasminogen activity level achieved normal range (70 – 130%): 117.5 ± 27.1% (112.4 ± 26.0% in adult subjects and 125.0 ± 29.2% in pediatric subjects). Plasminogen activity levels were above 70% till 6 hours post-dose in all subjects except one adult.

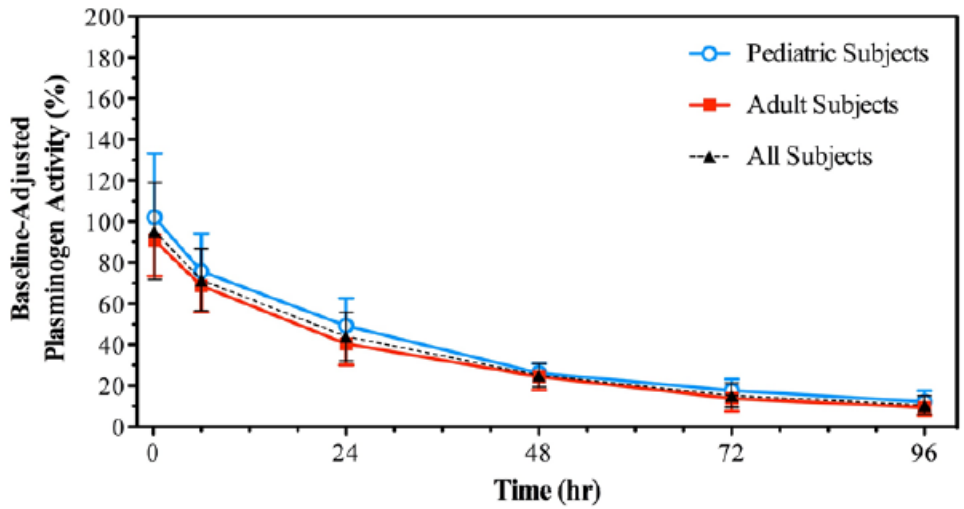
After 12 weeks treatment of Ryplazim, absolute plasminogen levels reached normal physiological levels (≥70%) within 6 hours post-infusion in all study subjects. The plasminogen activity levels were sustained for at least 24 hours post-infusion in majority subjects. After 12 weeks treatment, plasminogen activity levels were at least 10% above baseline at 96 hours post-infusion of Ryplazim in all study subjects.

**Figure 2. Mean (±SD) Plasminogen Activity Levels in Adult and Pediatric Subjects after First Dose of Ryplazim**

a. Absolute Plasminogen Activity Levels



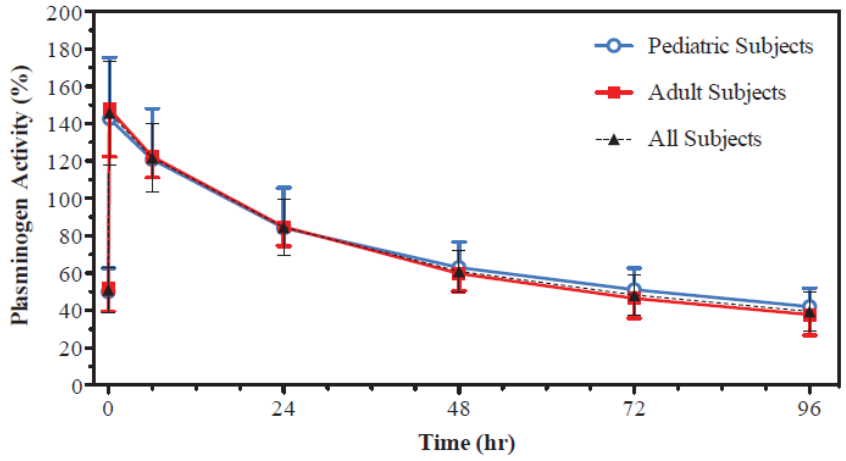

b. Baseline-adjusted Plasminogen Activity Levels



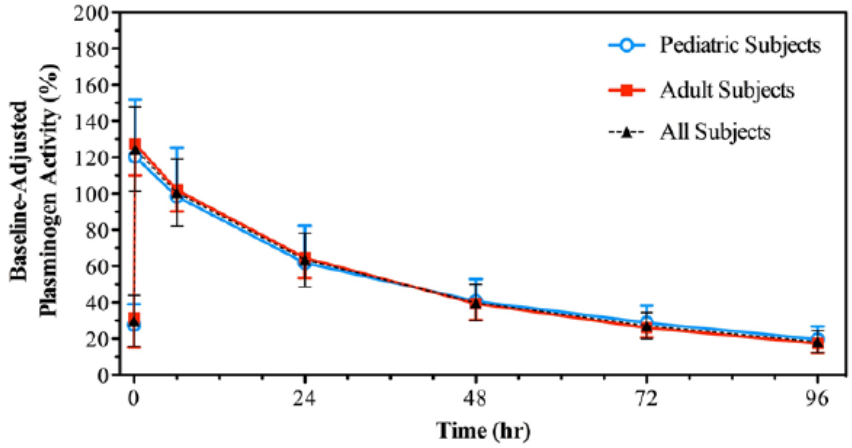

*Source: Applicant. Study # 2002C011G PK Report.*

**Figure 3. Baseline-adjusted Mean (±SD) Plasminogen Activity Levels in Adult and Pediatric Subjects after 12 Weeks Treatment of Ryplazim**

