CLINICAL PROTOCOL

2002C011G

A Phase 2/3, Open-Label, Repeat-Dose Study of the Pharmacokinetics, Efficacy, and Safety of Prometic Plasminogen Intravenous Infusion in Subjects with Hypoplasminogenemia

Clinical Development Phase:	2/3
Sponsor:	Prometic Biotherapeutics Inc. 1330 Piccard Drive, Suite 201 Rockville, MD 20850
Medical Monitor:	Joseph Parker, MD
Issue Date:	08August2018
Version:	Amendment 5

CONFIDENTIAL – PROPRIETARY INFORMATION

SIGNATURES

Sponsor Signature

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 Number: 2002C011G

Version/Date: Amendment 5 / 08August2018

Joseph M. Parker,

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Joseph Parker, M.D.

Senior Director, Clinical Development

Prometic Biotherapeutics Inc.

Signature of Principal Investigator

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
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I, the undersigned, have read the protocol and agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), and all applicable regulatory requirements

I will provide copies of the protocol and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the investigational product and the study. I understand that the study may be terminated or enrollment suspended at any time by sponsor with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

Signed: _____ Date: _____

Name:

Title:

Affiliation:

Address:

Tel:

E-mail:

Protocol Synopsis

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 Design	Multicenter, open-label, uncontrolled, repeat-dose
Indication	Systemic treatment of Type I plasminogen deficiency (hypoplasminogenemia)
Phase	2/3 (pivotal)
Investigational Medicinal Product	Plasminogen (Human) Intravenous (IV), lyophilized material reconstituted with Water for Injection to produce a sterile suspension with a concentration of 5.5 mg/mL
Objectives	**Primary objectives:** • To achieve an increase of individual trough plasminogen activity by at least an absolute 10% (i.e., 10 U/dL) from baseline in adult and pediatric subjects with hypoplasminogenemia during the 12 weeks of plasminogen replacement therapy in Segment 2; • To evaluate the efficacy of plasminogen replacement therapy on clinically evident or visible lesions of hypoplasminogenemia during 48 weeks of dosing in Segments 2 and 3. **Secondary objectives:** • To evaluate the safety and tolerability of plasminogen replacement therapy during the 48 weeks of dosing; • To evaluate the efficacy of plasminogen replacement therapy on clinically evident or visible symptoms of hypoplasminogenemia during the 12 weeks of dosing in Segment 2. • To evaluate the effect of plasminogen replacement therapy on pharmacokinetics and immunogenicity during the 48 weeks of dosing.
Study Sites	This study will be conducted in at least 2 sites, including at least 1 site in the US and 1 in Norway.
Study Design	Approximately 15 subjects aged 2 to 80 years with hypoplasminogenemia will be enrolled to ensure a sample size of at least 10 PK-evaluable subjects. At least 2 pediatric subjects, aged 2 to 18 years, will be enrolled. An evaluable subject for PK is defined as a subject who completes Segment 2

	of plasminogen replacement therapy (see below) of the study and provides at least 3 blood samples to measure trough plasminogen activity levels. The study consists of a screening period and 3 segments as illustrated in Figure 1. Subjects who have documented individual PK profiles with the sponsor (e.g., due to participation in the previous Phase 1 study and received 6 mg/kg Plasminogen) do not need to undergo Segment 1 and can proceed directly to Segment 2. **Screening** Subjects will be screened for study eligibility within a period of no more than 21 days before the start of dosing. Subjects will enter either Segment 1 or 2, depending on the availability of their prior individual PK profile. **Segment 1** For subjects undergoing Segment 1, each will receive a single dose of 6.6mg/kg Plasminogen IV infusion on Day -4. Blood samples for PK analysis will be drawn prior to infusion and subsequently through 96 hours after the infusion to establish individual PK profiles. The sample drawn prior to infusion will be used to measure the subject's baseline plasminogen activity and antigen as well as D-dimer levels. The last PK sample (96 hours post infusion) will be withdrawn on Week 1, Day 0, before the administration of the first dose in Segment 2. The resulting PK profile will be used to determine each subject's dosing interval in Segment 2. **Segment 2** Based on individual PK profiles, subjects will receive 6.6 mg/kg Plasminogen IV infusion every second, third, or fourth day for 12 weeks during Segment 2. Subjects will receive approximately 21 to 42 doses in Segment 2. For subjects who do not participate in Segment 1 and directly enter Segment 2, baseline assessments will be conducted before the first dose of Plasminogen IV infusion, including a blood sample to measure the baseline plasminogen activity and antigen as well as D-dimer levels. Their dosing interval will be every second, third, or fourth day, depending on each subject's PK profile on file. Subjects who have gone through Segment 1 will start with the every-third-day dosing interval until their individual PK results become available. This initial dosing regimen is based upon the aggregate PK obtained from the Phase 1 study. Once each subject's individual PK profile becomes available, his or her dosing interval will be adjusted to every second, third, or fourth day accordingly. The first dose of Plasminogen IV infusion in this segment will beadministered at the study site on Week 1, Day 0. Subjects will visit the study sites every 4 weeks and receive the investigational medicinal product (IMP) infusion at the study site. The infusions between study visits can be administered at the study site or an ancillary site by study personnel or at the

	subject's home by a home health nurse, by the subject (i.e., self-administration), or by a caregiver/family member (US subjects only). Subjects or caregivers may be trained for IMP administration as deemed appropriate by the Investigator (US subjects only). The final dose at the Week 12 visit (or at study discontinuation) in Segment 2 must be administered at the study site to allow for a repeat PK profile. Plasma samples will be drawn before IMP administration every 2 weeks to measure the trough levels of plasminogen activity and antigen and D-dimer. The samples will be obtained at each study visit at Weeks 4, 8 and 12 and by a home health nurse at Weeks 2, 6, and 10. Additional samples may be taken in addition if needed. Subjects will undergo clinical assessments of the disease at each study visit depending on the system and organ involvement of hypoplasminogenemia and the characteristics of lesions, including but not limited to: photographic measurements of visible lesions (e.g., ocular, gingival), spirometry for subjects with pulmonary involvement, and imaging study of nonvisible lesions (e.g., oropharyngeal, ureteral, bronchial), as deemed appropriate by the investigator. Safety assessments will include vital signs, physical examination, clinical laboratory tests (hematology, chemistry, urinalysis, fibrinogen and coagulation panels, and urine pregnancy test for women of childbearing potential), AE assessments, virology, and immunogenicity. In addition, subjects will be given a diary to record infusions, symptoms, concomitant medications and AEs at home between visits. At the end of Segment 2, subjects will have the option to participate in Segment 3. Subjects for whom there is no perceived or anticipated benefit from further dosing would not be enrolled in Segment 3 at the investigator's discretion and based on discussion with the Safety Monitoring Committee (SMC, see Section 3.7) and the sponsor. Any subject who discontinues the study during or at the end of Segment 2 should return to the study site for a Safety Follow-up visit 30 days after the final IMP dose. **Segment 3** Subjects who participate in Segment 3 will continue to receive Plasminogen IV for 36 additional weeks in Norway and until product licensing or study termination by the sponsor for subjects in the United States. The dose will be 6.6 mg/kg with the frequency determined during Segment 2, with the option of modification based on clinical response and plasminogen trough levels. Subjects (or their caregivers) may be trained to self-administer the IMP at home if deemed appropriate by the Investigator. Subjects will return to the study sites for assessments every 3 months to monitor subjects' clinical status and plasminogen trough levels. Subjects will be given a diary to record the dates of IMP administration, any AEs, concomitant medication and other relevant information. Subjects will be

	given instructions for how to document receipt of IMP and how to return all used IMP vials. Subjects at the Norway site in Segment 3 should return to the study site for a Safety Follow-up visit 30 days after the final IMP dose. Due to the delay in product approval, subjects at the United States (US) site in Segment 3 will be allowed to enroll in Treatment Protocol 2002C018G and continue ongoing IMP treatment without any break in treatment. If subjects decide to enter Treatment Protocol 2002C018G, then they will return to the study site and complete the End of Study visit and sign an informed consent/assent for that study and stop participation in the current study. If subjects decide to not enter Treatment Protocol 2002C018G, then they will stop IMP and return to the study site for a Safety Follow-up visit 30 days after the final IMP dose. **Stopping rules** Any subject who experiences any of the following occurrences will suspend the IMP treatment until further assessments: • Anaphylactic response to study drug administration • A significant AE that, in the investigator's opinion, necessitates suspension of treatment • Confirmed presence of neutralizing antibodies (in at least 2 measurements) in association with diminished plasminogen activity that obviates the potential benefit of plasminogen replacement therapy • Thrombotic or uncontrolled bleeding event requiring hospitalization The SMC will review safety data on an ongoing basis and will determine if a subject should stop treatment, or if there are unforeseen events (e.g., thromboembolic event) that would warrant halting or stopping the study. Such an event will be discussed with FDA before enrolling further subjects.
Duration	For each subject, the estimated duration of study participation is no more than 21 days for screening, 4 days for Segment 1, 12 weeks for Segment 2, and 40 weeks (36 weeks Treatment and 4 weeks Safety Follow-up) for subjects who participate in Segment 3 in Norway. For those subjects who participate in Segment 3 in the United States, it will be dependent on product approval and sponsor decision. A Safety Follow-up visit is required 30 days after the final IMP dose. However, due to the delay in product approval, subjects at the US site will be allowed to enroll in Treatment Protocol 2002C018G and continue ongoing IMP treatment without any break in treatment. If subjects decide to enter Treatment Protocol 2002C018G, then they will return to the study site and complete the End of Study visit and sign an informed consent/assent for that study and stop participation in the current study. If subjects decide to not enter Treatment Protocol 2002C018G, then they will stop IMP and return to the study site for a Safety Follow-up visit 30 days after the final IMP dose.

Administration & Dosage	**IMP Preparation** Plasminogen (Human) Intravenous lyophilized material will be reconstituted with sterile Water for Injection to yield a solution of 5.5 mg/mL for IV infusion. **Infusion** Only eligible and enrolled subjects will receive IMP. The entire dose of the Plasminogen IV solution should be calculated on the basis of each subject's body weight and infused over 10 to 30 minutes. **Dose and Dosing Interval** In Segment 1, a single dose of 6.6 mg/kg Plasminogen will be administered to each subject. However, subjects who have documented individual PK profiles with the sponsor (e.g., due to participation in the previous Phase 1 study and received 6.6 mg/kg Plasminogen) do not need to undergo Segment 1 and can proceed directly to Segment 2. In Segment 2, repeated doses of 6.6 mg/kg Plasminogen will be administered every second, third, or fourth day, depending on individual PK profile. Subjects will receive a range of 21 to 42 doses in Segment 2. The dosage and dosing interval in Segment 3 will be the same as Segment 2, with the possibility of modification based on discussion between the Investigator and the sponsor.
Inclusion criteria	1. Subject or legal guardian has provided informed consent (as well as assent by subjects with ages dictated by local Investigational Review Board [IRB] guidelines). 2. Subject is male or female between the ages of 2 and 80 years (inclusive). 3. Subject has a documented history of lesions and symptoms consistent with a diagnosis of hypoplasminogenemia. 4. Subject has plasminogen activity level $\leq$ 45%. 5. Subject has documented vaccination to hepatitis A virus (HAV) and hepatitis B virus (HBV), or has received the first dose of HAV and HBV vaccine prior to the first dose of IMP and is scheduled to receive the second vaccine dose. If subject has documented vaccination more than 1 year before screening but has a negative antibody titer to HAV and/or HBV at screening, subject is required to begin a re-vaccination series with the first dose of HAV and/or HBV vaccine prior to the first dose of IMP and is scheduled to receive the second vaccine dose. No revaccination is required if the documented vaccination took place within 1 year of screening. 6. Subject agrees to use contraceptive methods from screening through 14 days after last dose of study treatment (unless documented as biologically or surgically sterile (e.g., postmenopausal, vasectomized), or has not reached reproductive age.

Exclusion Criteria	1. Subject has a history of anaphylactic reactions to blood or blood products that may interfere with participation in the study in the opinion of the investigator. 2. Subject has uncontrolled hypertension. 3. Subject has clinical or laboratory evidence of an intercurrent infection as evidenced by symptoms including fever, tachycardia, or other systemic signs and symptoms. (Note: Subjects with an intercurrent clinically significant infection cannot participate; however, once the infection has resolved according to the investigator, they can be re-screened if enrollment is still open.) 4. Subject is pregnant and/or lactating. 5. Subject has a malignancy, except for basal or squamous cell skin cancer, within 3 years before screening. 6. Subject is a previous organ transplant recipient. 7. Subject is in receipt of exogenous plasminogen (ocular or IV), such as laboratory grade plasminogen, fresh frozen plasma, or Prometic Plasminogen (Human) within 2 weeks of the screening visit. 8. Subject has a psychiatric disorder, other mental disorder, or any other medical disorder that impairs the subject's ability to provide informed consent or to comply with the requirements of the study protocol. 9. Subject has evidence of renal dysfunction defined as of > 2 X the upper limit of normal (ULN) in serum creatinine. 10. Subject has evidence of hepatic dysfunction defined as > 3 x ULN in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP). 11. Subject has participated in another IRB-approved interventional clinical trial of a drug, biologic, or device within 30 days before the first dose of the IMP. 12. Subject has a chronic or acute clinically significant intercurrent illness (e.g., cardiac, hepatic, renal, endocrine, neurologic, hematologic, neoplastic, immunological, and skeletal) that the investigator determines could interfere with the assessments in this study.
Criteria of Evaluation	**Pharmacokinetics:** Blood samples will be drawn and analyzed for plasminogen activity and plasminogen antigen levels using validated assays at a central laboratory. **Segment 1** Blood samples are drawn on Day -4 before the IMP infusion to establish baseline levels for plasminogen activity, antigen, and D-dimer and at the following time points after the end of the infusion: between 5 and 15 minutes, 6 hours (± 30 minutes), 24 hours (± 2 hours, Day -3), 48 hours (± 2 hours, Day -2), 72 hours (± 2 hours, Day -1), and 96 hours (± 2 hours,

