CLINICAL PHARMACOLOGY BLA REVIEW

Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT)
Office of Tissues & Advance Therapies (OTAT)

STN 125659/0
Sponsor: PROMETIC BIOTHERAPEUTICS, INC.
Product: PLASMINOGEN (HUMAN), RYPLAZIM
Indication: Replacement therapy in adults and children with plasminogen deficiency
Submission Date: August 17, 2017
Reviewer: Iftekhar Mahmood, Ph. D.
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Study Title: A Phase 1, Dose Escalation, and Pharmacokinetic Study of ProMetic Plasminogen Administered as Intravenous Infusion in Adults and Children with Hypoplasminogenemia. 8

INTRODUCTION

Hypoplasminogenemia or type 1 plasminogen deficiency is a systemic disease characterized by markedly impaired extravascular fibrinolysis leading to the formation of ligneous pseudomembranes on mucosae during wound healing. Hypoplasminogenemia is a rare autosomal recessive genetic disorder caused by homozygous or compound-heterozygous mutations in the plasminogen gene. These mutations result in parallel reduction in both the level of plasminogen functional activity and its immunoreactivity.

Plasminogen is the inactive precursor of plasmin, a potent serine protease involved in the dissolution of fibrin clots. It is a single-chain glycoprotein containing 791 amino acid residues and 2 % carbohydrate, synthesized in the liver and maintained in plasma at a stable concentration of around 200 µg/mL in healthy adult subjects.

There are two main native forms of plasminogen in plasma, Glu- and Lys-plasminogen. Glu-plasminogen has a glutamic acid at the N-terminal whereas Lys-plasminogen has a lysine at the N-terminal.

ProMetic BioTherapeutics, is developing a human GluPlasminogen (RYPLAZIM) for the treatment of hypoplasminogenemia.

RYPLAZIM is a sterile, lyophilized preparation of purified plasma-derived plasminogen (human) to be reconstituted and administered by the intravenous route. Each vial of RYPLAZIM contains 68.8 mg of plasminogen. Following reconstitution with 12.5 mL of water for injection (WFI), the RYPLAZIM solution contains 5.5 mg/mL plasminogen and the following inactive ingredients: sodium citrate, sodium chloride, glycine, and sucrose. RYPLAZIM contains no preservative. Biological potency of the plasminogen is determined by a chromogenic assay (b) (4) .

RYPLAZIM is manufactured from human source plasma, collected from healthy North American donors by registered plasma sites. RYPLAZIM manufacturing process employs a series of (b) (4) to purify plasminogen and includes multiple steps and controls to ensure that the purified plasminogen is free of adventitious agents.

RECOMMENDATION

The study design, pharmacokinetic analysis, and the conclusions of the study are acceptable from clinical pharmacology perspective. The applicant should modify clinical pharmacology labeling as suggested by FDA.

CLINICAL PHARMACOLOGY LABELING COMMENTS

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. 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. Upon binding to a fibrin clot, plasminogen with an N-terminal glutamic acid (Glu-plasminogen) is readily cleaved and converted into a modified plasminogen with an N-terminal lysine (Lys-plasminogen). Glu-plasminogen has a circulating half-life of 2 to 2.5 days and Lys-plasminogen has a half-life of 0.8 days. ~~RYPLAZIM is a highly purified (> 95% purity) Glu-plasminogen.~~

Congenital plasminogen deficiency is a disease characterized by decreased plasminogen levels, which cause formation of fibrinous depositions on mucous membranes that impair normal tissue and organ function. The most common clinical manifestations are ligneous conjunctivitis and ligneous gingivitis. RYPLAZIM increases plasminogen levels over the ~~effective~~ dosing period and ~~treats~~ manages the clinical manifestations of the disease. The longer term clinical benefit of the increased plasminogen levels on mucosal lesions caused by congenital plasminogen deficiency has not been established.