a. Absolute Plasminogen Activity Levels




b. Baseline-adjusted Plasminogen Activity Levels




*Source: Applicant. Study # 2002C011G PK Report.*

Table 1 shows the pharmacokinetic parameters (plasminogen activity) of Ryplazim. The mean pre-dose plasminogen activity levels increased from 21.1 ± 10.8% in week 1 to 51.0 ± 12.0% at week 12. Mean baseline-adjusted plasminogen activity peak concentration increased from 95.0 ± 23.5% after the first dose of Ryplazim to 125.0 ± 23.3% after 12 weeks treatment of Ryplazim. The exposures (AUClast) after 12 weeks treatment were approximately 1.4- to 1.6-fold comparing to that after the first dose in pediatric and adult subjects, respectively. The mean clearance (Cl) and volume of distribution at steady state (Vss) decreased to approximately 64% and 78% of that after the first dose of Ryplazim in both subject populations.

**Table 1. Pharmacokinetic Parameters of Baseline-Adjusted Plasminogen Activity Levels in Adult and Pediatric Subjects**

| PK Parameter | Adult (N = 9) | | Pediatric (N = 6) | | Combined (N = 15) | |
|---|---|---|---|---|---|---|
| | First Dose | Week 12 | First Dose | Week 12 | First Dose | Week 12 |
| **$AUC_{LAST}$ (hr×%)** | | | | | | |
| Mean (SD) | 2860.9 (700.7) | 4665.6 (762.1) | 3367.6 (852.8) | 4641.6 (1393.4) | 3063.6 (778.7) | 4656.0 (1012.7) |
| CV% | 24.5 | 16.3 | 25.3 | 30.0 | 25.4 | 21.7 |
| Median | 2850.9 | 4693.4 | 3117.4 | 4965.2 | 3078.7 | 4693.4 |
| Min, max | 1970.1, 4198.9 | 3588.4, 5834.1 | 2403.9, 4751.8 | 2968.5, 6448.6 | 1970.1, 4751.8 | 2968.5, 6448.6 |
| Geometric mean | 2785.7 | 4610.4 | 3283.0 | 4453.7 | 2974.9 | 4547.1 |
| 95% CI | 2306.3 – 3364.7 | 4064.4 – 5229.7 | 2540.4 – 4242.7 | 3175.0 – 6247.5 | 2589.5 – 3417.6 | 2777.5 – 7444.0 |
| **$AUC_{INF}$ (hr×%)** | | | | | | |
| Mean (SD) | 3317.3 (915.7) | 5676.0 (1186.6) | 4038.5 (1104.2) | 5815.5 (1863.5) | 3605.8 (1023.9) | 5731.8 (1431.7) |
| CV% | 27.6 | 20.9 | 27.3 | 32.0 | 28.4 | 25.0 |
| Median | 3541.5 | 5615.2 | 3874.4 | 6415.1 | 3541.5 | 5691.7 |
| Min, max | 2024.7, 4728.6 | 4038.4, 7919.6 | 2639.8, 5397.0 | 3544.2, 8167.5 | 2024.7, 5397.0 | 3544.2, 8167.5 |
| Geometric mean | 3195.6 | 5567.3 | 3910.7 | 5538.7 | 3464.4 | 5555.8 |
| 95% CI | 2541.3 – 4018.2 | 4740.8 – 6537.8 | 2914.3 – 5247.6 | 3822.7, 8024.9 | 2936.1 – 4087.8 | 3155.5 – 9782.0 |
| **Cl (mL/hr/kg)** | | | | | | |
| Mean (SD) | 1.5 (0.5) | 0.9 (0.2) | 1.3 (0.4) | 0.9 (0.3) | 1.4 (0.5) | 0.9 (0.3) |
| CV% | 33.2 | 22.3 | 30.0 | 37.0 | 32.0 | 28.1 |
| Median | 1.4 | 0.9 | 1.3 | 0.8 | 1.4 | 0.9 |
| Min, max | 1.0, 2.4 | 0.6, 1.3 | 0.9, 1.9 | 0.6, 1.4 | 0.9, 2.4 | 0.6, 1.4 |
| Geometric mean | 1.5 | 0.9 | 1.27 | 0.9 | 1.4 | 0.9 |
| 95% CI | 1.1 – 1.9 | 0.8 – 1.1 | 0.9 – 1.7 | 0.6 – 1.3 | 1.2 – 1.6 | 0.5 – 1.6 |
| **$C_{max}$ (%)** | | | | | | |
| Mean (SD) | 91 (17.5) | 127 (17.4) | 102 (31.1) | 120 (31.6) | 95 (23.5) | 125 (23.3) |
| CV% | 19.3 | 13.6 | 30.5 | 26.3 | 24.7 | 18.7 |
| Median | 90 | 129 | 92 | 126 | 91 | 129 |
| Min, max | 76, 132 | 103, 155 | 78, 162 | 73, 162 | 76, 162 | 73, 162 |
| Geometric mean | 90 | 126 | 99 | 117 | 93 | 122 |
| 95% CI | 78 – 102 | 114 – 141 | 75 – 131 | 86 – 157 | 83 – 105 | 79 – 190 |