	Day 0). An individual PK profile will be developed based on these time points. Subjects who have had individual PK profile for 6.6 mg/kg Plasminogen with the sponsor, due to participation in the prior Phase 1 study, do not participate in Segment 1. **Segment 2** For subjects who do not undergo Segment 1, blood samples are drawn to measure plasminogen activity and antigen levels on Week 1, Day 0, before the first dose of the IMP is given, to establish the baseline levels. For all subjects, blood samples will be drawn every 2 weeks before IMP infusion to measure trough levels through the final dose. A full PK profile will also be done for all subjects at the end of Segment 2 (Week 12 visit) to evaluate the stability of individual PK profile after 12 weeks of IMP administration. As plasminogen is a consumable clotting factor, if significant lesion burden is present at the start of the study or if neutralizing antibody develops, a subject's PK profile may be altered by the end of the 12-week treatment period. At the Week 12 visit, blood samples are drawn before the IMP infusion and at the following time points after the end of the infusion: between 5 and 15 minutes, 6 hours (± 30 minutes), 24 hours (± 2 hours), 48 hours (± 2 hours), 72 hours (± 2 hours), and 96 hours (± 2 hours, Day 0). The PK profile will be developed for each subject and compared with his or her prior PK profile(s). Furthermore, additional PK analyses may be performed at other time points during Segment 2 as needed, such as when a subject's trough level or antibody test suggests the appearance of neutralizing antibody against the IMP. **Segment 3** Blood samples will be drawn at each study visit every 3 months before IMP infusion to measure trough levels. **Efficacy:** All subjects will be clinically evaluated by the investigator for the clinical manifestation and severity of hypoplasminogenemia. • Visible lesions (ocular, gingival) will be evaluated using photographs. • Nonvisible lesions (e.g., ureteral, oropharyngeal, andbronchial) may be evaluated via imaging studies, such as computed tomography [CT] scans, X-ray, or other imaging techniques, as deemed appropriate by the Investigator. • Functionality of affected organs may be assessed as deemed appropriate by the Investigator. Respiratory tract involvement may be assessed by spirometry to measure forced vital capacity

	(FVC), forced expiratory volume in 1 second (FEV1), peak expiratory flow (PEF), and FEV1/FVC ratio. • Clinical Global Impression scales • Quality of life assessment
Safety Assessments	Physical examinations, vital signs, and clinical laboratory tests will be assessed at each study visit. Virology will be assessed at Screening, Baseline, and every 12 weeks during dosing and at Study Discontinuation which is 30 days after the final dose of the IMP. An archive sample for virology will be taken at Baseline. Immunogenicity testing will be assessed at Screening and every 4 weeks during Segment 2, every 12 weeks during Segment 3 and at Study Discontinuation which is 30 days after the final dose of the IMP. At each IMP infusion during Segments 1 and 2 Study Visits, the study personnel will assess AEs and vital signs. Subjects will be provided a diary to record AEs and infusions between visits. All treatment-emergent AEs and SAEs will be documented, including assessments of their severity and relatedness to the IMP. Laboratory abnormalities, physical examination findings, and vital sign abnormalities that are clinically significant, as judged by the investigator, will be reported as AEs.
Statistical Methods	**Analysis datasets** Safety population: Includes any subject who receives at least one dose of the IMP and provides safety data for at least one non-screening visit. PK population: Includes any subject who has completed Segment 2 dosing and have provided sufficient samples for PK assessments. Full Analysis Set (FAS): Includes any subject who receives at least 1 dose of the IMP and provided data for at least one post-baseline efficacy assessments. **Pharmacokinetic Analysis** The primary PK endpoint is the number and percentage of subjects who achieve the target plasminogen activity trough levels for at least 3 measurements in 12 weeks during Segment 2. The target trough level is defined as an increase in plasminogen activity level of at least an absolute 10% (10 U/dL) from the subject's individual baseline level. Baseline is defined as the plasminogen activity level measured before the first dose of IMP at Segment 1, Day -4 for subjects who undergo Segment 1 or at Segment 2, Day 0 for those who do directly enter Segment 2. Primary endpoint success is defined as at least 80% of evaluable subjects (i.e., 8 or more) achieving the target trough levels for at least 3 measurements in 12 weeks.

	The secondary PK endpoints include individual PK profiles at the end of Segment 2, compared with their PK profiles at baseline, and trough plasminogen activity and antigen levels during Segment 2 and Segment 3. Plasminogen activity and antigen levels will be presented by individual subjects and summarized descriptively (number of subjects, mean, standard deviation [SD], coefficient of variation [CV], medium, minimum, maximum, geometric mean and associated CV). Individual and median profiles of the concentration-time data will be plotted using nominal times. Median profiles may be presented on both linear-linear and linear-log scales. Standard PK parameters, including area under the curve (AUC), clearance (CL), mean residence time (MRT), volume of distribution (V_d) and terminal half-life ($t_{1/2}$) will be calculated using non-compartmental analysis and baseline-adjusted plasminogen activity levels derived from Segment 1 data and, if a subject is suspected to develop neutralizing antibody to the IMP, plasminogen activity levels at the end of Segment 2. Additional PK compartmental analysis may be performed and best-fit model will be used for further individual PK prediction. D-dimer is monitored as a potential pharmacodynamic marker to better understand if there is a relationship between the levels of D-dimer in subjects over time and the subject's potential response to therapy. **Safety Analysis** For analysis of safety and tolerability, TEAEs and SAEs will be summarized descriptively. Clinical laboratory tests (hematology, biochemistry, urinalysis, fibrinolysis/coagulation) will be presented in summary and shift tables. The numbers of subjects who had changes from baseline in viral tests and immunogenicity tests will be presented in individual subject listings and summary tables. **Efficacy Analysis** The primary efficacy endpoint is: Overall 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 The secondary efficacy endpoints are • Overall 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 12 weeks • CGI scores at 12 and 48 weeks • Quality of life scores at 12 and 48 weeks

	Clinical success is considered achieved if 50% of subjects with visible or other measureable lesions demonstrate at least a 50% improvement in lesion number/size or functionality impact from baseline at 12 and/or 48 weeks. Visible lesions are defined as lesions which can imaged and analyzed with digital photography. Other measureable lesions are defined as lesions whose dimensions can be assessed by medical imaging studies (e.g., computed tomography, magnetic resonance imaging, ultrasound, etc.) or organ specific functional assessments (e.g., spirometry, audiogram, oximetry, etc.). All efficacy results will be presented descriptively by individual subjects, including summarized hypoplasminogenemia symptoms over time recorded in subject diaries. The small sample size and high variability of disease presentation do not allow formal statistical analyses.

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulation
CL	Clearance
C_{max}	Maximum concentration
CRA	Clinical research associate
CRO	Contract research organization
CT	Computed tomography
CV	Coefficient of variation
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EIA	Enzyme immunoassay
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FVC	Force vital capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GGT	Gamma glutamyltransferase
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV-1	Human immunodeficiency virus Type 1
HIV-2	Human immunodeficiency virus Type 2
ICF	Informed consent form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IND	Investigational New Drug Application

INR	International normalization ratio
IRB	Institutional Review Board
ITT	Intent to treat
IV	Intravenous
LDH	Lactic dehydrogenase
MRT	Mean residence time
NAT	Nucleic acid test
PAI-1	Plasminogen activator inhibitor-1
PEF	Peak expiratory flow
PI	Principal Investigator
PK	Pharmacokinetic
PT	Prothrombin time
PTT	Partial thromboplastin time
QA	Quality assurance
QC	Quality control
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SMC	Safety Monitoring Committee
$t_{1/2}$	Half-life
t_{max}	Time to maximum concentration
ULN	Upper limit of normal
US	United States
V_d	Volume of distribution
WFI	Water for Injection
WBC	White blood cell

1 Introduction

1.1 Background

1.1.1 Overview of Hypoplasminogenemia

Hypoplasminogenemia is a rare autosomal recessive genetic disorder that leads to a variety of significant clinical manifestations primarily associated with fibrous depositions on mucous membranes throughout the body (Schott *et al*., 1998). Plasminogen is a naturally occurring protein that is synthesized by the liver and circulates in the blood. Plasminogen is activated to form plasmin, an enzymatic component of the fibrinolytic system and is the main enzyme involved in the lysis of clots and clearance of extravasated fibrin (Collen *et al*., 1991). Plasmin is also involved in wound healing, cell migration, tissue remodeling, angiogenesis and embryogenesis (Castellino *et al*., 2005).

Hypoplasminogenemia is a multisystem disease that can affect the eyes, ears, nasal and oral cavities, sinuses, tracheobronchial tree, genitourinary tract, gastrointestinal tract, and gingiva. The most common clinical manifestation of hypoplasminogenemia is ligneous conjunctivitis, which is characterized by thick, woody (ligneous) growths on the conjunctiva of the eye. If left untreated, ligneous conjunctivitis can lead to blindness. Most affected cases are infants and children showing their first clinical manifestation at a median age of approximately 10 months (Schuster *et al*., 2007; Bateman *et al*., 1986). Ligneous conjunctivitis is believed to be triggered by local infections, injury, irritation or inflammation, and various surgical interventions into the eye (Schuster *et al*., 2003).

In addition to ligneous conjunctivitis, hypoplasminogenemia can cause tracheobronchial lesions including abnormal membranes with poor pulmonary toilette that can result in chronic obstruction of the affected pulmonary segment or even respiratory failure. Hydrocephalus occurs in approximately 10% of children with severe hypoplasminogenemia, apparently related to the deposition of fibrin in the cerebral ventricular system; treatment may require implantation of a shunt which can be complicated by repeated occlusions and may lead to death. Severely impaired skin-wound healing has also been reported (Schott *et al*., 1998).

Hypoplasminogenemia is listed as a rare disease by the National Institutes of Health (NIH) Office of Rare Diseases Research. Prevalence for hypoplasminogenemia is estimated at approximately 1.6 per 1,000,000 (Tefs *et al*., 2006).

1.1.2 Current Treatment for Hypoplasminogenemia

There are 2 forms of plasminogen: Glu and Lys. Most literature references of plasminogen replacement therapy are based on the Lys form; it is important to note the Prometic plasminogen

is the Glu form, which has a longer half-life (approximately 2.5 days in healthy subjects) than Lys-plasminogen (0.8 days) (Collen *et al*., 1991; Claeys *et al*., 1973).

Attempted treatments for ligneous conjunctivitis lesions include: surgical removal; high dose intravenous corticosteroid treatment; topical treatment with heparin, corticosteroids and alpha-chymotrypsin, or cyclosporine; azathioprine; and hyaluronidase. These treatments are not consistently or completely successful in either the treatment or the prevention of lesion regrowth (Schuster *et al.,* 2007; DeCock *et al.,* 1995; Silva *et al.,* 2006; Rubin *et al.,* 1991). After treatment, including surgical removal, the lesions will usually recur. Local administration of fresh frozen plasma (which contains plasminogen) and other plasminogen-containing eye drops, however, has shown effectiveness in treating eye lesions of ligneous conjunctivitis (Heidemann *et al*., 2003). Furthermore, continued topical administration of plasminogen-containing eye drops can treat the lesion and prevent regrowth. Other research shows that systemic administration of plasminogen concentrates results in partial resolution of the lesions (Schott *et al.,* 1998; Kraft *et al.,* 2000). A 6-month-old child treated with Lys-plasminogen preparation as a continuous infusion and later as daily bolus injections led to complete regression of ligneous conjunctivitis within 4 weeks and normalized hyperviscous secretions in the respiratory tract as well as skin wound healing (Schott *et al.,* 1998). Currently, there is no plasminogen replacement product approved for the treatment of plasminogen deficiency in the US.

1.2 Pre-clinical Experience with Plasminogen

A literature review revealed the following information regarding work done in plasminogen deficient animal models. Bugge *et al.* (1995) generated the first plasminogen-deficient homozygous (*PLG* $^{-/-}$) knockout mouse model to study the physiological role of plasminogen in development, hemostasis, and reproduction. The *PLG* $^{-/-}$ mice completed embryonic development, survived to adulthood and were fertile. However, the *PLG* $^{-/-}$ mice were predisposed to severe thrombosis, and young animals exhibited thrombotic lesions in the liver, stomach, rectum, lungs, pancreas and other tissues. Further histological examination of the mice between 5 and 21 weeks old revealed formation of fibrin deposits in the liver and ulcerated lesions in the gastrointestinal tract compared to controls. The authors concluded that plasminogen plays a critical role in fibrinolysis and hemostasis.

Ploplis *et al.* (1995) also generated homozygous knockout mice to investigate the effects of plasminogen disruption on thrombosis, growth, viability, and fertility in mice. Plasminogen-deficient mice survived embryonic development but developed spontaneous fibrin deposition due to impaired thrombolysis, suffered retarded growth (weighing significantly less than control and heterozygous knockouts), and had reduced fertility and survival. Approximately 20% of the homozygous $Pg^{-/-}$ mice developed rectal prolapse. Histological examination revealed fibrin deposits in the liver, lungs, and stomach, associated with gastric ulcers in 6 to 12 weeks old $Pg^{-/-}$

mice, but not in the controls or heterozygous littermates. These *PLG* $^{-/-}$ mice displayed a reduced capacity to dissolve spontaneous pulmonary plasma clots within 24 hours. Thus, the most prominent phenotype of plasminogen-deficient mice appears to be related to fibrin homeostasis; some of the lesions, such as gastric ulcers, indicated that the plasminogen system may play a role in the prevention and/or healing of tissue damage.

Bugge *et al.* (1996) also investigated the effects of combined homozygous plasminogen and fibrinogen deficiencies in mice by interbreeding of lines carrying disrupted plasminogen and fibrinogen-binding protein (*FIB*) genes. The double-deficient mice (*PLG* $^{-/-}$ and *FIB*$^{-/-}$) exhibited similar phenotypic survival patterns to control animals. These results demonstrate that the lack of fibrinogen prevents animals from early morbidity and premature death associated with a *PLG* $^{-/-}$ deficiency. The authors concluded that the fundamental, and possibly only, essential physiological role of plasminogen is fibrinolysis.