12.~~3~~ 2 Pharmacokinetics

The pharmacokinetics of RYPLAZIM were assessed ~~via measurements of~~ by plasminogen activity (chromogenic assay) (b) (4) in plasma. ~~Plasminogen activity is a measurement of functional plasminogen and plasminogen antigen is a measurement of total plasminogen, which includes plasminogen, plasmin, and plasmin-anti-plasmin complexes.~~

First-dose pharmacokinetic profiles for 6 subjects were based on the data from 6 mg/kg dose group in RYPLAZIM Trial 1. In RYPLAZIM Trial 2, pharmacokinetic analyses were conducted on the first 10 subjects (6 adults and 4 pediatrics) 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~~ Plasminogen concentrations 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. ~~First-dose pharmacokinetic profiles for 6 subjects were based on data from the 6 mg/kg dose group in RYPLAZIM Trial 1.~~ ~~Plasminogen was measured as both absolute and baseline-adjusted levels.~~

All 10 subjects achieved the ~~protocol-specified~~ target plasminogen activity trough levels (≥ ~~absolute~~ 10% above baseline) for at least 3 measurements in 12 weeks (primary endpoint; Table 4). Such activity was sustained for at least 5 time points (describe the duration rather than time points) during the 12-week treatment period.

Table 4: Pharmacokinetic Parameters of Mean (± Standard Deviation) Baseline-Adjusted Plasminogen Activity Levels in Adult and Pediatric Subjects After the First Dose and 12 Weeks RYPLAZIM (Assay method?)

PK Parameter	Adult (N = 6)		Pediatric (N = 4)		Combined (N = 10)	
	First Dose	Week 12	First Dose	Week 12	First Dose	Week 12
AUC_{Last} (hr*%)	2973 (775)	4556 (806)	3573 (1016)	5055 (1440)	3213 (880)	4756 (1057)
AUC_{INF} (hr*%)	3377 (945)	5543 (1400)	4373 (1256)	6270 (1948)	3776 (1134)	5834 (1580)
CL (µg/[hr*%]/kg)	1.94 (0.578)	1.24 (0.314)	1.61 (0.625)	1.14 (0.472)	1.81 (0.587)	1.20 (0.363)
C_{max} (%)	91.8 (20.9)	132 (15.5)	107 (38.9)	133 (26.8)	97.9 (28.4)	132 (19.3)
Half-life (hr)	29.3 (6.56)	38.1 (8.37)	38.5 (12.1)	39.7 (4.29)	33.0 (9.77)	38.7 (6.77)
MRT_{INF} (hr)	42.2 (8.85)	52.6 (10.4)	54.1 (14.9)	56.1 (6.39)	46.9 (12.5)	54.0 (8.79)
V_{ss} (µg/%/kg)	78.1 (13.7)	62.8 (5.40)	82.9 (21.5)	62.1 (18.3)	80.1 (16.3)	62.5 (11.3)

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.

~~Pharmacokinetic parameters for plasminogen antigen levels were confounded by large inter-subject variability.~~

Please provide actual trough concentrations data in adults and pediatrics as a function of weeks in a tabulated form.

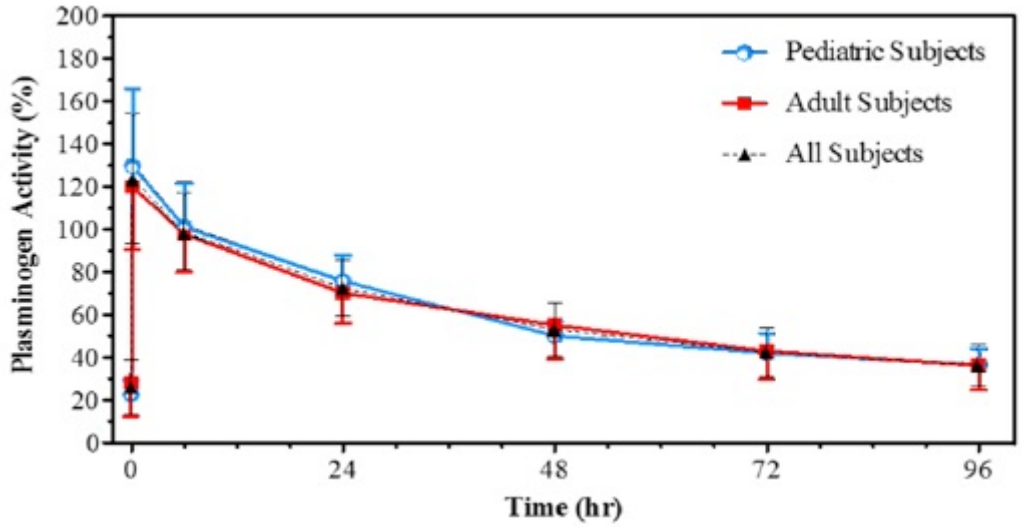
~~The pharmacokinetics of RYPLAZIM were similar between adult and pediatric subjects after the first and Week 12 infusions (Table 5). An accumulation ratio of 1.5 was seen between the first and Week 12 infusions. Similar results were seen for absolute plasminogen antigen levels in both adult and pediatric subjects but with more inter subject variability than for plasminogen activity levels.~~