| PK Parameter | Adult (N = 9) | | Pediatric (N = 6) | | Combined (N = 15) | |
|---|---|---|---|---|---|---|
| | First Dose | Week 12 | First Dose | Week 12 | First Dose | Week 12 |
| **$T_{1/2}$ (hr)** | | | | | | |
| Mean (SD) | 32.4 (13.1) | 38.5 (7.1) | 36.3 (10.0) | 40.3 (5.0) | 34.0 (11.7) | 39.2 (6.2) |
| CV% | 40.4 | 18.5 | 27.6 | 12.5 | 34.5 | 15.9 |
| Median | 31.0 | 37.1 | 32.3 | 39.4 | 31.9 | 37.7 |
| Min, max | 17.0, 62.6 | 29.4, 51.6 | 27.2, 54.9 | 35.1, 47.2 | 17.0, 62.6 | 29.4, 51.6 |
| Geometric mean | 30.4 | 38.0 | 35.3 | 40.0 | 32.3 | 38.8 |
| 95% CI | 22.7 – 40.7 | 33.1 – 43.6 | 27.2 – 45.8 | 35.2 – 45.6 | 26.9 – 38.8 | 27.7 – 54.4 |
| **$MRT_{LAST}$ (hr)** | | | | | | |
| Mean (SD) | 29.7 (3.7) | 33.0 (1.6) | 31.8 (2.0) | 34.2 (1.5) | 30.6 (3.2) | 33.5 (1.6) |
| CV% | 12.5 | 4.8 | 6.2 | 4.3 | 10.5 | 4.8 |
| Median | 31.3 | 33.0 | 31.6 | 34.5 | 31.5 | 33.8 |
| Min, max | 22.8, 33.3 | 30.9, 35.8 | 29.6, 35.0 | 31.5, 36.0 | 22.8, 35.0 | 30.9, 36.0 |
| Geometric mean | 29.5 | 33.0 | 31.7 | 34.2 | 30.4 | 33.5 |
| 95% CI | 26.6 – 32.7 | 31.8 – 34.2 | 29.8 – 33.8 | 32.7 – 35.8 | 28.5 – 32.4 | 30.2 – 37.1 |
| **$V_{ss}$ (mL/kg)** | | | | | | |
| Mean (SD) | 62.8 (11.2) | 47.2 (5.6) | 64.1 (12.9) | 52.5 (15.2) | 63.3 (11.4) | 49.3 (10.4) |
| CV% | 17.8 | 11.8 | 20.1 | 28.9 | 18.1 | 21.0 |
| Median | 62.6 | 45.8 | 66.7 | 49.5 | 63.8 | 45.8 |
| Min, max | 41.7, 82.1 | 39.6, 56.9 | 41.6, 76.3 | 35.0, 75.4 | 41.6, 82.1 | 35.0, 75.4 |
| Geometric mean | 61.9 | 46.9 | 62.9 | 50.7 | 62.3 | 48.4 |
| 95% CI | 53.6 – 71.5 | 42.9 – 51.3 | 49.6 – 79.6 | 37.5 – 68.5 | 55.9 – 69.4 | 31.8 – 73.8 |

AUCINF = area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUCLAST = area under the plasma concentration-time curve from time 0 to the last measured time point; CI = confidence interval; Cl = clearance; $C_{max}$ = maximum plasma concentration; CV% = coefficient of variation; max = maximum; Min = minimum; MRT = mean residence time; PK = pharmacokinetic; SD = standard deviation; $T_{1/2}$ = terminal half-life; $V_{SS}$ = volume of distribution at steady state.

*Source: Applicant. Study Report # 2002C011G.*

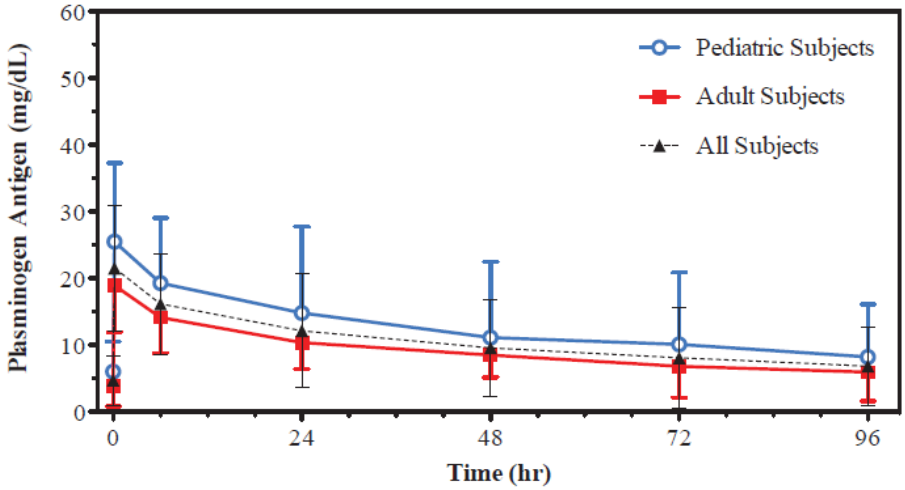
**Plasminogen Activity**

Plasma plasminogen antigen levels were also measured for PK assessment. Plasminogen antigen measurement measures total plasminogen, which includes both functional and inactive plasminogen as well as plasmin-antiplasmin complexes.