Lijnen *et al.* (1996) administered bolus injections of purified mouse plasminogen to *PLG* $^{-/-}$ mice and showed that the levels of plasminogen antigen and activity were increased to normal levels. Moreover, plasminogen administration was associated with significant restoration of thrombolytic potential and markedly reduced fibrin deposition in the liver after 24 hours of treatment.

These studies in the plasminogen knockout mice (*PLG* $^{/-}$) confirm the fundamental role of plasminogen in fibrinolysis and help establish the scientific understanding of the symptoms/lesions associated with plasminogen deficiency in humans. However, systemic administration of human plasminogen to plasminogen knockout mice would result in the development of cross-species anti-human antibodies in mice, making the mouse model impractical for studying the pharmacology of human plasminogen. No other suitable animal models for studying systemic treatment of plasminogen deficiency have yet been identified.

1.3 Clinical Experience with Plasminogen

Prometic Biotherapeutics, Inc. (hereafter referred to as the sponsor), is developing Plasminogen (Human) Intravenous Lyophilized Solution (the investigational medicinal product [IMP]), for the treatment of hypoplasminogenemia. The IMP is derived from pooled plasma donated by US blood donors and has undergone multiple steps of viral testing and inactivation.

The clinical development program for Plasminogen (Human) in subjects with hypoplasminogenemia consists of a completed Phase 1, single-ascending-dose study in adolescent and adult subjects (2002C005G), an ongoing pivotal Phase 2/3 repeat dose study in pediatric and adult subjects (2002C011G), and supportive data from 3 ongoing single-subject, repeat-dose, Expanded Access studies (2002C013G, 2002C016G, and 2002C017G). In the Phase 1 study 2002C005G, 5 subjects received a single IV infusion of Plasminogen (2 mg/kg) and 7 subjects received a single IV infusion of Plasminogen (6.0 mg/kg). Both doses were well tolerated.

In addition to the Phase 1 study, Prometic provided Plasminogen to an infant with hypoplasminogenemia in Germany on the compassionate-use basis. Prometic was contacted by a German physician who made a request to obtain Plasminogen for a patient. The patient is a 22-month-old child with hypoplasminogenemia. Within 2 weeks after birth, he presented with problems with his eyes and respiratory tract and was diagnosed with hypoplasminogenemia. From then onward, he has been through various treatments, including surgery in combination with antibiotics, and other medications. He had also received fresh frozen plasma infusions as part of his treatment. When Prometic was contacted, the patient was in critical condition in a pediatric ICU receiving ventilatory and circulatory support. He had a collapsed left lung and right lower lobe related to viscous bronchial secretions and to obstructing ligneous lesions in the bronchial tree. On 15 September 2015, the physician gave an initial dose of 4 mg/kg the IMP, which was increased to 6 mg/kg and then 6.5 mg/kg every second day. The patient was extubated within a matter of days. To date, no adverse events (AEs) associated with administration of Plasminogen have been observed.

In the current study, an interim analysis was performed after the first 10 subjects completed 12 weeks of treatment with a data cutoff at 30 November 2016. All 10 of these subjects achieved target PK trough levels demonstrating the ability of Prometic's Plasminogen (Human) to serve as effective replacement therapy. Preliminary efficacy evaluation at 12 weeks revealed that 13 of 14 visible lesions had resolved, and the remaining lesion had improved from 15 × 5 mm at baseline to too small to be measured at 12 weeks. There were no recurrences and no new lesions during this period of observation. There were no deaths, serious adverse events (SAEs), or AEs resulting in discontinuation of study drug. The most frequent AEs were headache and nasopharyngitis. Nausea, diarrhea, rhinorrhea, sinusitis, epistaxis, back pain, pain in extremity, and hematuria were also frequent in adult subjects, and upper abdominal pain and cough were frequent AEs in pediatric subjects. A US Biologics Licensing Application was submitted based on these interim data; this application is under review. As of 14Dec2017 study enrollment is complete and all 15 enrolled subjects received at least 48 weeks of treatment. Three subjects in Norway completed the study as planned, with the remaining 12 subjects in the US continuing treatment until product licensing or study termination by the Sponsor. However, due to the delay in product approval, subjects at the US site will be allowed to enroll in Treatment Protocol 2002C018G and continue ongoing IMP treatment without any break in treatment. If subjects decide to enter Treatment Protocol 2002C018G, then they will return to the study site and complete the End of Study visit and sign an informed consent/assent for that study and stop participation in the current study. If subjects decide to not enter Treatment Protocol2002C018G,

then they will stop IMP and return to the study site for a Safety Follow-up visit 30 days after the final IMP dose.

Subject dosing has been revised throughout the protocol from 6.0 mg/kg to 6.6 mg/kg of plasminogen to reflect the true concentration and dosing as agreed with FDA during the 05Oct2016 Pre-BLA Meeting (CRMTS# 10393).

Details of these studies can be found in the Investigator's Brochure (IB).

1.4 Benefit Versus Risk and Study Rationale

The prognosis of hypoplasminogenemia is variable depending on the extent, location(s), length, and site of the lesions. A number of patients have died or have suffered loss of affected organ functions, such as sight and dentition, as a result of hypoplasminogenemia (Mehta and Shapiro, 2008). The one clearly documented effective therapy that leads to resolution and halts re-formation of ophthalmologic lesions is systemic or topical plasminogen concentrates (Heidemann *et al*., 2003; Watts *et al.,* 2002; Pergantou *et al*., 2011; Tabarra *et al.,* 2004). There is no effective licensed local or systemic plasminogen replacement therapy available for hypoplasminogenemia.

Prometic is developing purified human plasminogen as replacement therapy from its proprietary PPPS plasma fractionation process for the systemic treatment of hypoplasminogenemia. This rare disease represents an area of unmet medical need, where optimal treatment is likely to be systemic replacement of plasminogen to reduce or resolve the clinical manifestations in patients and to prevent or suppress lesion recurrence. Prior to generation of this material by Prometic, no purified Glu-plasminogen has been available for evaluation in plasminogen deficient subjects. We hypothesize based on pharmacokinetic data in the Phase 1 study using Glu-plasminogen that a trough level of >10% plasminogen activity above baseline is achievable with every other day or every third day dosing. Potential clinical benefit will be assessed during Segment 2 and Segment 3 to monitor and correlate plasminogen replacement therapy with clinical response in visibly evident lesions.

In support of this strategy, results from a case study indicate the benefit of repeat dosing as demonstrated in a named patient in Germany treated with Prometic's plasminogen. The plasminogen deficient subject had a collapsed left lung and right lower lobe related to viscous bronchial secretions and to obstructing ligneous lesions in the bronchial tree. Pharmacokinetic results for this subject showed that the trough values 10% above baseline were achieved with the current dosing regimen. The subject was extubated within a matter of days of administration of intravenous Plasminogen (Human). To date, no adverse events have been observed associated with administration of Plasminogen (Human) in this subject.

This is a Phase 2/3 pivotal study of Prometic Plasminogen (Human) Intravenous Lyophilized solution.

As the IMP is derived from pooled plasma, there are potential safety risks associated with the IMP, including a low inherent risk of transmission of blood-borne pathogens. These are unlikely, given current viral donor testing and robust virus elimination/inactivation processes performed during manufacturing. The IMP was well tolerated in the Phase 1 single-dose study at 2 mg/kg and 6 mg/kg.

Additionally, there is a risk that subjects will develop antibodies to exogenous plasminogen since plasminogen deficiency is a heterogeneous disease with a variety of genetic mutations resulting in altered plasminogen protein. It is unknown if such antibodies will be neutralizing and perhaps interfere with the efficacy of Plasminogen (Human). The effects of potential neutralizing antibodies will be assessed during the study.

Given the absence of effective licensed treatment for hypoplasminogenemia, the potential benefits of this study to the affected population and study participants outweigh the risk of their participation.

1.5 Dose Rationale

A successful outcome for this study is defined as achieving a trough level of plasminogen that is at least 10% above the subject's baseline level for at least 3 measurements during the 12 weeks of treatment in Segment 2. Table 1 shows the results of a single IV infusion of Plasminogen 6 mg/kg, in the 5 adult subjects in Cohort 2 of the Phase 1 study. Red highlighted cells indicate when a trough level less than 10% above the baseline level was obtained at 72 or 96 hours, while orange cells indicate a value exceeding but close to the desired >10% level. All subjects achieved a trough level at 48 hours above the 10% level over baseline. These data are used to establish the dosing regimens in this Phase 2/3 study. For example, if Subjects 2, 6 and 7 were to enter the Phase 2/3 study, they would require dosing every second day to routinely avoid a trough level <10% above baseline, while Subjects 1 and 8 would require dosing every 3 days. This data may be augmented by PK modeling of repeat dosing to aid the investigator with the selection of the appropriate dose for the subject.

Therefore, subjects who enter the Phase 2/3 study will be commenced on an initial regimen of 6.6 mg/kg every 2, 3, or 4 days, with the decision based on each subject's individual known PK profile if they have been dosed in Cohort 2 at 6 mg/kg in the Phase 1 study. New subjects will undergo a PK study (Segment 1) with blood samples taken up to 96 hours after injection and will be started on an every-third-day dosing regimen at 6.6 mg/kg until their individual PK results are available, at which time dosing will tailored accordingly (Section 3.2). A change in dosing interval to provide an increase or decrease in the trough levels may be required at the discretion of the principal investigator (PI) and the Sponsor, based on the actual results in each individual patient.

Table 1. Plasminogen Activity Levels from Cohort 2 (6 mg/kg) of the Phase 1 Study

Time	Subject # 1		Subject # 2		Subject # 6		Subject # 7		Subject # 8	
	Plg %	**Increase from Baseline**	**Plg %**	**Increase from Baseline**	**Plg %**	**Increase from Baseline**	**Plg %**	**Increase from Baseline**	**Plg %**	**Increase from Baseline**
Baseline	**30**	**-**	**52**	**-**	**33**	**-**	**19**	**-**	**4**	**-**
5-15 min	162	132	146	94	110	77	95	76	86	82
1 h	160	130	126	74	105	72	98	79	84	80
6 h	126	96	109	57	93	60	80	61	79	75
24 h	90	60	79	27	69	36	55	36	53	49
48 h	65	35	74	22	56	23	41	22	32	28
72 h	53	23	55	3	46	13	33	14	21	17
96 h	42	12	49	-	39	6	28	9	17	13

Abbreviations: Plg=plasminogen, min=minutes.

At the end of Segment 2, subjects will be asked to participate in long-term therapy in Segment 3, if this is deemed appropriate by the Investigator, Safety Monitoring Committee (SMC), and Sponsor. Plasminogen deficiency is a life-long disorder, and continued plasminogen replacement therapy to suppress lesion development and/or worsening disease is likely necessary for patients with a history of frequent or recurrent lesions.

2 Study Objectives

2.1 Primary Objectives

The primary objectives of the study are:

- To achieve an increase of individual trough plasminogen activity by at least an absolute 10% (i.e., 10 U/dL) from baseline in adult and pediatric subjects with hypoplasminogenemia during the 12 weeks of plasminogen replacement therapy in Segment 2; and
- To evaluate the efficacy of plasminogen replacement therapy on clinically evident or visible symptoms of hypoplasminogenemia during the 48 weeks of dosing in Segments 2 and 3.

2.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of plasminogen replacement therapy during the 48 weeks of dosing; and
- To evaluate the efficacy of plasminogen replacement therapy on clinically evident or visible symptoms of hypoplasminogenemia during the 12 weeks of dosing in Segment 2; and
- To evaluate the effect of plasminogen replacement therapy on pharmacokinetics and immunogenicity during the 48 weeks of dosing.

3 Study Design

3.1 Overall Study Design

Approximately 15 subjects aged 2 to 80 years with hypoplasminogenemia will be enrolled to ensure a sample size of at least 10 PK-evaluable subjects. At least 2 pediatric subjects, aged 2 to 18 years, will be enrolled. An evaluable subject for PK is defined as a subject who completes Segment 2 of plasminogen replacement therapy (see below) of the study and provides at least 3 blood samples to measure trough plasminogen activity levels.

The study consists of a screening period and 3 segments as illustrated in Figure 1. Subjects who have documented individual PK profiles with the sponsor (e.g., due to participation in the previous Phase 1 study and received 6 mg/kg Plasminogen) do not need to undergo Segment 1 and can proceed directly to Segment 2.

Screening

Subjects will be screened for study eligibility within a period of no more than 21 days before the start of dosing. Subjects will enter either Segment 1 or 2, depending on the availability of their prior individual PK profile.

Segment 1

For subjects undergoing Segment 1, each will receive a single dose of 6.6 mg/kg Plasminogen IV infusion on Day -4. Blood samples for PK analysis will be drawn prior to infusion and subsequently through 96 hours after the infusion to establish individual PK profiles. The sample drawn prior to infusion will be used to measure the subject's baseline plasminogen activity and antigen as well as D-dimer levels. The last PK sample (96 hours post infusion) will be withdrawn on Week 1, Day 0, before the administration of the first dose in Segment 2. The resulting PK profile will be used to determine each subject's dosing interval in Segment 2.

Segment 2

Based on individual PK profiles, subjects will receive 6.6 mg/kg Plasminogen IV infusion every second, third, or fourth day for 12 weeks during Segment 2. Subjects will receive approximately 21 to 42 doses in Segment 2.

For subjects who do not participate in Segment 1 and directly enter Segment 2, baseline assessments will be conducted before the first dose of Plasminogen IV infusion, including a blood sample to measure the baseline plasminogen activity and antigen as well as D-dimer levels. Their dosing interval will be every second, third, or fourth day, depending on each subject's PK profile on file.

Subjects who have gone through Segment 1 will start with the every-third-day dosing interval until their individual PK results become available. This initial dosing regimen is based upon the aggregate PK obtained from the Phase 1 study. Once each subject's individual PK profile becomes available, his or her dosing interval will be adjusted to every second, third, or fourth day accordingly.