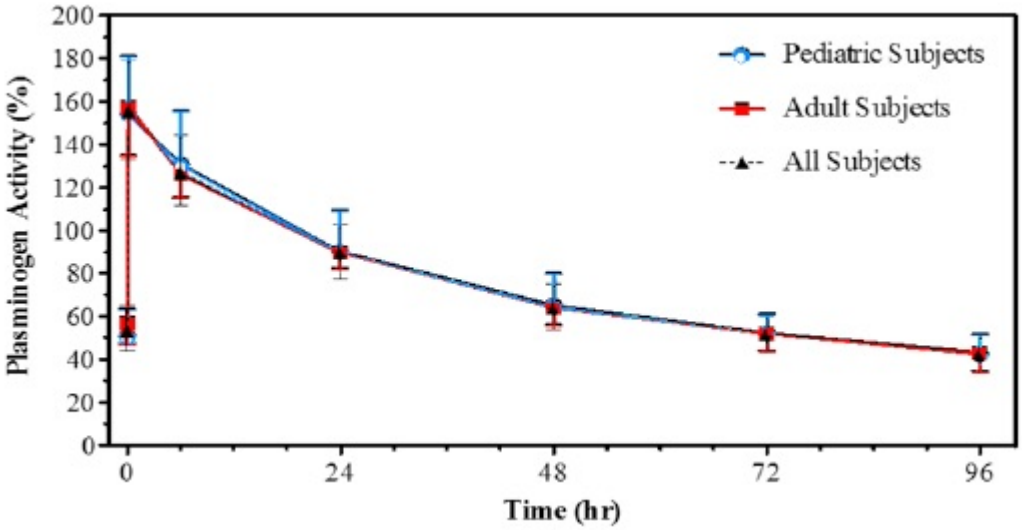
~~Table 5:~~ ~~Achievement of Protocol-Specified Target Plasminogen Activity Trough Levels Through Week 12~~

~~Parameter~~	**Time Points of Plasminogen Activity Trough Levels**					
	Week 2	**Week 4**	**~~Week 6~~**	**~~Week 8~~**	**~~Week 10~~**	**~~Week 12~~**
~~Total number of subjects who achieved protocol-specified target plasminogen activity trough levels (N = 10)~~	~~10/10~~	~~10/10~~	~~10/10~~	~~10/10~~	~~9/10~~	~~10/10~~
~~Adult subjects (N = 6)~~ Trough concentrations	~~6/6~~	~~6/6~~	~~6/6~~	~~6/6~~	~~5/6~~	~~6/6~~
~~Pediatric subjects (N = 4)~~ Trough concentrations	~~4/4~~	~~4/4~~	~~4/4~~	~~4/4~~	~~4/4~~	~~4/4~~

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 96 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 that were sustained for approximately 48 hours and continued to maintain ~~an absolute~~ 10% above baseline 96 hours after dosing (Figure 1 [bottom panel]).

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





Study Title: A Phase 1, Dose Escalation, and Pharmacokinetic Study of ProMetic Plasminogen Administered as Intravenous Infusion in Adults and Children with Hypoplasminogenemia.

