STATISTICAL ANALYSIS PLAN

ProMetic Study 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

SAP Version: Final 1.04

SAP Date: 01Feb2017

Protocol Version: Amendment 2 13 June2016

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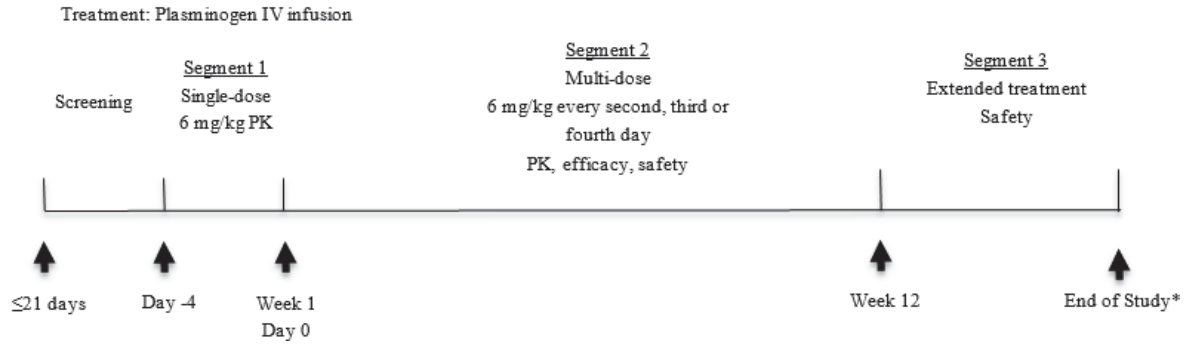
1. INTRODUCTION

This document describes the planned data summaries and statistical analyses for Study No. 2002C011G, entitled "A Phase 2/3, Open-Label, Repeat-Dose Study of the Pharmacokinetics, Efficacy, and Safety of ProMetic Plasminogen Intravenous Infusion in Subjects with Hypoplasminogenemia". It is meant to supplement the study protocol, Amendment 2 dated 13 June 2016, which should be referred to for details regarding the objectives and design of the study. Any deviation to this analysis plan will be described in the Clinical Study Report.

2. SUMMARY OF STUDY DESIGN

Figure 1. Study Design Diagram



The actual dose was 6.6 mg/kg not 6 mg/kg.
*End of study = Week 48 in Norway and product licensing or study termination by Sponsor in the United States. A Safety Follow-up visit is required 30 days after the last dose of study drug in any segment.

The study consists of a screening period and 3 segments as illustrated in Figure 1. Subjects who have documented individual pharmacokinetic (PK) profiles with the sponsor (e.g., due to participation in the previous Phase 1 study and received 6.6 mg/kg Plasminogen [Human] Intravenous) do not need to undergo Segment 1 and can proceed directly to Segment 2.

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 of the study and provides at least 3 blood samples to measure trough plasminogen activity levels.

Segment 1:

- Each subject undergoing in Segment 1 will receive a single dose of 6.6 mg/kg Plasminogen (Human) Intravenous infusion on Day -4. Blood samples for PK analysis will be drawn prior to infusion and subsequently through 96 hours after the completion of 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 (Human) Intravenous 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 (Human) Intravenous 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.

- 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) 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 dose of study drug.

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 will return to the study sites for assessments every 3 months to monitor subjects' clinical status and plasminogen trough levels.

- All subjects in Segment 3 should return to the study site for a Safety Follow-up visit 30 days after the final dose of study drug.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objectives 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;
- 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.

3.2. Secondary Objectives

The secondary efficacy variables for this study are to examine to effects of the study drug on the following:

- 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 PK and immunogenicity during the 48 weeks of dosing.

4. DETERMINATION OF SAMPLE SIZE

Approximately 15 subjects aged 2 to 80 years with hypoplasminogenemia will be enrolled to ensure a sample size of 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.

5. ANALYSIS POPULATION

5.1. Full Analysis Set

Full Analysis Set (FAS): Includes any subject who receives at least 1 dose of study drug and provided data for at least one post-baseline efficacy assessments. FAS population will be used for the final analysis of efficacy.

5.2. Interim Analysis (IA) Population

IA population: Includes any subject who completes Segment 2 dosing and provides data for at least one post-baseline efficacy assessment. The IA population will be used for the interim analysis of efficacy.

5.3. PK Population

PK population: Includes any subject who has completed Segment 2 dosing and have provided sufficient samples for PK assessments. PK population will be used for all PK analyses.