The first dose of Plasminogen IV infusion in this segment will be administered at the study site on Week 1, Day 0. Subjects will visit the study sites every 4 weeks and receive the IMP infusion at the study site. The infusions between study visits can be administered at the study site or an ancillary site by study personnel or at the subject's home by a home health nurse, by the subject (i.e., self-administration), or by a caregiver/family member (US subjects only). Subjects or caregivers may be trained for IMP administration as deemed appropriate by the Investigator (US subjects only). Subjects administering IMP at home (home administration in the US only) are not required to take vital signs with the infusion. Vitals for home administration subjects will only be taken when the nurse draws trough levels (Week 2, 6, and 10) and when the subject returns to the site for visits (Week 4, 8, and 12) and every 12 weeks thereafter in Segment 3. The final dose at

the Week 12 visit (or at study discontinuation) in Segment 2 must be administered at the study site to allow for a repeat PK profile.

Plasma samples will be drawn before IMP administration every 2 weeks to measure the trough levels of plasminogen activity and antigen and D-dimer. The samples will be obtained at each study visit at Weeks 4, 8 and 12 and by a home health nurse at Weeks 2, 6 and 10. Additional samples may be taken in addition if needed.

Subjects will undergo clinical assessments of the disease at each study visit depending on the system and organ involvement of hypoplasminogenemia and the characteristics of lesions, including but not limited to: photographic measurements of visible lesions (e.g., ocular, gingival), spirometry for subjects with pulmonary involvement, and imaging study of nonvisible lesions (e.g., oropharyngeal, ureteral, bronchial), as deemed appropriate by the investigator.

Safety assessments will include vital signs, physical examination, clinical laboratory tests (hematology, chemistry, urinalysis, fibrinogen and coagulation panels, and urine pregnancy test for women of childbearing potential), AE assessments, virology, and immunogenicity.

In addition, subjects will be given a diary to record infusions, symptoms, concomitant medications and AEs at home between visits.

At the end of Segment 2, subjects will have the option to participate in Segment 3. Subjects for whom there is no perceived or anticipated benefit from further dosing would not be enrolled in Segment 3 at the investigator's discretion and based on discussion with the Safety Monitoring Committee (SMC, see Section 3.7) and the sponsor.

Any subject who discontinues the study during or at the end of Segment 2 should return to the study site for a Safety Follow-up visit 30 days after the final IMP dose.

Segment 3

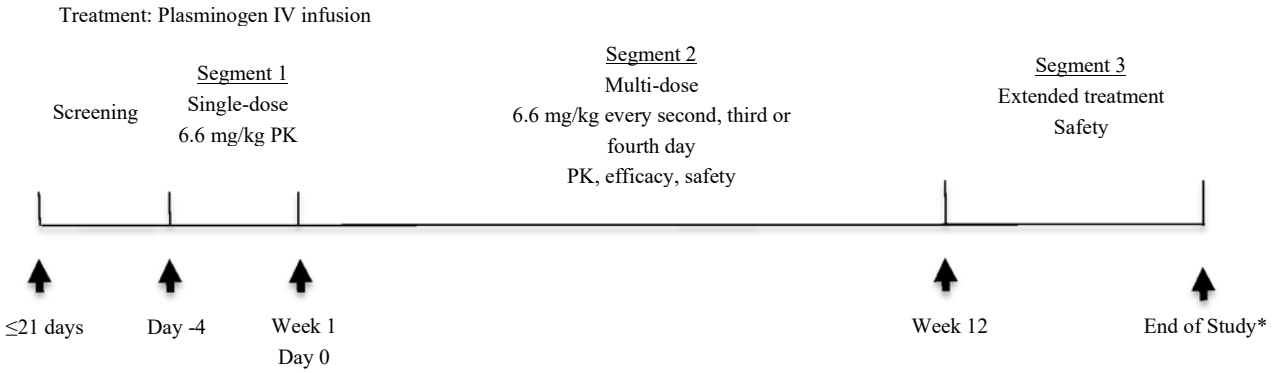
Subjects who participate in Segment 3 will continue to receive Plasminogen IV for an additional 36 weeks in Norway and until product licensing or study termination by the sponsor for subjects in the United States. The dose will be 6.6 mg/kg with the frequency determined during Segment 2, with the option of modification based on clinical response and plasminogen trough levels. Subjects (or their caregivers) may be trained to self-administer the IMP at home if deemed appropriate by the Investigator.

Subjects will return to the study sites for assessments every 3 months to monitor subjects' clinical status and plasminogen trough levels. Subjects will be given a diary to record the dates of IMP administration, any AEs, concomitant medication and other relevant information. Subjects will be given instructions for how to document receipt of IMP and how to return all used IMP vials.

Subjects at the Norway site in Segment 3 should return to the study site for a Safety Follow-up visit 30 days after the final IMP dose.

Due to the delay in product approval, subjects at the US site in Segment 3 will be allowed to enroll in Treatment Protocol 2002C018G and continue ongoing IMP treatment without any break in treatment. If subjects decide to enter Treatment Protocol 2002C018G, then they will return to the study site and complete the End of Study visit and sign an informed consent/assent for that study and stop participation in the current study. If subjects decide to not enter Treatment Protocol 2002C018G, then they will stop IMP and return to the study site for a Safety Follow-up visit 30 days after the final IMP dose.

Figure 1. Study Design Diagram



*End of study = Week 48 in Norway and product licensing or study termination by sponsor in the US. A Safety Follow-up visit is required 30 days after the last IMP dose in any segment, Due to the delay in product approval, subjects at the US site in Segment 3 will be allowed to enroll in Treatment Protocol 2002C018G and continue ongoing IMP treatment without any break in treatment. If subjects decide to enter Treatment Protocol 2002C018G, then they will return to the study site and complete the End of Study visit and sign an informed consent/assent for that study and stop participation in the current study. If subjects decide to not enter Treatment Protocol 2002C018G, then they will stop IMP and return to the study site for a Safety Follow-up visit 30 days after the final IMP dose.

3.2 Treatment, Dosage, and Duration

In Segment 1, a single dose of 6.6 mg/kg Plasminogen will be administered to each subject. However, subjects who have documented individual PK profiles with the sponsor (e.g., due to participation in the previous Phase 1 study and received 6 mg/kg Plasminogen) do not need to undergo Segment 1 and can proceed directly to Segment 2.

In Segment 2, repeated doses of 6.6 mg/kg Plasminogen will be administered every second, third, or fourth day, depending on individual subject's PK profile. Individual dosing intervals will be determined by the longest time point that the subject's plasminogen activity level remains 10% (absolute) above their baseline value. For example, if a subject's plasminogen activity level remains above 10% (absolute %) above their baseline at 48 hours and their activity level at 72

hours drops below 10% (absolute %) then that subject will be dosed every second day. Subjects will receive a range of 21 to 42 doses in Segment 2.

The dosage and dosing interval in Segment 3 will be the same as Segment 2, with the possibility of modification based on discussion between the Investigator and the sponsor. In the event that a subject does not achieve the expected/optimum clinical response by the completion of Segment 2, the principal investigator may reduce the dosing interval during Segment 3 by one day increments until the trough plasminogen activity level exceeds 45%.

For each subject, the estimated duration of study participation is no more than 21 days for screening, 4 days for Segment 1, 12 weeks for Segment 2, and 40 weeks (36 weeks of treatment and 4 weeks of safety follow-up) for Segment 3 for subjects in Norway. For those subjects in the United States who participate in Segment 3, it will be dependent on product approval and sponsor decision. A Safety Follow-up visit is required 30 days after the final IMP dose. However, due to the delay in product approval, subjects at the US site will be allowed to enroll in Treatment Protocol 2002C018G and continue ongoing IMP treatment without any break in treatment. If subjects decide to enter Treatment Protocol 2002C018G, then they will return to the study site and complete the End of Study visit and sign an informed consent/assent for that study and stop participation in the current study. If subjects decide to not enter Treatment Protocol 2002C018G, then they will stop IMP and return to the study site for a Safety Follow-up visit 30 days after the final IMP dose.

3.3 Subject Population

A total of 15 subjects with hypoplasminogenemia will be enrolled in the study to ensure at least 10 evaluable subjects. At least 2 pediatric subjects (aged 2 to 18 years) will be enrolled.

3.3.1 Inclusion Criteria

Subjects must meet all the criteria below to participate in this study:

1. Subject or legal guardian has provided informed consent (as well as assent by subjects with ages dictated by local Investigational Review Board [IRB] guidelines).
2. Subject is male or female between the ages of 2 and 80 years (inclusive).
3. Subject has a documented history of lesions and symptoms consistent with a diagnosis of hypoplasminogenemia.
4. Subject has plasminogen activity level $\leq 45\%$.
5. Subject has documented vaccination to hepatitis A virus (HAV) and hepatitis B virus (HBV), or has received the first dose of HAV and HBV vaccine prior to the first dose of IMP and is scheduled to receive the second vaccine dose. If subject has documented

vaccination more than 1 year before screening but has a negative antibody titer to HAV and/or HBV at screening, subject is required to begin a re-vaccination series with the first dose of HAV and/or HBV vaccine prior to the first dose of IMP and is scheduled to receive the second vaccine dose. No revaccination is required if the documented vaccination took place within 1 year of screening.

6. Subject agrees to use contraceptive methods from screening through 14 days after last dose of study treatment (unless documented as biologically or surgically sterile (e.g., postmenopausal, vasectomized), or has not reached reproductive age.

3.3.2 Exclusion Criteria

Subjects must meet none of the criteria below:

1. Subject has a history of anaphylactic reactions to blood or blood products that may interfere with participation in the study in the opinion of the investigator.
2. Subject has uncontrolled hypertension.
3. Subject has clinical or laboratory evidence of an intercurrent infection as evidenced by symptoms including fever, tachycardia, or other systemic signs and symptoms. (Note: Subjects with an intercurrent infection cannot participate; however, once the infection has resolved as judged by the investigator, they can be re-screened if enrollment is still open.)
4. Subject is pregnant and/or lactating.
5. Subject has a malignancy, except for basal or squamous cell skin cancer, within 3 years before screening.
6. Subject is a previous organ transplant recipient.
7. Subject is in receipt of exogenous plasminogen (ocular or IV), such as laboratory grade plasminogen, fresh frozen plasma, or Prometic Plasminogen (Human) within 2 weeks of the screening visit.
8. Subject has a psychiatric disorder, other mental disorder, or any other medical disorder that impairs the subject's ability to provide informed consent or to comply with the requirements of the study protocol.
9. Subject has evidence of renal dysfunction defined as of > 2 X the upper limit of normal (ULN) in serum creatinine.
10. Subject has evidence of hepatic dysfunction defined as > 3 x ULN in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP).

11. Subject has participated in another IRB-approved interventional clinical trial of a drug, biologic, or device within 30 days before the first dose of the IMP.
12. Subject has a chronic or acute clinically significant inter-current illness (e.g., cardiac, hepatic, renal, endocrine, neurologic, hematologic, neoplastic, immunological, and skeletal) that the investigator determines could interfere with the assessments in this study.

3.4 Measures to Minimize or Avoid Bias

3.4.1 Randomization

Subjects will not be randomized.

3.4.2 Blinding

This study will not be blinded.

3.5 Study Procedures

The schedule of events is provided in Table 2.

Table 2. Schedule of Events by Visit

		Segment 1[a]		Segment 2[l]							Segment 3[l]	End of Study Visit for Subjects at US Site Only[o]	Safety Follow-up
	Screening (≤ 21 days)	Day -4	Day -3, Day -2, Day -1	Week 1 Day 0	Week 2[b]	Week 4	Week 6[b]	Week 8	Week 10[b]	Week 12[c]	Every 12 Weeks		30 days post final dose
Informed consent/ assent	X												
Eligibility review	X												
Demographics	X												
Medical history	X	X[j]		X[j]									
Disease history & treatment	X	X[j]		X[j]									
Medication history	X	X[j]		X[j]									
Weight	X	X[j]		X[j]						X	X	X	X
Physical examination	X	X[j]		X[j]						X	X	X	X
Urine pregnancy test[d]	X	X[j]		X[j]		X		X		X	X		
Genetic test[e]	X	X[j]		X[j]									
Hematology	X	X[j]		X[j]		X		X		X	X	X	X
Biochemistry	X	X[j]		X[j]		X		X		X	X	X	X
Urinalysis	X	X[j]		X[j]		X		X		X	X	X	X
Fibrinolysis & coagulation panels	X	X[j]		X[j]		X		X		X	X	X	X
Virology	X	X[j]		X[j]						X	X	X	X
Retention virology sample		X[j]		X[j]									
Anti-plasminogen antibody		X[j]		X[j]		X		X		X	X	X	X
Plasminogen activity and antigen, D-dimer: trough levels	X			X	X	X	X	X	X	X	X		X
Plasminogen activity and antigen, D-dimer: spot levels												X	

		Segment 1[a]		Segment 2[l]							Segment 3[l]	End of Study Visit for Subjects at US Site Only[o]	Safety Follow-up
	Screening (≤ 21 days)	Day -4	Day -3, Day -2, Day -1	Week 1 Day 0	Week 2[b]	Week 4	Week 6[b]	Week 8	Week 10[b]	Week 12[c]	Every 12 Weeks		30 days post final dose
Plasminogen activity and antigen, D-dimer: PK profile[f]		X	X	X[k]						X			
Clinical assessments[g]		X[j]		X[j]		X		X		X	X	X	X
Clinical Global Impression		X[j]		X[j]		X		X		X	X[n]		
Quality of life assessment		X[j]		X[j]		X		X		X	X[n]		
Chest X-ray		X[j,m]		X[j,m]						X[m]			
Vital signs[h]	X	X		X	X	X	X	X	X	X	X		
IMP infusion[i]		X		X	X	X	X	X	X	X	X		
Concomitant medications		X	X	X		X		X		X	X	X	X
AE assessment		X	X	X		X		X		X	X	X	X
Subject diary				X		X		X		X	X	X	X

AE = adverse event; IMP = investigational medicinal product; PK = pharmacokinetic.