This was an open-label, single-arm, dose-escalating phase I study to evaluate the pharmacokinetics, safety and tolerability of lyophilized gluplasminogen. A total of 11 patients with hypoplasminogenemia received a single intravenous (IV) infusion of gluplasminogen. There were 3 males and 8 females, age ranging from 13 to 38 years in the study. Two doses of gluplasminogen were studied; five subjects in Cohort 1 (2 mg/kg) and seven subjects in Cohort 2 (6 mg/kg); five subjects participated in both cohorts.

Gluplasminogen was administered IV at a rate dependent on the volume in order to complete the total dose (regardless of cohort) in less than 10 minutes (optimally) or a maximum of 15 minutes. The infusion rate was 1 mL/min for the first minute, 3 mL/min for the second minute, and remained at 3 mL/min for the next 8 minutes.

Blood samples were obtained from each patient at baseline immediately prior to dosing (pre-dose) and at 5-15 minutes, 1, 6, 24, 48, 72, 96, 120, 168, and 216 hours post dose. Plasminogen activity and antigen plasma levels were determined using validated chromogenic assay (b) (4) and (b) (4) respectively. The normal reference range of plasminogen activity was determined to be 70-130% and the reportable range was 5-160%. The normal reference range of plasminogen antigen was determined to be 6-20 mg/dL and the reportable range was 0.5-500 mg/dL. Pharmacokinetic parameters were estimated by noncompartmental analysis using baseline-adjusted plasminogen activity and antigen levels.

At baseline, plasminogen activity levels ranged from 31% to 38% in Cohort 1 and from 4% to 52% in Cohort 2. Baseline-adjusted plasminogen activity levels for C_{max} rose proportionally as gluplasminogen dose increased from 2 mg/kg to 6 mg/kg. From Cohort 1 to Cohort 2, mean (±sd) C_{max} increased from 36 ± 7% to 95 ± 23%. However, AUC_{last} and AUC_{inf} did not increase proportionally. AUC_{last} rose from 1370 ± 726 to 3530 ± 1060 hr*%, and AUC_{inf} rose from 1685 ± 823 to 3744 ± 1184 hr*%. Mean terminal half-life was 36 ± 18 hours in Cohort 1 and 36 ±12 hours in Cohort 2. However, the individual half-lives widely varied and ranged from 14.5 hours to 53.3 hours in Cohort 1 and from 17.2 hours to 50.0 hours in Cohort 2.

Baseline antigen levels ranged from 3 to 15 mg/dL and <0.5 to 24 mg/dL in Cohort 1 and 2, respectively. A total of 4 subjects in Cohort 1 and 6 subjects in Cohort 2 were included in the pharmacokinetic analysis.

Following a single and multiple (week 12) dosing of RYPLAZIM, there is accumulation of RYPLAZIM in plasma. In adults and adolescents, the accumulation ratio was 1.5 and 1.4, respectively.

Pharmacokinetic parameters based on plasminogen activity levels and plasminogen antigen levels are shown in Tables 1-2. In Figures 1-4, concentration or activity-time profiles (absolute and baseline corrected) are shown.

Table 1: Pharmacokinetic parameters based on plasminogen activity levels

Parameters	Cohort 1 (n = 5)	Cohort 2 (n =7)
C_{max} (%)	36 ± 7	95 ± 23
AUC_{last} (hr*%)	1370 ± 726	3530 ± 1060
$AUC_{infinity}$ (hr*%)	1685 ± 823	3744 ± 1184
Clearance (mL/h per kg)*	1.1 ± 0.7	1.3 ± 0.5
Half-life (hours)	36 ± 18	36 ± 12
Vss (mL/kg)*	51 ± 17	64 ± 11

*In order to calculate clearance and volume of distribution at steady state (V_{ss}), plasminogen activity levels were converted to mg/mL. Conversion based on 1% plasminogen activity equal to 0.00132 mg/mL (100% activity = 13.2 mg/mL) plasminogen concentration in normal human plasma.