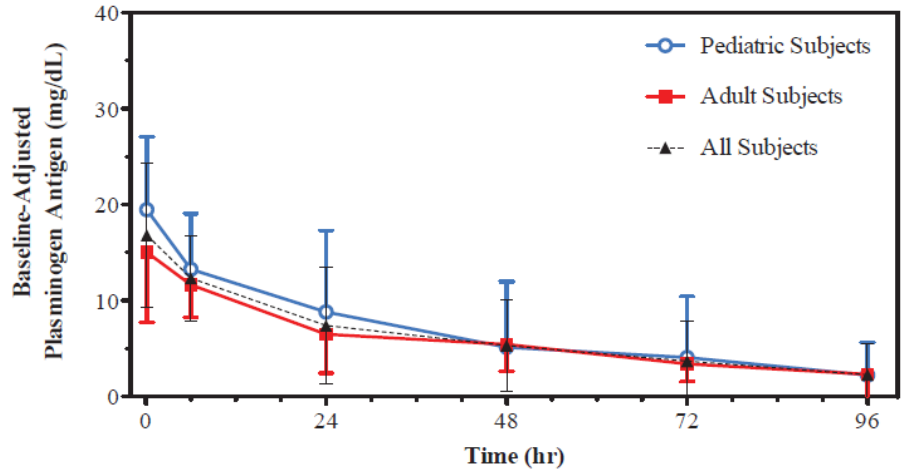
Similar absolute and baseline-adjusted plasminogen antigen profiles were observed in adult and pediatric populations (Figure 4 and Figure 5). Compared to plasminogen activity PK profiles, plasminogen antigen PK profiles had larger inter-subject variability. Plasminogen antigen PK parameters were shown in Table 2.