a. For subjects who do not have PK profile for 6 mg/kg Plasminogen on file only. Those who have PK profile on file (e.g., they participated in the previous Phase 1, Cohort 2 study) do not need to go through Segment 1 and can directly enter Segment 2.
b. Weeks 2, 6 and 10 visits may be performed at subject's home by a home health nurse or at an ancillary site in lieu of the study site.
c. The Week 12 visit is the end of treatment in Segment 2. Subjects are asked to Segment 3 based on Investigator's and Sponsor's decision. Subjects who discontinue the study during Segment 2 are required to undergo these assessments as well, except IMP infusion.
d. Women with child-bearing potential only.
e. Genetic test for hypoplasminogenemia is optional. Subjects who already have known test results or who do not wish to participate can omit the test.
f. See Section 3.5.2.6 for PK sampling time points.
g. The types and timing of clinical assessments depend on each subject's disease presentation and include but are not limited to: 1) measurement of visible lesions using photographs, 2) functionality tests (e.g., spirometry), 3) imaging of non-visible lesions (e.g., ureteral, oropharyngeal and bronchial) based on the investigator's discretion. See Section 3.5.2.13 for details.
h. Vital signs are taken within 15 minutes before and 15 minutes after each infusion that takes place at the study site and when a home health nurse is present during a visit.
   i. At each study visit, the IMP is infused by study staff on site. Between study visits, the IMP is infused at the site or an ancillary site, or at home by a home health nurse or self-administered by the subject or a caregiver. See Section 3.2 for details. Subjects' infusions window for both Segment 2 and Segment 3 is +/- 1 day.
j. For subjects who participate in Segment 1, these baseline assessments are performed on Day -4 only. For subjects who do not participate in Segment 1 and are directly entering Segment 2, these baseline assessments

are performed on Day 0 only. Any of these assessments that have already been performed at Screening within the past 7 days may be omitted.

k. A pre-infusion sample for PK profile is required for subjects in Segment 1 only (i.e., the 96-hour time point). Subjects directly entering Segment 2 do not require PK profile.
l. Visit windows for Segment 2 are +/- 1 day and for Segment 3 are +/- 7 days. Visit windows for the Safety Follow-up, 30 days post final dose, are +/-3 days.
m. A chest X-ray will be performed at baseline and Week 12 at the investigator's discretion.
n. The Clinical Global Impression and Quality of life assessment will be performed at the Week 48 Visit only in Segment 3.
o. Subjects who decide to enter Treatment Protocol 2002C018G will return to the study site and complete the End of Study visit and sign an informed consent/assent for that study and stop participation in the current study. Subjects who decide not to enter Treatment Protocol 2002C018G will stop IMP and return to the study site for the Safety Follow-up visit 30 days after the final IMP dose.

3.5.1 Procedures by Visit

3.5.1.1 Screening

- Informed consent/assent
- Eligibility review
- Demographics
- Medical history
- Disease history and past and current treatment
- Medications taken in the past year
- Weight
- Vital signs (temperature, respiratory rate, BP, and heart rate)
- Physical examination
- Blood sample for genetic test (if not on file)
- Blood and urine samples for clinical laboratory tests (hematology, biochemistry, urinalysis, fibrinolysis panel, coagulation panel) (Appendix 15.2)
- Blood samples for plasminogen activity, antigen, D-dimer
- Blood sample for virology serology (results are not required to begin dosing)

3.5.1.2 Baseline Assessments (Either Segment 1, Day -4 or Segment 2, Day 0)

The following baseline assessments will occur before the first dose of IMP. For subjects participating in Segment 1, the baseline assessments will occur on Day -4. For subjects directly entering Segment 2, the assessments will occur on Day 0.

Any of the assessments that have been conducted at Screening within 1 week before Baseline may be omitted at the Investigator's discretion, and the results from Screening may be used as Baseline values.

- Weight
- Vital signs
- Physical examination
- Changes in medical history, disease history and current medications
- Blood and urine samples for clinical laboratory tests (hematology, biochemistry, urinalysis, fibrinolysis panel, coagulation panel)
- Blood samples for plasminogen activity, antigen, D-dimer
- Retention blood samples for virology (PCR)
- A blood sample for virology serology
- A blood sample for anti-plasminogen antibody
- Clinical assessments (Section 3.5.2.13)
    - Measurements and photographs of visible lesions
    - Imaging of non-visible lesions
    - Functionality testing
- Clinical Global Impression
- Quality of life assessment
- Chest X-ray, at the investigator's discretion
- Urine pregnancy test (women of childbearing potential)

3.5.1.3 Segment 1, Week 0, Day -4 (Participants Only)

Segment 1 is required only for subjects without a prior PK profile on file for 6 mg/kg Plasminogen (Section 3.1). Baseline assessments (Section 3.5.1.2) should be completed before the IMP administration.

- Vital signs (before and 15 minutes after infusion)
- IMP infusion
- Blood samples (post-dose) for PK profile: plasminogen activity, antigen, and D-dimer (Section 3.5.2.6)
- Concomitant medications
- AE assessment

3.5.1.4 Segment 1, Week 0, Day -3, Day -2, and Day -1 (Participants Only)

- Blood samples for PK profile: plasminogen activity, antigen, and D-dimer (Section 3.5.2.6)
- Concomitant medications
- AE assessment

3.5.1.5 Segment 2, Week 1, Day 0

For subjects with prior PK profile on file and directly entering Segment 2, the Baseline assessments (Section 3.5.1.2) will be completed before the IMP administration, followed by the procedures below.

Any of the assessments that have been conducted at Screening within 2 weeks before this visit may be omitted, and the results from Screening may be used as Baseline values.

- Vital signs (before and 15 minutes after infusion)
- IMP infusion
- Concomitant medications
- AE assessment
- Provision of subject diary and instructions

For subjects entering Segment 2 after completing Segment 1, Baseline assessments are not needed. Instead, the following procedures will be conducted:

- Prior to IMP infusion, blood samples for trough plasminogen activity, antigen, and D-dimer (i.e., the 72-hour sample after first dose)
- Vital signs (before and 15 minutes after infusion)
- IMP infusion
- Concomitant medications
- AE assessment
- Provision of subject diary and instructions

3.5.1.6 Segment 2, Week 2, Week 6, Week 10

These visits will occur either at the study site or ancillary site, or at the subject's home by a home health nurse (US subjects only).

- Prior to IMP infusion, blood samples for trough plasminogen activity, antigen, and D-dimer
- Vital signs (before and 15 minutes after infusion)

- IMP infusion

3.5.1.7 Segment 2, Weeks 4 and 8

- Clinical assessments (Section 3.5.2.13)
    - Measurements and photographs of visible lesions
    - Imaging of non-visible lesions
    - Functionality testing
- Clinical Global Impression
- Quality of life assessment
- Urine pregnancy test (women of childbearing potential)
- Prior to IMP infusion, blood and urine samples for clinical laboratory tests (hematology, biochemistry, urinalysis, fibrinolysis panel, coagulation panel)
- Prior to IMP infusion, a blood sample for anti-plasminogen antibody
- Prior to IMP infusion, blood samples for trough plasminogen activity, antigen, and D-dimer
- Vital signs (before and 15 minutes after infusion)
- IMP infusion
- Concomitant medications
- AE assessment
- Review and provision of subject diary

3.5.1.8 Segment 2, Week 12 or Discontinuation

The following assessments will be conducted at the study site at Week 12 or at the final visit if a subject discontinues treatment:

- Weight
- Physical examination
- Urine pregnancy test (women of childbearing potential)
- Clinical assessments (Section 3.5.2.13)
    - Measurements and photographs of visible lesions
    - Imaging of non-visible lesions
    - Functionality testing
- Clinical Global Impression
- Quality of life assessment

- Chest X-ray, at the investigator's discretion
- Prior to IMP infusion, blood and urine samples for clinical laboratory tests (hematology, biochemistry, urinalysis, fibrinolysis panel, coagulation panel)
- Prior to IMP infusion, blood samples for virology (serology and PCR) testing
- Prior to IMP infusion, a blood sample for anti-plasminogen antibody
- Prior to IMP infusion, blood samples for trough plasminogen activity, antigen, and D-dimer
- Vital signs (before and 15 minutes after infusion)
- IMP infusion (not administered if subject is discontinuing treatment)
- Blood samples for PK profile: plasminogen activity, antigen, and D-dimer (Section 3.5.2.6, not conducted if subject is discontinuing treatment)
- Concomitant medications
- AE assessments
- Review and collection of subject diary

3.5.1.9 Segment 3

The following assessments will be conducted at the study site every 12 weeks for 36 weeks in Norway or until the IMP licensing or study termination by the sponsor in the United States. During Segment 3, subjects will continue to receive the IMP at the same dosage and interval as Segment 2, with the possibility of modification based on discussion between the investigator and the sponsor. Subjects or their caregivers may administer the IMP at home if properly trained.

- Weight
- Vital signs
- Physical examination
- Urine pregnancy test (women of childbearing potential)
- Clinical assessments (Section 3.5.2.13), if indicated
    - Measurements and photographs of visible lesions
    - Imaging of non-visible lesions
    - Functionality testing
- Prior to IMP infusion, blood and urine samples for clinical laboratory tests (hematology, biochemistry, urinalysis, fibrinolysis panel, coagulation panel)
- Prior to IMP infusion, blood samples for virology (serology and PCR) testing
- Prior to IMP infusion, blood samples for anti-plasminogen antibody
- Prior to IMP infusion, blood samples for trough plasminogen activity, antigen, and D-dimer

- Vital signs (before and 15 minutes after infusion)
- IMP infusion
- Concomitant medications
- AE assessments
- Provision and review of subject's diary
- Clinical Global Impression (performed at the Week 48 Visit only)
- Quality of life assessment (performed at the Week 48 Visit only)

3.5.1.10 End of Study Visit for Subjects at the US Site Only

The following assessments will be conducted for subjects at the US site who decide to enter Treatment Protocol 2002C018G:

- Weight
- Physical examination
- Blood and urine samples for clinical laboratory tests (hematology, biochemistry, urinalysis, fibrinolysis panel, coagulation panel)
- Blood sample for virology (serology and PCR) testing
- Blood sample for anti-plasminogen antibody
- Blood samples for spot plasminogen activity, antigen, and D-dimer
- Concomitant medications
- AE assessment
- Review and collection of subject diary

Safety Follow-up VisitThe following assessments will be conducted 30 days after the last dose of IMP has been administered

- Weight
- Physical examination

- Blood and urine samples for clinical laboratory tests (hematology, biochemistry, urinalysis, fibrinolysis panel, coagulation panel)
- Blood sample for virology (serology and PCR) testing
- Blood samples for trough plasminogen activity, antigen, and D-dimer
- Blood sample for anti-plasminogen antibody

- Concomitant medications
- AE assessment
- Review and collection of subject diary

3.5.2 Description of Assessments

3.5.2.1 Informed Consent/Assent

Informed consent is a process that includes the signing of the Informed Consent Form (ICF) for all subjects. Assent will be required from subjects younger than 18 years with consent from their legally authorized representative according to state law. Patients should be approached according to site policies regarding confidentiality. Potential subjects should be informed about the study according to the requirements of International Conference of Harmonisation (ICH) Good Clinical Practice (GCP). The informed consent process involves the investigator, and the subject should have the opportunity to discuss all aspects of the study, ask questions, consider the ICF/assent and statements, and provide an informed decision regarding any potential risks and any potential benefits. Both ICFs and assent, if applicable, must be signed prior to any study procedures being conducted. The informed consent/assent process continues throughout a subject's participation in the study. Subjects have the right to withdraw from the study for any reason and at any time. A separate genetic testing consent will be required.

3.5.2.2 Demographics

Demographic information will be collected, including the subject's date of birth, race, ethnicity, and sex.

3.5.2.3 Medical History and Disease History and Symptoms

A complete medical and surgical history will be obtained. If the subject is biologically or surgically unable to reproduce offspring, the reason for sterility should be recorded as a diagnosis (males and females).

At least 1 year of documented general history are recorded.

As part of the medical history assessment the investigator or designee will obtain a complete and detailed documented history regarding the progression of hypoplasminogenemia within at least 1 year before screening, including any surgeries performed, other treatments, and all symptoms of the disease (e.g., ligneous conjunctivitis). In addition, the investigator will interview the subject and record any self-reported lifetime history and treatment of the disease, including the date when the disease was originally diagnosed.

3.5.2.4 Prior Medications and Treatments

Documented prior and current medications within at least 1 year before screening will be recorded, including non-prescription, prescription, herbal/natural, blood products, and birth control for males and females who are able to reproduce at the time of screening. Records will include dates of use, indications, routes, doses, and schedules as appropriate. Corresponding diagnoses will also be recorded in the medical history with dates of diagnoses.

3.5.2.5 Plasminogen Genetic Test

Optional plasminogen genetic testing will be conducted at screening for those subjects who provide written informed consent form for genetic testing. A blood sample will be obtained, centrifuged, transferred to, and frozen in a cryovial and stored at -20°C. Genetic testing will be conducted by a Central Laboratory using a validated method developed by Machaon. Please see Laboratory Manual for more details on processing and shipping of blood samples. The genetic test is not necessary if the subject has undergone genetic testing in the past and the test result is available.

3.5.2.6 PK Analyses for Plasminogen Activity and Antigen Levels

Blood samples will be drawn and analyzed for plasminogen activity and plasminogen antigen levels at a Central Laboratory using validated assays. Plasminogen activity is assessed with a chromogenic assay developed and validated at a central specialty laboratory. Plasminogen antigen levels are determined by ELISA (Cell Sciences) and validated at a central specialty laboratory. For each sample taken for Plasminogen activity and antigen testing in Segments 1, 2, and 3 a backup sample will also be taken and stored at the Central Laboratory facility in case of repeat testing requirements. No backup sample is needed at the End of Study visit for subjects who decide to enter the treatment protocol.

Segment 1

Blood samples are drawn on Day -4 before the IMP infusion to establish baseline levels for plasminogen activity, antigen, and D-dimer and at the following time points after the end of the infusion: between 5 and 15 minutes, 6 hours (± 30 minutes), 24 hours (± 2 hours, Day -3), 48 hours (± 2 hours, Day -2), 72 hours (± 2 hours, Day -1), and 96 hours (± 2 hours, Day 0). An individual PK profile will be developed based on these time points.