Table 2: Pharmacokinetic parameters based on antigen levels

Parameters	Cohort 1 (n = 4)	Cohort 2 (n = 6)
C_{max} (mg/dL)	6 ± 1	31 ± 22
AUC_{last} (mg*hr/dL)	109 ± 91	1220 ± 755
$AUC_{infinity}$ (mg*hr/dL)	183 ± 95	1436 ± 969
Clearance (mL/h per kg)	1.3 ± 0.4	0.6 ± 0.4
Half-life (hours)	36 ± 10	42 ± 20
Vss (mL/kg)	62 ± 22	30 ± 12

There were 4 adolescents (13-15 years of age) in the study. The pharmacokinetic parameters in adolescents was slightly different than the adults. Compared with adults, the $AUC_{(0\text{-}last)}$ was 20% and 11% higher in adolescents after the first dose and after 12 weeks of dosing, respectively. Half-life was longer in adolescents by 8 hours than adults. These differences are not substantial and may not be of any clinical value. Furthermore, due to small sample size, a definite conclusion regarding the PK difference between adults and adolescents cannot be drawn.

Conclusions: The PK study of RYPLAZIM indicates that RYPLAZIM has a long half-life (>30 hours) and slow clearance (<100 mL/hour). Following multiple dosing, RYPLAZIM accumulates in plasma. There is a slight difference in the PK between adults and adolescents.