**Figure 4. Mean (±SD) Plasminogen Antigen Levels in Adult and Pediatric Subjects after First Dose of Ryplazim**

a. Absolute Plasminogen Antigen Levels



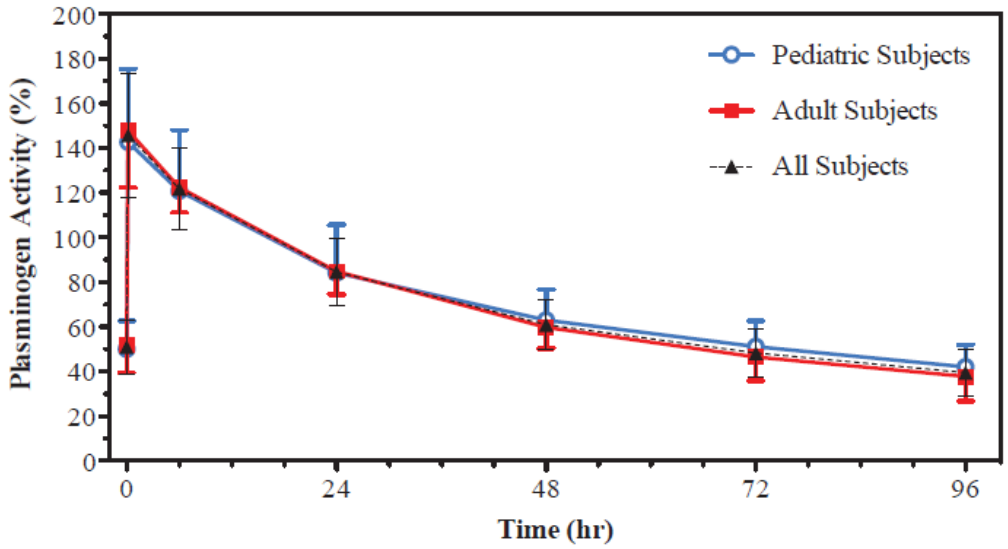

b. Baseline-adjusted Plasminogen Antigen Levels



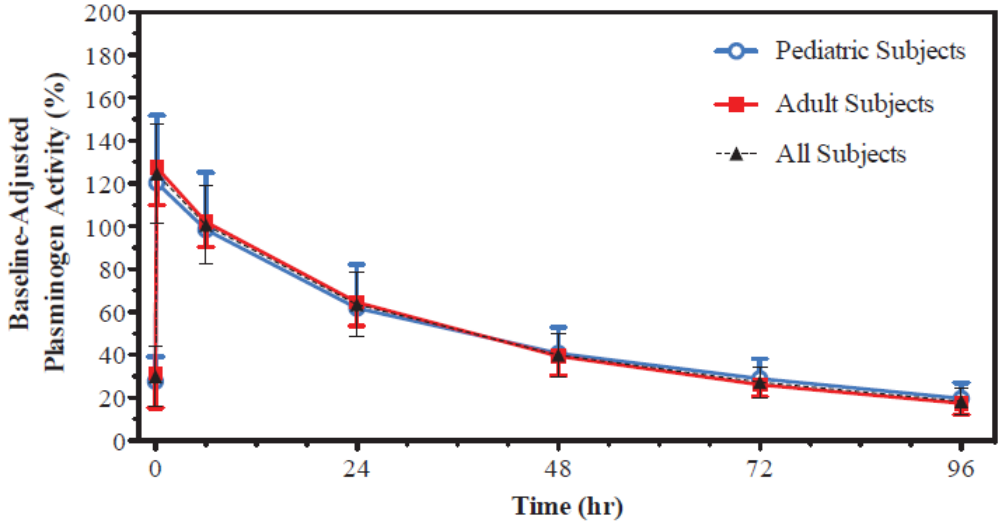

*Source: Applicant. Study # 2002C011G PK Report.*

**Figure 5. Baseline-adjusted Mean (±SD) Plasminogen Antigen Levels in Adult and Pediatric Subjects after 12 Weeks Treatment of Ryplazim**

a. Absolute Plasminogen Antigen Levels




b. Baseline-adjusted Plasminogen Antigen Levels




*Source: Applicant. Study # 2002C011G PK Report.*

**Table 2. Pharmacokinetic Parameters of Baseline-Adjusted Plasminogen Antigen Levels in Adult and Pediatric Subjects After First Dose of Ryplazim**

| PK Parameters | Statistics | Adult (N=9) | Pediatric (N=6) | Combined Adult and Pediatric (N=15) |
|---|---|---|---|---|
| **AUC LAST (hr*mg/dL)** | N | 9 | 6 | 15 |
| | Mean (SD) | 533.5 (235.6) | 624.2 (607.9) | 569.8 (407.2) |
| | CV% | 44.2 | 97.4 | 71.5 |
| | Median | 433.4 | 377.9 | 423.4 |
| | Min, Max | 299.5, 941.1 | 286.7, 1858.2 | 286.7, 1858.2 |
| | Geometric Mean | 491.9 | 486.4 | 489.7 |
| | 95% CI | 356.0 – 679.6 | 238.8 – 990.8 | 368.2 – 651.3 |
| **AUC INF (hr*mg/dL)** | N | 6a | 5b | 11a, b |
| | Mean (SD) | 601.0 (274.6) | 821.5 (943.8) | 701.2 (638.2) |
| | CV% | 45.7 | 114.9 | 91.0 |
| | Median | 499.1 | 389.6 | 459.1 |
| | Min, Max | 339.6, 1099.9 | 304.8, 2501.9 | 304.8, 2501.9 |
| | Geometric Mean | 557.14 | 567.6 | 561.9 |
| | 95% CI | 361.0 – 859.7 | 195.9 – 1645.2 | 371.5 – 849.8 |
| **Cl (mL/hr/kg)** | N | 6a | 5b | 11a, b |
| | Mean (SD) | 1.2 (0.5) | 1.4 (0.8) | 1.3 (0.6) |
| | CV% | 39.4 | 52.9 | 45.5 |
| | Median | 1.3 | 1.7 | 1.31 |
| | Min, Max | 0.6, 1.9 | 0.2, 2.2 | 0.2, 2.2 |
| | Geometric Mean | 1.1 | 1.1 | 1.1 |
| | 95% CI | 0.7 – 1.8 | 0.4 – 3.5 | 0.7 – 1.8 |
| **Cmax (mg/dL)** | N | 9 | 6 | 15 |
| | Mean (SD) | 15.6 (6.7) | 19.9 (7.4) | 17.3 (7.1) |
| | CV% | 43.0 | 37.2 | 40.8 |
| | Median | 12.9 | 16.8 | 16.7 |
| | Min, Max | 8.2, 28.5 | 14.5, 34.0 | 8.2, 34.0 |
| | Geometric Mean | 14.4 | 18.9 | 16.1 |
| | 95% CI | 10.5 – 19.9 | 13.5 – 26.5 | 13.0 – 20.0 |

| PK Parameters | Statistics | Adult (N=9) | Pediatric (N=6) | Combined Adult and Pediatric (N=15) |
|---|---|---|---|---|
| | N | 6a | 5b | 11a, b |
| **T1/2 (hr)** | Mean (SD) | 24.0 (5.7) | 27.7 (14.0) | 25.7 (10.0) |
| | CV% | 23.9 | 50.6 | 38.8 |
| | Median | 25.0 | 25.2 | 25.2 |
| | Min, Max | 16.7, 31.4 | 13.9, 49.6 | 13.9, 49.6 |
| | Geometric Mean 95%CI | 23.4 18.0 – 30.4 | 25.1 13.6 – 46.5 | 24.1 18.9 – 30.8 |
| **MRTLAST (hr)** | N | 9 | 6 | 15 |
| | Mean (SD) | 33.8 (7.9) | 28.4 (7.6) | 31.6 (8.0) |
| | CV% | 23.2 | 26.8 | 25.2 |
| | Median | 32.1 | 28.9 | 30.7 |
| | Min, Max | 22.8, 49.5 | 19.9, 40.8 | 19.9, 49.5 |
| | Geometric Mean 95%CI | 33.0 27.8 – 39.2 | 27.5 20.9 – 36.4 | 30.7 26.7 – 35.2 |
| **Vss (mL/kg)** | N | 6a | 5b | 11a, b |
| | Mean (SD) | 44.0 (14.2) | 44.2 (21.0) | 44.1 (16.6) |
| | CV% | 32.2 | 47.5 | 37.7 |
| | Median | 48.2 | 39.0 | 47.2 |
| | Min, Max | 25.8, 63.0 | 17.6, 74.6 | 17.6, 74.6 |
| | Geometric Mean 95%CI | 41.9 29.0 – 60.6 | 39.9 20.6 – 77.3 | 41.0 30.9 – 54.3 |