Subjects who have had individual PK profile for 6 mg/kg Plasminogen with the sponsor, due to participation in the prior Phase 1 study, do not participate in Segment 1.

Segment 2

For subjects who do not undergo Segment 1, blood samples are drawn to measure plasminogen activity and antigen levels on Week 1, Day 0, before the first dose of the IMP is given, to establish the baseline levels.

For all subjects, blood samples will be drawn every 2 weeks before IMP infusion to measure trough levels through the final dose.

A full PK profile will also be done for all subjects at the end of Segment 2 (Week 12 visit) to evaluate the stability of individual PK profile after 12 weeks of IMP administration. As plasminogen is a consumable clotting factor, if significant lesion burden is present at the start of the study or if neutralizing antibody develops, a subject's PK profile may be altered by the end of the 12-week treatment period. At the Week 12 visit, blood samples are drawn before the IMP infusion and at the following time points after the end of the infusion: between 5 and 15 minutes, 6 hours (± 30 minutes), 24 hours (± 2 hours), 48 hours (± 2 hours), 72 hours (± 2 hours), and 96 hours (± 2 hours). The PK profile will be developed for each subject and compared with his or her prior PK profile(s).

Furthermore, additional PK analyses may be performed at other time points during Segment 2 as needed, such as when a subject's trough level or antibody test suggests the appearance of neutralizing antibody against the IMP or when the dosing frequency has changed.

Segment 3

Blood samples will be drawn at each study visit every 3 months before IMP infusion to measure trough levels. Plasminogen activity and antigen, D-dimer spot levels will be measured at the End of Study visit for subjects who decide to enter Treatment Protocol 2002C018G.

PK Sample Handling:

Blood samples will be obtained, centrifuged, and resulting plasma will be transferred to, and frozen in a cryovial and stored at -20°C. All samples will be shipped frozen to a Central Laboratory for analysis. Details on processing and shipping of blood samples are provided in the Laboratory Manual.

3.5.2.7 Clinical Laboratory Tests

Specimens for laboratory analysis will be obtained to ascertain if the subject meets eligibility criteria and to assess for abnormal changes and possible AEs during the study. The laboratory tests include hematology, serum chemistry, urinalysis, fibrinolysis and coagulation panels, and urine pregnancy test (as applicable). See Appendix 15.2 for a list of specific tests to be conducted.

Abnormal laboratory results will be reviewed by the investigator. Clinically significant abnormalities or changes from baseline will be reported as AEs, according to the investigator's judgment. However, changes that are associated with clinical improvement (for example, blood clot discharged in urine, increases in D-dimer) are not reported as AEs.

Details of sample collection and shipping will be outlined in the Laboratory Manual provided by the Central Laboratory.

3.5.2.8 Vital Signs

Vital signs will be collected to include body temperature, blood pressure, respiratory rate, and heart rate. In each subject, the same arm will be used to collect all blood pressure readings, and every attempt will be made to use the same equipment and investigator/designee at each visit.

3.5.2.9 Physical Examination

The investigator will perform a physical exam to include a gross neurological exam and major body systems. The exam will focus on systems and organs known to be affected by hypoplasminogenemia.

3.5.2.10 Antibodies to Plasminogen

A blood sample will be obtained, centrifuged, and resulting serum sample transferred to and frozen in a cryovial, stored at -20°C, and shipped frozen to a Central Laboratory for detection of anti-plasminogen antibodies. Testing for anti-plasminogen antibodies is performed by ELISA. If neutralizing antibodies are suspected based on the plasminogen activity levels, an assay for assessing binding versus non-binding antibodies will be implemented. Details on processing and shipping of blood samples are provided in the Laboratory manual. For each sample taken for Plasminogen a ntibody testing in Segments 1, 2, and 3 a backup sample will also be taken and stored at the Central Laboratory facility in case of repeat testing requirements. No backup sample is needed at the End of Study visit for subjects who decide to enter the treatment protocol.

3.5.2.11 Virology

Screening serology testing will be conducted for HIV-1, HIV-2, HCV, HBV, HAV, and B19 (Appendix 15.2). Provided the subject meets all inclusion/Exclusion criteria, the subject may begin IMP infusion in Segment 1 or 2 without waiting for the virology results. Retention samples for virology at baseline will be tested with PCR.

3.5.2.12 Subject Diary

A diary will be provided to subjects during Segments 2 and 3 to record hypoplasminogenemia symptoms, IMP administration and any AEs between visits. The diary will be reviewed by the study personnel at each visit. Subjects will return the diary at the End of Study visit or Safety Follow-Up visit.

3.5.2.13 Clinical Assessments

All subjects will be clinically evaluated by the investigator for the clinical manifestation and severity of hypoplasminogenemia at the time points specified in the Schedule of Events table.

Measurement of Visible Lesions

The size (length and width) of visible lesions, such as ocular and gingival lesions, in subjects who have ligneous conjunctivitis will be measured and documented using photography at each visit. The procedure of photographic measurements is described in the Study Manual.

Imaging

Nonvisible lesions (ureteral, oropharyngeal, and bronchial) may be qualitatively evaluated as appropriate via imaging studies, such as computed tomography (CT) scans, X-ray, or other suitable imaging techniques at the Investigator's discretion. For example, if there is lung involvement suspected, lesions may be monitored via a CT scan obtained at Screening (unless already available within the past 6 months) and at the Week 12 visit, and at other time points if warranted.

Functionality Testing

Spirometry may be performed in subjects who have respiratory tract involvement of hypoplasminogenemia, if deemed appropriate by the investigator. The spirometry will measure forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), peak expiratory flow (PEF), and FEV1/FVC ratio. If applicable, these tests may be performed at Screening and Baseline (before the first dose of IMP), and every 4 weeks subsequently. However, no testing beyond Baseline is warranted if the subject's lung function is within normal limits at Screening and/or Baseline. Spirometry does not need to be repeated at Baseline if Screening is within 3 weeks of Baseline. Other functional tests appropriate for the affected organ system may be performed and analyzed as determined by the PI.

3.5.2.14 Clinical Global Impression – Global Improvement (CGI-I) Scale

The Clinical Global Impression-Global Improvement (CGI-I) Scale is a single, clinician-completed scale designed to capture the clinician's impression of the subject's disease improvement over time (Appendix 15.3). Clinicians are asked to consider their experience in this patient population and rate the change relative to the subject's state at baseline using a 7-point scale (1 = very much improved, 7 = very much worse).

3.5.2.15 Quality of life assessment

Subjects are asked to rate their overall quality of life using a 10-point scale (0 = non-functioning, 10 = normal; Appendix 15.4), adapted from a scale developed by the American Chronic Pain Association.

3.6 Stopping Rules and Withdrawal

3.6.1 Study Termination

The sponsor and/or a principal investigator may elect to terminate the study early as defined by the clinical trial agreement.

Any decision to voluntarily suspend or terminate a clinical trial will be carefully reviewed and fully justified. The sponsor will notify the FDA and the IRB of any suspension or termination, along with justification for restarting or terminating the study as applicable.

3.6.2 Stopping Rules

Any subject who experiences any of the following occurrences will suspend the IMP treatment until further assessments:

- Anaphylactic response to study drug administration
- A significant AE that, in the investigator's opinion, necessitates suspension of treatment
- Confirmed presence of neutralizing antibodies (in at least 2 measurements) in association with diminished plasminogen activity that obviates the potential benefit of plasminogen replacement therapy.
- Thrombotic or uncontrolled bleeding event requiring hospitalization

The SMC will review safety data on an ongoing basis and will determine if a subject should stop treatment, or if there are unforeseen events (e.g., thromboembolic event) that would warrant halting or stopping the study. Such events will be discussed with FDA before enrolling further subjects.

3.6.3 Withdrawal and Replacement of Subjects

Subjects will be withdrawn for the following reasons:

- The subject withdraws consent (no justification is required); and/or
- The subject develops a condition that in the investigator's opinion makes it medically necessary that the subject not continue in the study.

After a discussion between the investigator and sponsor, subjects may be withdrawn for the following reasons:

- An AE that in the investigator's or sponsor's opinion requires the subject be withdrawn from the study;
- Violation of eligibility criteria;
- Major protocol violations or deviations from the treatment plan (e.g., incorrect IMP administration);

- Lost to follow-up after all attempts at contacting the subject; and/or
- Death.

In all cases, the reasons for withdrawal will be recorded in the subject's source documentation and in the Case Report Form (eCRF). It is possible that some subjects may become lost to follow-up during the study. Every reasonable effort will be made to contact these subjects; all available efficacy and safety data collected for these subjects will be used, even if incomplete. Subjects withdrawn from the study may be replaced so that there are at least 10 evaluable subjects.

Subjects who do not meet the entry criteria at screening will be ineligible for treatment and will be deemed screen failures. Subjects who are screen failed will not receive IMP; therefore, no PK or safety data will be collected for these subjects, and only demographic information will be collected on the eCRF. Subjects who screen fail will be considered screened but not enrolled. A screen failed subject may re-enter the study if they pass the re-screening. Only subjects who qualify for treatment will be enrolled.

3.7 Safety Monitoring Committee

The SMC is composed of the sponsor's Medical Monitor and an independent Medical Monitor and will review the safety data (e.g., AE listings, laboratory data, vital sign data, trough levels) biweekly during Segments 1 and 2, as data become available. Formal meetings of the SMC will be convened if warranted based on data obtained at any time during Segments 1 and 2. Any AEs will be discussed between SMC members in an ongoing basis. The SMC will continue to review the safety data periodically during Segment 3.

3.8 Subject Identification

Subjects will be identified by their initials and a numerical code in the database. All subjects who sign the ICF/assent will receive a Subject Identification Number according to the following format: XX-YYY (site number-subject number) to be defined in a Study Manual. The anonymity of subjects will be maintained insofar as is required by law and to protect the subjects' rights to privacy. Personally identifying information may only be obtained by the investigator or their designee to complete the requirements of the protocol and must be kept by the investigator in strictest confidence and may not be released unless required by law. See Section 11 for additional information regarding confidentially.

3.9 Treatment Compliance

The IMP will be provided by the sponsor and delivered to participating sites. IMP administration will be performed and recorded by study personnel or home nurse, or by subjects or their caregivers trained in self-administration.

Subjects will be given instructions how to document the receipt of IMP and how to return the used vials for accountability. The subjects will document IMP administration in the study diary. The study personnel will review the diary at each visit and document all doses used and missed in the CRF.

3.10 Protocol Deviations

Every effort should be made to avoid deviations from the protocol during the conduct of the trial. When protocol deviations do occur, the Investigator should promptly inform the Monitor, and the implications of each deviation must be reviewed and discussed. Any deviation must be documented, stating the reasons, date, actions taken, and the impact for the subject and/or trial for each deviation. This documentation must be kept in the Sponsor Files and Investigator Files. In case of any major protocol deviations (i.e., violations), the investigator and sponsor will decide on the further participation of the affected subject, after having discussed all relevant aspects. Such deviations will be reported to the IRB by the site according to its local IRB requirements. Deviations occurring outside of the study site, by vendors will be documented by the Sponsor and supplied to the site for IRB submission.

4 Restrictions

4.1 Concomitant and Prohibited Medications

The administration of concomitant medications, in accordance with the standard of care for subjects with hypoplasminogenemia, is permitted during the study. Any medications (e.g., prescription and non-prescription medications, blood products, herbal/natural products) taken by the subject within 30 days prior to Visit 1 (Screening) and/or during the course of the study will be recorded in the eCRF, including the dates of use, reason for use, dose, and dosage/schedule.

Any product containing plasminogen is not allowed from Screening to the end of the study.

4.2 Other Restrictions

None.

5 Reporting of Adverse Events

Adverse events will be recorded from the first dose of IMP administration through 30 days after administration of IMP and collected by observation and reporting. AEs will be elicited from subjects by asking questions regarding changes in the subject's status at each visit.

5.1 Definitions

5.1.1 Adverse Event

An AE is any untoward medical occurrence (whether or not considered to have a causal relationship to IMP) 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.

5.1.2 Adverse Drug Reaction

All noxious and unintended responses to an IMP related to any dose should be considered ADRs. The phrase "responses to an IMP" means that a causal relationship between the IMP and the AE is at least a reasonable possibility, that is, the relationship cannot be ruled out.

5.1.3 Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (i.e., the subject was at immediate risk of death from the AE as it occurred. This does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug) or
- Is a medically important event or reaction:

Events that did not result in death or hospitalization but may, based on appropriate medical judgment, jeopardize the subject or require intervention, to prevent one of the outcomes in the definition of SAE listed above, should also be considered SAEs.

5.1.4 Assessment of Severity

The severity of all AEs and SAEs must be assessed according to the following categories:

- **Mild** – The AE/SAE is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities; or
- **Moderate** – The AE/SAE is sufficiently discomforting to interfere with normal everyday activities; or

- **Severe** – The AE/SAE prevents the subject from engaging in normal everyday activities.

The term "severe" is used to describe the intensity of a specific event. The event itself may be of relatively minor medical significance (such as a severe headache). "Severe" is not the same as "serious", which is defined on subject/event outcome or action criteria usually associated with events that pose a threat to a subject/subject's life or ability to carry out life functions. Seriousness is a medical term, while severity is a subjective term.

5.1.5 Assessment of Causality

The following 4-point scale will be used by the investigator to rate the relationship of the adverse event to the IMP:

- **Definitely related:** A clinical event (including laboratory test abnormality) occurring in a plausible time relationship to IMP administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitively associated pharmacologically, using a satisfactory re-challenge procedure, if necessary; or
- **Probably related:** A clinical event (including laboratory test abnormality) with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition; or
- **Possibly related:** A clinical event (including laboratory test abnormality) with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear; or
- **Not related:** An event for which sufficient information exists to conclude that the etiology of the event is unrelated to the IMP.