Figure 1: Cohort 1 – Mean ± SD Absolute Plasminogen Activity %

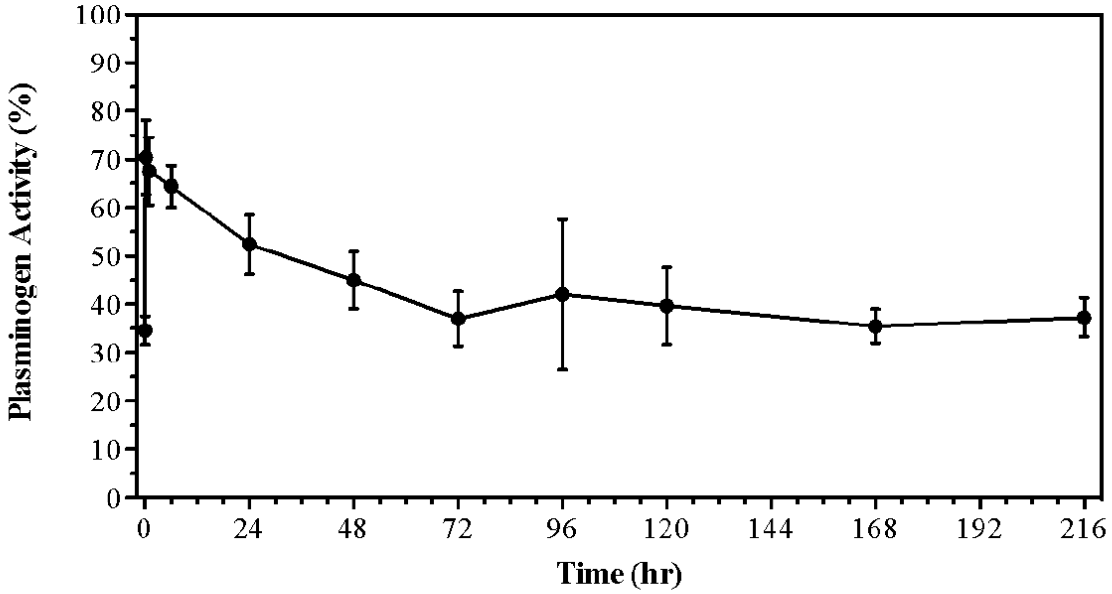


Figure 2: Cohort 1 – Mean ± SD Baseline Corrected Plasminogen Activity %

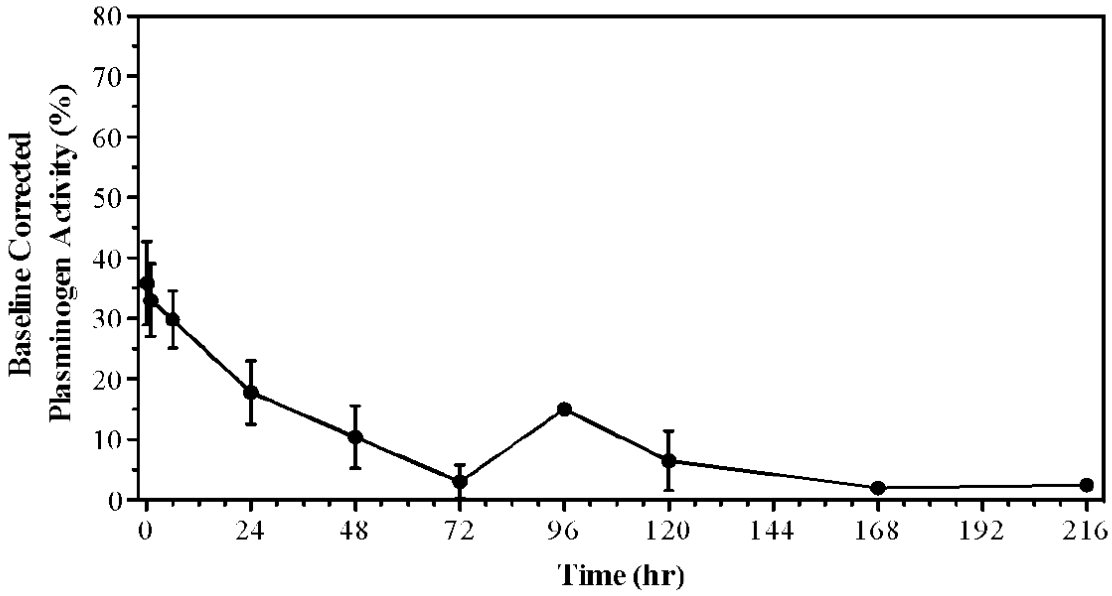


Figure 3: Cohort 1 – Mean ± SD Absolute Plasminogen Antigen mg/dL

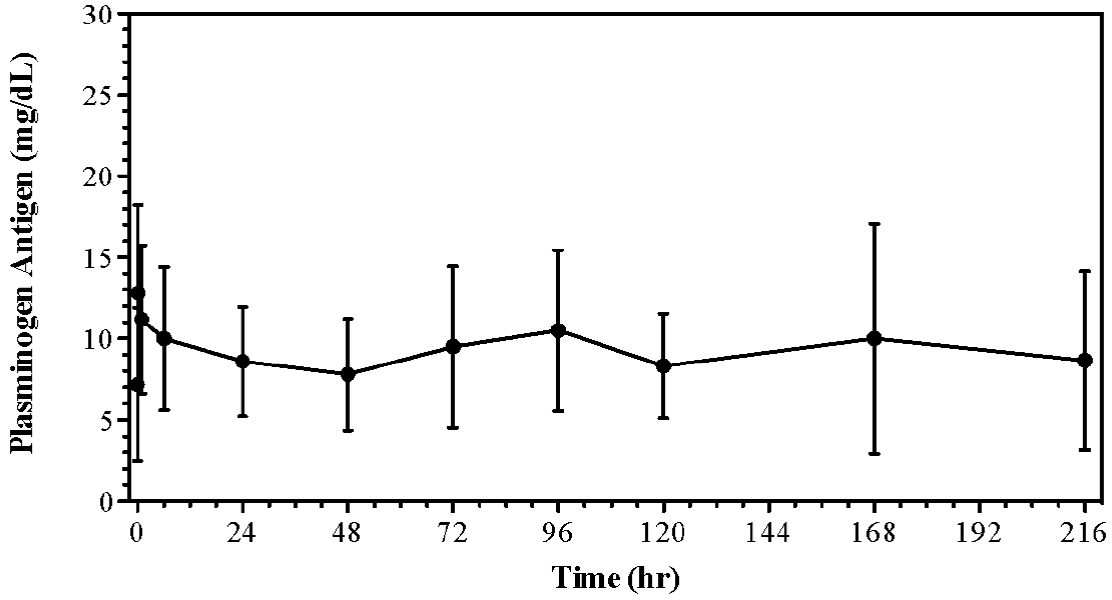


Figure 4: Cohort 1 – Mean ± SD Baseline Corrected Plasminogen Antigen mg/dL