*Source: Applicant. Study 2002C011G PK Report.*

a. $T_{1/2}$, $AUC_{INF}$, Cl, and $V_{ss}$ for adult subjects (b) (6) did not meet PK acceptance criteria and were not included in summary statistics.

b. $T_{1/2}$, $AUC_{INF}$, Cl, and $V_{ss}$ for pediatric subjects (b) (6) did not meet PK acceptance criteria and were not included in summary statistics

**Table 3. Pharmacokinetic Parameters of Baseline-Adjusted Plasminogen Antigen Levels in Adult and Pediatric Subjects After 12 Weeks Treatment of Ryplazim**

| PK Parameters | Statistics | Adult (N=9) | Pediatric (N=6) | Combined Adult and Pediatric (N=15) |
|---|---|---|---|---|
| **AUC LAST (hr*mg/dL)** | N | 9 | 6 | 15 |
| | Mean (SD) | 538.1 (160.6) | 515.6 (205.9) | 529.1 (173.2) |
| | CV% | 29.8 | 39.9 | 32.7 |
| | Median | 605.4 | 455.8 | 543.8 |
| | Min, Max | 278.8, 773.7 | 321.3, 846.9 | 278.8, 846.9 |
| | Geometric Mean | 514.6 | 484.0 | 502.1 |
| | 95% CI | 400.1 – 661.9 | 323.0 – 725.0 | 416.08 – 606.0 |
| **AUC INF (hr*mg/dL)** | N | 6a | 2b | 8a, b |
| | Mean (SD) | 578.7 (229.9) | 440.2 (51.7) | 544.1 (205.5) |
| | CV% | 39.7 | 11.8 | 37.8 |
| | Median | 552.9 | 440.2 | 462.7 |
| | Min, Max | 291.3, 928.3 | 403.6, 476.8 | 291.3, 928.3 |
| | Geometric Mean | 539.9 | 438.7 | 512.61 |
| | 95% CI | 349.0 – 835.2 | 152.2 – 1264.2 | 377.2 – 696.7 |
| **Cl (mL/hr/kg)** | N | 6a | 2b | 8a, b |
| | Mean (SD) | 1.3 (0.5) | 1.5 (0.2) | 1.3 (0.5) |
| | CV% | 41.9 | 15.3 | 35.4 |
| | Median | 1.3 | 1.5 | 1.4 |
| | Min, Max | 0.7, 2.2 | 1.3, 1.6 | 0.7, 2.2 |
| | Geometric Mean | 1.21 | 1.5 | 1.3 |
| | 95% CI | 0.8 – 1.9 | 0.4 – 5.8 | 0.9 – 1.7 |
| **Cmax (mg/dL)** | N | 9 | 6 | 15 |
| | Mean (SD) | 19.3 (6.7) | 19.9 (11.9) | 19.5 (8.7) |
| | CV% | 34.5 | 59.9 | 44.6 |
| | Median | 20.6 | 15.0 | 17.3 |
| | Min, Max | 10.2, 27.7 | 12.1, 43.7 | 10.2, 43.7 |
| | Geometric Mean | 18.2 | 17.9 | 18.1 |
| | 95% CI | 13.6 – 24.3 | 11.0 – 29.1 | 14.5 – 22.5 |