The degree of certainty with which an AE or SAE is attributed to treatment with IMP (or alternative causes, e.g., natural history of underlying diseases, concomitant therapy) will be determined by how well the event can be understood with regard to one or more of the following:

- Known pharmacology of the IMP;
- Reaction of similar nature being previously observed with this medication or class of medications;
- The event having often been reported in literature for similar medications as related; and/or
- There is a temporal relationship between IMP administration and the event.

Refer to the Investigator's Brochure for all available relevant information about the IMP.

The investigators will assign causality at their respective sites during the study. The medical monitor responsible for the study will review the assigned causality for all AEs and SAEs prior to data-base lock. This assignment will be included in the study database and final study report.

5.2 Eliciting and Reporting Adverse Events

The condition of the patient will be monitored throughout the study. At each visit, AEs will be elicited using a standard non-leading question such as "*How have you been since the last visit / during the previous study period?*" AEs will also be elicited through the use of Subject Diary cards, which the investigator will review in detail with the subject at each visit, ensuring accuracy and completeness of entries recorded by the subject.

Any AE or ADR occurring during the study will be noted in detail on the appropriate pages of the eCRF. If the patient reports several signs or symptoms, which represent a single syndrome or diagnosis, the latter should be recorded in the eCRF. The investigator will grade the severity of all AEs or ADRs (mild, moderate or severe), the seriousness (non-serious or serious) and relatedness, as defined in Section 5.1.

In the event of clinically significant abnormal laboratory findings, the tests will be repeated and followed-up, as needed. Diseases, signs and symptoms, and/or laboratory abnormalities already existing before the first administration of IMP are not considered as AEs when observed at a later stage unless they represent a worsening.

The investigator should always provide detailed information concerning any abnormalities and the nature of, and reasons for any necessary action(s), as well as any other observations or comments, which are useful for the interpretation and understanding of the subjects' AEs or ADRs.

5.3 Serious Adverse Event Reporting

All AEs must be evaluated as potential serious adverse events (SAEs). All AEs assessed as serious must be reported beginning from the time of first dose of IMP until 30 days post dose. SAEs must be followed until the event resolves, the event or sequelae stabilize, or it is unlikely that additional information can be obtained after demonstration of due diligence with follow-up efforts (i.e., the subject or investigator is unable to provide additional information or, the subject is lost to follow-up).

5.3.1 SAE Reporting to the CRO

All SAEs will be reported within 24 hours of the investigator becoming aware of the event to the Pharmacovigilance (PV) CRO Safety Department submitting the Safety Report 24/7 on the fax number below.

Toll Free Fax US: 1-866-246-1693

Toll Free Fax Norway: 800-24-747.

Full details of SAE reporting to the PV CRO will be defined in the Safety Management Plan. The telephone number for ITSI is 1-888-784-2723 in US. Alternately any safety information can be sent via email to Prometic_Safety@integratedtsi.com.

It should be noted that reporting to the PV CRO Safety Department within 24 hours of awareness is required for all SAEs regardless of their causal relationship with the IMP.

The PV CRO Safety Department, together with the sponsor's medical monitor, will review all safety information/documentation and follow up with the investigative site to obtain any other required information. Follow-up information should be actively sought by the investigator and reported to the PV CRO Safety Department as it becomes available using the Safety Report.

The sponsor is responsible for reporting SAEs to IND/CTA under the oversight of the FDA and NMA (Norwegian Medicines Agency), respectively, as applicable.

5.3.2 Institutional Review Board/Ethics Committee

All AEs will be reported to the IRB/EC according to the guidelines of the IRB/EC. However, as a general guideline, IRBs/EC need to know about any AEs that are unexpected or of a greater severity than what is reported in the IB. Reporting is always required for all SAEs. Any new safety data (or other finding) that might affect an IRB/EC's judgments regarding their risks versus benefits analysis should always be reported to the IRB/EC. The sponsor and the CRA will assist the investigator in determining which events require reporting and in what timeframes.

5.3.3 Expedited SUSAR Reporting (Sponsor Responsibility)

The sponsor will submit a written IND Safety Report (i.e., completed FDA Form 3500A and/or CIOMS form) within 15 calendar days of receipt to the responsible review division of the FDA and the Norwegian Medicines Agency, as required, for any observed or volunteered SAE that is:

1) Suspected to be associated with the investigational drug or study treatment(s); and

2) Unexpected.

Any SUSARs that will be filed to the IND for the purpose of notifying FDA, and will be filed electronically via EudraVigilance for the purpose of notifying the Norwegian Medicines Agency.

In addition, if the event is fatal or life-threatening and meets the above criteria, a telephone or facsimile notification will be sent to the FDA as soon as possible, but no later than 7 calendar days after the sponsor's initial receipt, followed by a completed FDA Form 3500A within 15 calendar days after initial receipt.

Each IND Safety Report will be prominently labeled "IND Safety Report," and a copy will be provided to all participating site investigators.

For each written IND Safety Report, the sponsor will identify all previously submitted IND Safety Reports that addressed a similar adverse event experience and will provide an analysis of the significance of the newly reported adverse event in light of the previous, similar report(s).

If the results of the sponsor's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting, the sponsor will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days after the determination was made.

Follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the relevant information is available.

5.4 Pregnancy

Every effort must be made to avoid a pregnancy during the trial. Contraception should be used in accordance with Inclusion Criterion #6, and the techniques discussed at Screening should preferably not be changed during the course of the trial. A pregnancy test will be performed at Screening and at each study visit.

In case a subject becomes pregnant during the trial, she has to be withdrawn. Pregnancies occurring during the study after exposure to the IMP need to be reported. The pregnancy notification form has to be sent to the CRO Safety Department. Follow-up information on the outcome of both mother and fetus must also be reported.

5.5 Procedure for Breaking the Blind

This is not a blinded study.

5.6 Follow-up of Adverse Events

The responsible investigator will follow up each AE until it is resolved or until the medical condition of the patient has returned to baseline, and all relevant follow-up information has been reported to the sponsor.

6 Statistical Analysis

6.1 Datasets for Analysis

Safety population: Includes any subject who receives at least one dose of the IMP and provides safety data for at least one non-screening visit.

PK population: Includes subjects who have completed Segment 2 dosing and have provided sufficient samples for PK assessments.

Full Analysis Set (FAS): Includes any subject who receives at least 1 dose of the IMP and provided data for at least one post-baseline efficacy assessments.

6.2 Handling of Missing Data

No missing data will be imputed. Missing plasminogen activity or antigen data will be ignored in the calculation of PK parameters.

6.3 Analyses Plan

Details will be provided in a Statistical Analysis Plan (SAP), which will be finalized before the database lock.

6.3.1 Demographics and Baseline Characteristics

Subjects' demographic and baseline clinical characteristics will be summarized descriptively. Continuous variables will be presented as mean, standard deviation, median, and range. Categorical parameters will be presented as numbers and percentages.

6.3.2 Pharmacokinetic/Pharmacodynamic Analysis

The primary endpoint is the number and percentage of subjects who achieve the target plasminogen activity trough levels for at least 3 measurements in 12 weeks during Segment 2. Primary endpoint success is defined as at least 80% of evaluable subjects (i.e., 8 or more) achieving the target trough levels for at least 3 measurements in 12 weeks. The target trough level is defined as an increase in plasminogen activity level of at least an absolute 10% (10 U/dL) from the subject's individual baseline level. Baseline is defined as the plasminogen activity level measured before the first dose of IMP at Segment 1, Day -4 for subjects who undergo Segment 1 or at Segment 2, Day 0 for those who do directly enter Segment 2.

The secondary PK endpoints include individual PK profiles at the end of Segment 2, compared with their PK profiles at baseline, and trough plasminogen activity and antigen levels during Segment 2 and Segment 3.

Plasminogen activity and antigen levels will be presented by individual subjects and summarized descriptively (number of subjects, mean, standard deviation [SD], coefficient of variation [CV], medium, minimum, maximum, geometric mean and associated CV). Individual and median profiles of the concentration-time data will be plotted using nominal times. Median profiles may be presented on both linear-linear and linear-log scales.

Standard PK parameters, including area under the curve (AUC), clearance (CL), mean residence time (MRT), volume of distribution (V_d) and terminal half-life ($t_{1/2}$) will be calculated using non-compartmental analysis and baseline-adjusted plasminogen activity levels derived from Segment

1 data and, if a subject is suspected to develop neutralizing antibody to the IMP, plasminogen activity levels at the end of Segment 2.

Additional PK compartmental analysis may be performed and best-fit model will be used for further individual PK prediction.

The summary statistics will include the number of subjects, mean, median, standard deviation, minimum, and maximum. The PK parameters will be summarized with the geometric mean and 95% confidence interval around the geometric mean

D-dimer is monitored as a potential pharmacodynamic marker to better understand if there is a relationship between the levels of D-dimer in subjects over time and the subject's potential response to therapy.

6.3.3 Efficacy Analysis

The primary endpoint is:

Overall Clinical Success in number and size of lesions or change in organ functionality at 48 weeks

The secondary efficacy endpoints are:

- Overall Clinical Success in number and size of lesions or change in organ functionality at 12 weeks
- CGI scores at 12 and 48 weeks
- Quality of life scores at 12 and 48 weeks

Overall clinical success is defined as 50% of subjects with visible or other measureable lesions achieving at least a 50% improvement in lesion number/size or functionality impact from baseline. Visible lesions are defined as lesions which can imaged and analyzed with digital photography. Other measureable lesions are defined as lesions whose dimensions can be assessed by medical imaging studies (e.g. computed tomography, magnetic resonance imaging, ultrasound, etc) or functional assessments (e.g. spirometry, audiogram, oximetry, etc).

Clinical success will be further described as a graded evaluation of potential clinical responses; 1) Excellent response: $\geq$ 75% decrease; 2) Good response: $\geq$ 50% and < 75% reduction; 3) Moderate response: $\geq$ 25% to < 50% reduction; 4) Minimal response: < 25% reduction; 5) No response: an increase or no reduction in the size of the lesion. Clinical responses will determined by the principal investigator for the assessment of clinical success.

All efficacy results will be presented descriptively by individual subjects, including summarized hypoplasminogenemia symptoms over time recorded in subject diaries. The small sample size and high variability of disease presentation do not allow formal statistical analyses.

6.3.4 Safety Analysis

For safety analyses, treatment emergent adverse events (TEAEs) and SAEs will be summarized descriptively. Clinical laboratory tests (hematology, biochemistry, urinalysis, fibrinolysis/coagulation) will be presented in summary and shift tables. The numbers of subjects who had changes from baseline in viral tests and immunogenicity tests will be presented in individual subject listings and summary tables.

6.4 Sample Size

Approximately 15 subjects with hypoplasminogenemia will be enrolled in this study to achieve at least 10 evaluable subjects. No formal calculation was made for sample size because of the rarity of the disease. The sample size is based on known patients who have hypoplasminogenemia.

6.5 Interim Analysis

The data in this study will be conducted in stages. An initial analysis of the PK data will be conducted when at least 10 subjects have completed Segment 2 dosing and have provided sufficient samples for PK assessments. The second data analysis will be conducted when all subjects have either completed the Week 48 visit or have withdrawn consent and completed the final safety visit. The final data analysis will occur when all subjects have completed the final safety visit or remain in the study in Segment 3 (US subjects only). Additional details for these analyses will be included in the Statistical Analysis Plan (SAP).

7 Management of Investigational Medicinal Product

7.1 Packaging and Labeling in the US

The IMP for IV administration is in a lyophilized presentation and will be available in 50 mL vial size. Each vial contains 62.5 mg Plasminogen, which will yield a concentration of 5 mg/mL after it is reconstituted in 12.5 mL of Water for Injection. The IMP is labeled as below:

Protocol #: 2002C011G 50 mL

Plasminogen Human

LOT NO: 2388 - XXX

Caution: New Drug-Limited by Federal (US) Law to

Investigational Use – For Clinical Trial Use Only

Mfg Date: XXXXXXX Store at ≤ 2 °C to 8 °C

Manufactured by ProMetic BioProduction Inc, Laval, Quebec, H7V 1B7 and

Emergent BioSolutions Inc, Baltimore, MD, 21230

For ProMetic BioTherapeutics Inc., Rockville, MD, 20850

There will be a separate IMP manual for Norway which will include the label with expiry date.

7.2 Storage

The plasminogen IMP must be stored lyophilized at ≤ 2 °C to 8 °C in a secured area until used. The temperature in the storage area should be monitored with properly calibrated instruments and monitored on a temperature log. Subjects receiving and storing IMP at home can store their IMP in a non-monitored refrigerator at home.

7.3 Accountability

The principal investigator is responsible for ensuring that accurate inventory records of IMP are properly maintained. The principal investigator or designee will inventory all shipments upon receipt, acknowledge possession by signing all required documentation, and return the required documentation to the sponsor or CRO. The principal investigator must ensure that IMP is kept in a secure location onsite per site SOPs and in accordance with required storage conditions. The inventory records for the IMP will include:

- Protocol name, number and sponsor.
- Product name and description.
- Trial site and principal investigator name.
- Product lot number and Expiry Date(s)/Re-test date.
- Number of vials, sizes received from the Central Drug Repository.
- Number of vials dispensed, date and time of dispensing and study subject for whom product was dispensed.
- Product balance.
- Name and title of qualified individual dispensing product.

These records will be reviewed by the Monitor, and may be reviewed by regulatory agencies.

All correspondence with the sponsor regarding the stability and product release should be kept with the study specific documents at site and/or the pharmacy as applicable.

The subject identifier (i.e., subject ID number) must be recorded on the IMP Drug Accountability Log. All used and unused IMP must be maintained for drug accountability.

7.4 Shipment, Returns, and Destruction

IMP will be shipped from Prometic Biotherapeutics to a selected Central Drug Repository (one in the US and one in Norway). The Central Drug Repositories will ship IMP to the sites and/or directly to subjects' homes or treating study nurse office location. Details regarding the drug shipping and receipt will be provided in the Pharmacy Manual which will include detailed instructions for subjects covering the receipt, storage, preparation of IMP as well as return of used and unused vials. Inventory should be entered into the IMP Drug Accountability Log at the Study site. At the end of the trial, or upon request of the sponsor, all unused, partially used or empty IMP containers will be returned to Prometic Biotherapeutics or the CRO or destroyed at the site after accountability has been completed by the Monitor.