5.4. Safety Population

The safety population is defined as any subject who receives at least one dose of study drug and provides safety data for at least one non-screening visit. Safety analysis will be based on the safety population.

5.5. General Considerations

Descriptive statistics for continuous variables will include the number of observations, mean, standard deviation (SD), median, minimum, and maximum values. For categorical variables, summary measures will include the number and percentage of subjects in each category.

Individual subject data will be presented in listings by segment and, where appropriate, assessment.

All data summaries and tabulations will be prepared by using SAS® Version 9.1 or later.

Unless specifies otherwise, analysis will be presented by segments for adult population, pediatric population and adult and pediatric population combined. Analyses will combine all dosing frequencies.

At the end of Segment 2 (12 weeks), all analyses will be generated using the end of Segment 2 data cut. Overall column will combine Segments 1 and 2 data only.

The same set of analyses will be updated after Segment 3 data is complete, and overall column will combine segment 1, 2 and 3 data.

The primary efficacy analysis will be, for adult and pediatric populations, comparing post-baseline data to baseline data using FAS population, and safety analysis using safety population.

The secondary efficacy analysis will be, for adult and pediatric populations, comparing post-baseline data to baseline data using IA population, and safety analysis using safety population.

5.6. 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 IA population for the efficacy analysis includes subjects who completed Segment 2 and had at least 1 post-baseline efficacy assessment. All AE data collected as of the end of Segment 2 (Week 12) will be summarized after Segment 2 is complete.

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 (US subjects only).

5.7. Methods for Missing Data

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

5.8. Visit Windows

Data will be summarized and listed using the recorded nominal visit values, regardless of the actual study day on which a value was collected.

5.9. Baseline Measures

Baseline measures are assessments made before a subject received the first dose of study drug.

For summary tables including change from baseline (e.g. clinical laboratory, virology, and vital signs), the baseline measures are defined as below:

- For subjects participate in Segment 1, Segment 1 Day -4 baseline assessment will be used; If this is not done due to Day -4 is within the past 7 days of screening visit, baseline assessment at screening visit will be used;

- For subjects who do not participate in Segment 1 and directly enter Segment 2, baseline on Segment 2 Day 0 will be used.

There are no segment-specific baseline assessments or re-measured baseline assessments for later segments.

6. SUBJECT ENROLLMENT AND DISPOSITION

6.1. Subject Disposition

Subject disposition information will be summarized for all subjects. Summaries will include: the number of enrolled subjects, the number of subjects in each analysis population, the number of subjects completing the study, the number of subjects discontinuing the study, and the primary reason for discontinuation.

6.2. Protocol Deviations

All protocol deviations will be documented throughout the study and will be provided in a listing.

7. EVALUATION OF BASELINE MEASUREMENTS

7.1. Demographics and Baseline Characteristics

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

All demographic data will be listed.

For subjects who participate in Segment 1 and continue to Segment 2, demographics and baseline characteristics from Segment 1 will be included in Segment 2's demographics and baseline characteristics analysis table. This is to ensure there is a corresponding summary of demographics and baseline characteristics to the Segment 2's safety tables and to facilitate better safety evaluation. Similarly, for subjects who participate in Segment 2 and continue to Segment 3, demographics and baseline characteristics from Segment 2 will be included in Segment 3's demographics and baseline characteristics analysis table.

7.2. Medical History

Medical and disease history data will be coded and will be summarized by System Organ Class and Preferred Terms.

All medical and disease history data will be listed. Disease treatment and medication history will also be listed.

Similar to the handling of demographics and baseline characteristics, medical history of subjects from earlier segment will be included in the subsequent segment's reporting.

7.3. Genetic Data

Screening plasminogen genetic data will be listed.

8. EVALUATION OF TREATMENT EXPOSURE AND COMPLIANCE

8.1. Exposure to Study Drug

Subject exposure to study drug, displayed as number of infusions received, total dose received, and lots of study drug will be summarized and listed. Study drug administration data will also be provided in a listing.

8.2. Compliance to Study Drug

Study drug data will be summarized for the total number of doses received.
The actual number of doses taken will be listed.

9. EFFICACY ANALYSIS

9.1. Primary Efficacy Endpoint

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.

9.2. Secondary Efficacy Endpoints

The secondary 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

The size of visible lesions will be calculated from photographs taken by the study staff. The photographs will include a scale to measure the length and width of each lesion.