| PK Parameters | Statistics | Adult (N=9) | Pediatric (N=6) | Combined Adult and Pediatric (N=15) |
|---|---|---|---|---|
| | N | 6a | 2b | 8a, b |
| **T1/2 (hr)** | Mean (SD) | 28.7 (14.0) | 35.8 (5.6) | 30.5 (12.5) |
| | CV% | 48.8 | 15.6 | 40.9 |
| | Median | 23.3 | 35.8 | 28.5 |
| | Min, Max | 17.4, 54.8 | 31.8, 39.7 | 17.4, 54.8 |
| | Geometric Mean 95% CI | 26.4<br>16.9 – 41.3 | 35.5<br>8.7 – 145.5 | 28.5<br>20.6 – 39.4 |
| **MRTLAST (hr)** | N | 9 | 6 | 15 |
| | Mean (SD) | 29.5 (5.4) | 32.6 (4.1) | 30.8 (5.0) |
| | CV% | 18.4 | 12.5 | 16.3 |
| | Median | 31.2 | 32.4 | 32.1 |
| | Min, Max | 20.0, 36.6 | 25.9, 36.9 | 20.0, 36.9 |
| | Geometric Mean 95% CI | 29.1<br>25.0 – 33.8 | 32.4<br>28.2 – 37.1 | 30.3<br>27.5 – 33.5 |
| **Vss (mL/kg)** | N | 6a | 2b | 8a, b |
| | Mean (SD) | 49.2 (6.9) | 75.1 (5.5) | 55.7 (13.5) |
| | CV% | 14.0 | 7.3 | 24.2 |
| | Median | 50.3 | 75.1 | 52.4 |
| | Min, Max | 37.7, 57.5 | 71.2, 79.0 | 37.7, 79.0 |
| | Geometric Mean 95% CI | 48.8<br>41.8 – 57.0 | 75.0<br>38.7 – 145.2 | 54.3<br>44.6 – 66.2 |

*Source: Applicant. Study 2002C011G PK Report.*

a. $T_{1/2}$, $AUC_{INF}$, Cl, and $V_{ss}$ for adult subjects (b) (6) did not meet PK acceptance criteria and were not included in summary statistics.

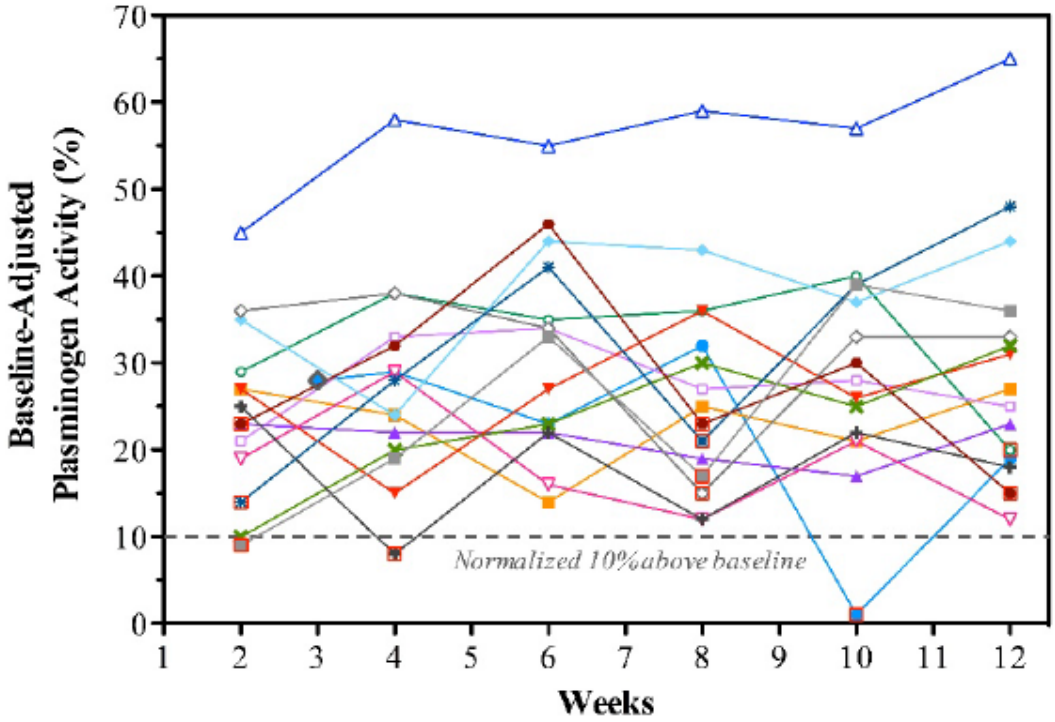
b. $T_{1/2}$, $AUC_{INF}$, Cl, and $V_{ss}$ for pediatric subjects (b) (6) did not meet PK acceptance criteria and were not included in summary statistics

### 6.2.2 Plasminogen Trough Levels

Per the protocol, a successful PK outcome of this clinical study was the plasminogen trough activity levels in each subject were at least 10% above the subject's baseline level for at least 3 measurements during the first 12 weeks of treatment in Segment 2.

As shown in Figure 6, target plasminogen activity trough levels (≥ absolute 10% above baseline) were achieved for at least 3 measurements for all 15 subjects during the 12 weeks of plasminogen replacement therapy in Segment 2.