7.5 Preparation

IMP infusions should be prepared by a pharmacist or a qualified designee (subjects will be trained by site personnel for home preparation and infusion).

IMP must be removed from refrigerated storage and brought to room temperature for reconstitution with 12.5 mL of Water for Injection using sterile technique. The IMP should be reconstituted by addition of water slowly with swirling until dissolved. After reconstitution, the plasminogen solution should be colorless and clear to slightly opalescent. Reconstituted plasminogen must be used within 3 hours after reconstitution.

Please see the Pharmacy Manual for complete details regarding drug reconstitution.

7.6 Administration

Only eligible and enrolled subjects will receive IMP. The entire dose of the Plasminogen IV solution should be calculated on the basis of each subject's body weight and infused over a period of 10 to 30 minutes. IMP will be administered using a syringe with filter or disk filter according to the instructions in the Pharmacy Manual.

8 Records Management

8.1 Direct Access to Source Data/Documents

The investigator will permit study-related monitoring, audits, IRB review, and regulatory inspection(s), providing direct access to source data and documents.

The investigator or designee must record study participation details including enrollment, safety, and efficacy information for each subject onto source documents. The investigator is responsible for maintaining complete and adequate case histories in the source records of each subject.

Source data must be preserved for the maximum period of time permitted by local regulations and made available by the investigator in the cases described above.

8.2 Data Collection and Management

Data generated as per protocol will be entered onto the eCRF in accordance with the ICH Topic E6 (R1) Guidelines for GCP (CPMP/ICH/135/95). When the eCRFs have been completed, a monitor, with the assistance of the study site coordinator, will verify the source documentation records and review the data.

Subsequent electronic review of the data may result in queries being generated that will be forwarded simultaneously to the appropriate investigator or designee and the CRO appointed for the study for prompt resolution. Resolutions will be sent back to Data Management in a timely fashion. All data modifications resulting from review or querying of the data will be electronically tracked.

Any errors detected by either the CRA or the investigator after query resolution should be communicated via eCRF data change forms. In all cases, an investigator or designee signature will be required.

Coding of AEs and SAEs will be performed automatically by the Data Management using the MedDRA dictionary. Similarly, coding of all medications will occur using the WHO Drug Dictionary.

The medical monitor or designee will perform a periodic medical review of the coding and of the AE profile.

8.3 Record Keeping

The investigator is responsible for maintaining all records pertaining to the clinical trial and for ensuring complete and accurate documentation.

The investigator is responsible for maintaining a subject identification log. This confidential subject identification log provides the link between named subject source records in the subject file and anonymous eCRF data provided to the sponsor.

The sponsor requires that each investigator retain records (all regulatory documents such as the protocol, study approval letters, all eCRFs, drug dispensing and accountability logs, all original subject consent forms, and all correspondence pertaining to the conduct of the study) for a period of no less than 2 years from the date of final regulatory approval or as per local regulations, whichever is longer. If the study is discontinued, or if no application/license is to be filed or if the application/license is not approved for such indication, records should be retained for 7 years after the investigation is discontinued or as per local regulations, whichever is longer.

In all instances, it is prohibited for study documents to be destroyed without prior written agreement between the investigator and the sponsor. If the investigator wishes to assign the study records to another party, or move them to another location, the sponsor must be notified in writing.

9 Quality Control and Quality Assurance

9.1 Quality Control by the Monitoring Team

The Clinical Research Associates (CRA) will monitor the data collected throughout the study thus providing Quality Control (QC) of the study. Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically at selected sites by qualified Quality Assurance (QA) auditors.

The investigator must make himself or herself available for CRAs during their visits and ensure that CRAs have direct access to all documents that they require, including direct access to the subjects' files. The investigator agrees to cooperate with the CRAs to make certain that any problems detected in the course of monitoring visits are resolved. The investigator will permit direct access to the source data and documents to the appropriate regulatory authorities to verify the accuracy of this data.

The present study sponsored Prometic Biotherapeutics will be conducted in accordance with ICH GCP. The clinical team at the CRO will systematically control the essential documents generated during this trial. The trial will be monitored by the clinical team and will be subject to internal audits by Quality Assurance. All clinical study monitoring visits and audits by QA will be followed by internal reports and corrective actions, if needed. Follow-up letters will be forwarded to sites after all visits and any findings should be addressed by the investigator. The follow-up letters should be filed with the study correspondence and other essential documentation.

9.2 Quality Assurance by an Audit Team

Any study site may be selected for audit at any time by an audit team originating from the sponsor or from an external organization acting on behalf of the sponsor. The investigator agrees to cooperate with the auditor to ensure that any problems detected in the course of these audit visits are resolved.

9.3 Quality Assurance by Data Management

The CRO or delegate will be responsible for QA and QC of the database and data management.

10 Ethics and Responsibility

10.1 Investigational Review Board/Ethics Committee

Where possible a list of IRB/EC members should be obtained by the investigator and provided to the sponsor. The investigator/sponsor will obtain prior approval for this clinical trial, its corresponding ICFs, and any material viewed by the subject. The IRB/EC will be provided with the following documents for review:

- Clinical protocol and corresponding ICF(s);
- Modifications (amendments) to the clinical protocol and corresponding ICFs;
- Advertisements (i.e., directed at potential research subjects) for study recruitment, and any other material presented to a subject.
- Any other document they request for review
- Clinical Investigational Drug Brochure

The IRB/EC must operate in compliance with FDA regulations 21 CFR 50 and 21 CFR 56 and/or EU Directives, and in conformance with applicable ICH E6 Guidelines on GCP. IRB/EC review documents should refer to the study be exact protocol title and number, and should identify the documents reviewed and the date of the review. The investigator is responsible for keeping the IRB/EC updated regarding any new safety data.

10.2 Ethical Conduct of the Trial

The clinical study will be conducted in accordance with the current IRB/EC-approved clinical protocol; ICH E6 Guidelines on GCP; and relevant policies, requirements, and regulations of the IRB/EC and applicable federal agencies. Any violations by sites, CRO, or sponsor will also be submitted to IRBs and relevant regulatory agencies.

The IRB/EC and the FDA/ Norwegian Competent Authority will be notified promptly of discontinuation of the entire clinical study. Respective protocol modifications will be submitted prospectively to the IRB/EC and to the FDA/Norwegian Competent Authority for discontinuation or modification of parts of the clinical study. Enrolled subjects, investigators, and sub-investigators will be notified immediately of discontinuation of parts of the clinical study or if the study ends or the discontinuation of a subject is necessary.

If there are changes to the protocol and a new informed consent has been approved, subjects should be informed of the changes and of any changes to the risks/benefits of participation. Subjects will need to go through the informed consent process and sign a new approved ICF to be eligible to continue on the study.

If a subject decides she or he does not want to continue with the treatment portion of the study, a subject can give consent to be followed for safety only and can continue to allow access to Protected Health Information (PHI) even after withdrawal. However, the amended and approved ICF will need to be signed, and discontinuing treatment only should be clearly documented in a progress note in the subject's source documents. A subject still retains the right to withdraw participation in the study at any time and to discontinue further access to PHI. However, all data collected to that point will be made available to the sponsor and CRO.

10.3 Informed Consent and Assent

The investigator must explain to each subject the nature of the study, the purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any discomfort it may entail. The investigational product(s) should be identified as "experimental" and that its side effects are not completely known. This information must be provided in language that the subject understands. Each subject must be informed that participation in the study is voluntary and that they may withdraw from the study at any time, and that withdrawal of consent/assent will not affect their subsequent medical treatment or relationship with the treating physician. The subject should be given sufficient time to read the informed consent/assent form and the opportunity to ask questions and consider the statement before signing and dating it, and should be given a copy of the signed document(s).

Informed consent will be obtained from each subject (or subject's legally authorized representative) before the subject is admitted to the study. Assents will be obtained from each child. The assent will be presented to the child at an appropriate level of understanding for the particular child. The assent consists of the same components as the consent and requires discussion between the child and the parent or guardian and the investigator. The child will provide verbal assent and provide their signature or mark on the assent form (the parent or guardian may fill out the time and date, if necessary). No subject can enter the study before informed consent/assent has been obtained**.**

The sponsor or its designee will supply a model informed consent/assent form that complies with regulatory requirements and is considered appropriate for the study, as well as a model informed consent/assent form for optional genetic testing for plasminogen. Any changes to the sample consent form suggested by the investigator must be agreed to by the sponsor or its designee before submission to the IRB/EC, and a copy of the approved version must be provided to the sponsor or the designated medical monitor after IRB/EC approval.

During the study, subjects will be given any new information that may affect their decision to continue participation. Should a protocol amendment be required, the consent/assent may be revised to reflect the changes of the protocol. If the consent/assent form is revised, it is the

investigator's responsibility to ensure that an amended consent/assent form is reviewed and approved by the IRB or ethics committee, and this amended form is signed by all subjects subsequently entered in the study as well as those currently in the study.

10.4 Changes in the Conduct of the Study

The investigator may change the protocol without IRB/EC or sponsor approval only if it is necessary in order to safeguard the safety or rights of the subjects (i.e., in emergent situations). Any protocol amendment must be submitted for information or consideration to the applicable regulatory agencies.

IRB approval will be requested for any change to this protocol, which could affect the safety of subjects, the scope or design of the study. Minor procedural changes will be implemented by Study Notes to File, with supporting documentation at each site, if appropriate. A non-substantial amendment of a study protocol includes minor correction or clarification that have no significant impact on the way the clinical study is to be conducted and no effect on subject safety (i.e., administrative changes like change of telephone number(s), logistical changes, etc.). Any changes of the protocol (substantial amendments and non-substantial amendments) will be integrated into an updated study protocol, with a listing of all changes and reasoning for them.

11 Confidentiality

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the IMP used in this study.

The investigator will ensure that the subjects' anonymity will be maintained. The privacy rules of the US HIPAA will be followed to obtain authorization for most uses and disclosures of Protected Health Information. On eCRFs or other documents submitted to the sponsor or its designee, subjects will not be identified by their names, but by an identification code, consisting of the combination of subject's initials and study number. Documents not for submission to sponsor or its designee (e.g., the site confidential subject enrollment log and original subjects' consent forms) will be maintained by the investigator in strict confidence. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss, or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records

for study-related monitoring, audit, IRB, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

12 Publication Policy

In collaboration with the sponsor, the CRO will prepare a draft study report after the completion of the study. The final draft study report will be submitted to the selected investigators for information, review, and comments.

Publication of data generated in the study is governed by the Investigator Clinical Trial Agreement.

13 Liabilities and Insurance

The sponsor will pay for all study related costs. A separate financial agreement will be made (as appropriate) with the investigator and/or institutions.

The sponsor also carries insurance coverage for incidents of damage or injury to study subjects while participating in the study or taking IMP.

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15 Appendices

15.1 Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added) 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added) 59th WMA General Assembly, Seoul, Republic of Korea, October 2008 64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,
"The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be

evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

30. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient- physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified

as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

15.2 Clinical Laboratory Tests

Hematology	red blood cell count (RBC), white blood cell count (WBC), platelets, hemoglobin, and hematocrit
Biochemistry	albumin, AST, ALT, ALP, creatinine, blood urea nitrogen (BUN), lactate dehydrogenase (LDH), and bilirubin
Urinalysis	protein, albumin, and RBC; pregnancy test (female of child-bearing potential only)
Fibrinolysis/ coagulation	Fibrinolysis panel: • D-dimer* • Alpha 2-antiplasmin (chromogenic assay) • Fibrin monomer (hemagglutination) • Alpha-1-antitrypsin Coagulation panel: • Prothrombin time (PT) • Partial thromboplastin time (PTT) • International normalization ratio (INR)
Immunogenicity	anti-plasminogen antibody
Pharmacokinetic and trough level sampling*	• Plasminogen antigen and activity levels • D-dimer*
Virology	• At screening, serology for HIV-1, HIV-2, HCV, HBV, parvovirus B19, and HAV. • At the End-of-Treatment visit, serology and PCR for HIV-1, HIV-2, HCV, HBV; PCR for B19 and HAV. • 30 days after last IMP dose (in Segment 2 or 3): serology and PCR for HIV-1, HIV-2, HCV, HBV; PCR for B19 and HAV.

*D-dimer is measured as part of the fibrinolysis panel and along with plasminogen trough level or PK level.

15.3 Clinical Global Impression – Global Improvement (CGI-I)

Patient Name: Date:

Clinician Name:

Protocol number: 2002C011G

Clinical Global Impression – Global Improvement (CGI –I) Scale

Rate total improvement whether or not, in your clinical judgment, it is due entirely to drug treatment.

Compared to his/her condition at baseline, how much has he/she changed?

- ☐ 0 = Not assessed
- ☐ 1 = Very much improved
- ☐ 2 = Much improved
- ☐ 3 = Minimally improved
- ☐ 4 = No change
- ☐ 5 = Minimally worse
- ☐ 6 = Much worse
- ☐ 7 = Very much worse

15.4 Quality of life assessment

Quality Of Life Scale

A Measure Of Function
For People With Pain

0 Non-functioning	Stay in bed all day Feel hopeless and helpless about life
1	Stay in bed at least half the day Have no contact with outside world
2	Get out of bed but don't get dressed Stay at home all day
3	Get dressed in the morning Minimal activities at home Contact with friends via phone, email
4	Do simple chores around the house Minimal activities outside of home two days a week
5	Struggle but fulfill daily home responsibilities No outside activity Not able to work/volunteer
6	Work/volunteer limited hours Take part in limited social activities on weekends
7	Work/volunteer for a few hours daily. Can be active at least five hours a day. Can make plans to do simple activities on weekends
8	Work/volunteer for at least six hours daily Have energy to make plans for one evening social activity during the week Active on weekends
9	Work/volunteer/be active eight hours daily Take part in family life Outside social activities limited
10 Normal Quality of Life	Go to work/volunteer each day Normal daily activities each day Have a social life outside of work Take an active part in family life