**Figure 6. Plasminogen Activity Trough Levels Trough Week 12**

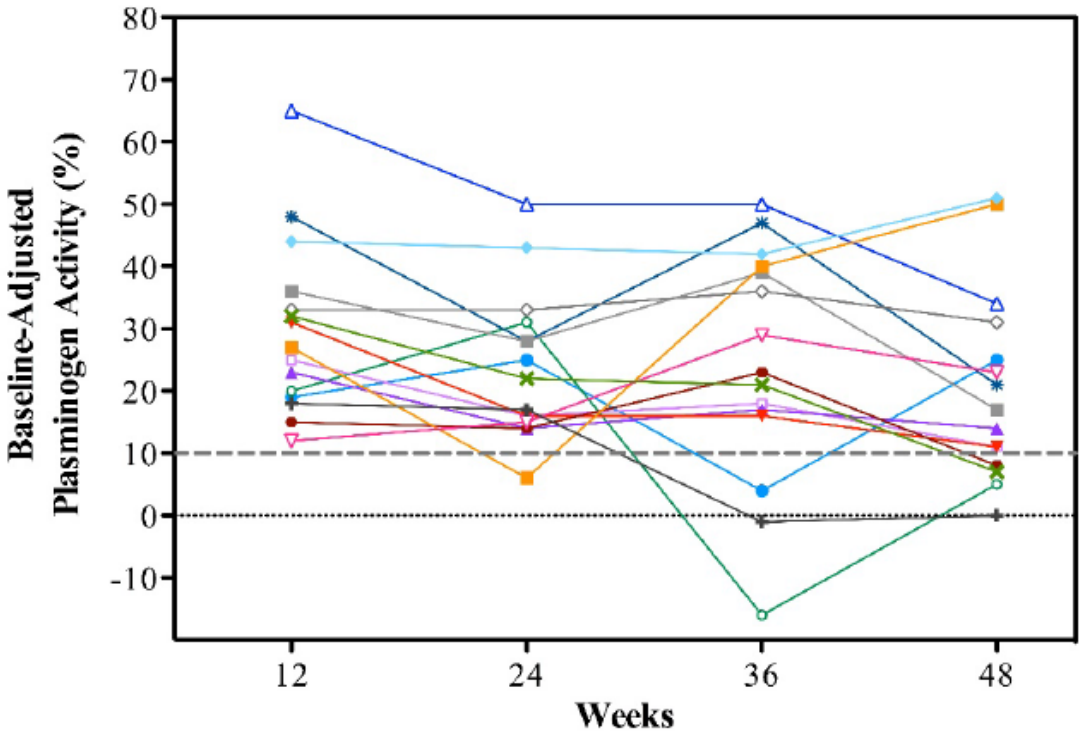



*Source: Applicant. Study Report # 2002C011G.*

There were 3 cases for whom plasminogen activity trough levels were below target plasminogen activity trough levels during the 12-week treatment period due to delayed dosing of Ryplazim.

In segment 3 (Week 12 to Week 48), the dosing frequency were reduced in most subjects. Plasminogen activity levels generally remained above target levels.

**Figure 7. Plasminogen Activity Trough Levels between Week 12 and Week 48**




*Source: Applicant. Study Report # 2002C011G.*

There were eight cases of plasminogen activity trough levels below target levels in six subjects (Figure 7 and Table 4). For the majority of cases, the decrease of plasminogen activity trough levels was due to interrupted dosing (delayed dosing) or reduced dosing frequency. The decrease of plasminogen activity trough level was transient. Plasminogen activity trough levels returned to above target levels in all subjects except one, who was discontinued from the study by investigator (due to no-compliance) and did not have follow-up plasminogen activity trough level data.

**Table 4. Plasminogen Activity Trough Levels Between Week 12 and Week 48**

| Study Population | Plasminogen Activity Trough Levels (%) | | | | |
|---|---|---|---|---|---|
| | Baseline | Week 12 | Week 24 | Week 36 | Week 48 |
| **Adult (N = 9)** | 20.3 (13.7) | 51.7 (12.3) | 45.0 (14.4) | 42.3(9.0) | 36.6 (11.1) |
| **Pediatric (N = 6)** | 22.3 (5.1) | 50.0 (12 6) | 45.0 (11.6) | 50.2 (17.7) | 49.3 (22.2) |
| **Combined (N = 15)** | 21.1 (10.8) | 51.0 (12.0) | 45.0 (17.0) | 45.5 (13.2) | 41.7 (17.0) |

Plasminogen activity levels measured with a chromogenic assay. Normal range: 70%-130%, as determined by the laboratory. Individual plasminogen activity values reported as < 5% were set at 5% for mean calculation.

### 6.2.3 Immunogenicity

There were 5 confirmed anti-plasminogen antibody positive samples observed in 3 subjects. The immune responses (development of anti-plasminogen antibodies) were transient in subjects. The development of anti-plasminogen antibody did not affect clinical efficacy in study subjects.

**Conclusions:**

- The pharmacokinetic profiles of Ryplazim were similar in adult and pediatric subjects. After the first dose of Ryplazim, absolute plasminogen activity level achieved physiological range (70 – 130%): 117.5 ± 27.1% in both subject populations.
- After 12 weeks of treatment with Ryplazim at the dose of 6.6 mg/kg every 2 to 4 days, mean exposure (AUClast) of baseline-adjusted plasminogen activity levels increased by approximately 1.4- to 1.6-fold comparing to the levels after the first dose in pediatric and adult subjects, respectively. Mean clearance and volume of distribution at steady-state decreased to approximately 64% and 77% of that after the first dose of Ryplazim in both subject populations.
- 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., ≥ absolute 10% above baseline) for at least 3 measurements for all 15 subjects.
- Between Week 12 to Week 48, plasminogen activity levels generally remained above target levels despite of decreased dosing frequency in most subjects.