Overall clinical success is defined as 50% of subjects with visible or other measurable lesions achieving at least a 50% improvement in lesion number/size or functionality impact from baseline. Visible lesions are defined as lesions which can be imaged and analyzed with digital photography. Other measurable 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: > 75% decrease; 2) Good response: > 50% and < 75% reduction; 3) Moderate response: > 25% to < 50% reduction; 4) Minimal response: < 25% reduction; 5) No response: an increase or no reduction in the size of the lesion.

All efficacy data will be presented descriptively by scheduled visits and listed by individual subjects. The small sample size and high variability of disease presentation do not allow formal statistical analyses.

10. EVALUATION OF SAFETY PARAMETERS

Evaluation of safety includes the analysis of treatment-emergent adverse events (AEs) and the analysis of laboratory investigations.

All AEs experienced will be recorded during the study and coded using the Medical Dictionary for Regulatory Activities (MedDRA). Details to be collected include AE diagnosis, date and time of onset and resolution, whether the event is ongoing, whether the

event is serious, frequency, severity, outcome status, action taken and relationship to study drug.

Safety endpoints will be summarized using safety population. All AE data collected as of the end of Segment 2 (Week 12) will be summarized after Segment 2 is complete. The second safety analyses will be based on Segments 1, 2 and 3 data combined at the end of Week 48, and the final safety analyses will be based on all subjects who completed the final safety visit or remained in the study in Segment 3 (US subjects only).

10.1. Adverse Events

An overall summary table of AEs, including the number and percentage of subjects experiencing at least one AE, at least one SAE, related to study drug, discontinued due to AE, and death, will be presented.

AEs will be summarized by MedDRA system organ class and preferred term, showing the number and percentage of subjects experiencing a given event. In addition, AEs will be summarized by system organ class, preferred term, and worst severity, and by system organ class, preferred term and investigator-assessed relationship to study drug.

Serious adverse events will be similarly summarized and summarized in a listing.

A subject will be counted only once for each preferred term when multiple AEs are coded to the same preferred term. If a subject experiences multiple AEs coded to the same preferred term, the maximum severity will be used for the summary.

10.2. Death

Subjects whose AE outcome is death will be listed.

10.3. Discontinuation due to AE

Subjects who discontinued from the study because of an AE will be listed. Subject discontinuation will be determined from the evaluation (where reason for termination is an AE) and the specific AE will be determined from the AE CRF page (where action taken is discontinuation of study drug).

10.4. Clinical Laboratory Evaluations

Laboratory parameters will be summarized using descriptive statistics at baseline and at each subsequent time points for hematology, chemistry, urinalysis, and coagulation. Changes from baseline will also be summarized. In addition, lab data will be graded according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007, and shift tables will be provided to assess shift in laboratory values from baseline to follow-up.

All laboratory results will be tabulated for the safety population.

All laboratory results will be provided as a listing, and any values that lie outside the normal range or are clinically significant will be flagged.

10.5. Prior and Current Medications

Prior and current medication will be coded using the World Health Organization Drug Dictionary (WHO Drug) and will be summarized by drug class and generic name, and will also be listed for each Segment. In addition, baseline concomitant medications will be summarized and listed.

10.6. Physical Examination and Vital Signs

All vital signs (weight, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and body temperature) will be summarized by time points and listed with any values that lie outside the normal range or are clinically significant will be flagged for each segment. Body weight will be summarized by visit, and change and percent change from baseline will be summarized for visits post baseline for each segment.

10.7. Pregnancy Tests

All pregnancy test data will be listed.

10.8. Viral Tests

Viral testing data and change from baseline will be summarized by each segment and listed with normal ranges and flags of abnormality.

10.9. Plasminogen Antibody Tests

Plasminogen antibody data will be summarized as shift tables by normal, abnormal and total for each visit. The plasminogen antibody data will also be listed.

10.10. Subject Diary

Subject diary data will be listed by subject.

11. 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. 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 study drug 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. For subjects who enter directly in segment 2, the PK profile at the end of segment 2 is compared to PK obtained in phase 1 study.

Plasminogen activity and antigen levels will be presented by individual subjects and summarized descriptively (number of subjects, mean, 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.

PK compartmental analysis will be performed and best-fit model will be selected to predict individual PK profile following 6.6 mg/kg Plasminogen IV infusion every second, third, or fourth day for 12 weeks during Segment 2.

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.

12. SCHEDULE OF ASSESSMENTS

12.1. Schedule of Events by Visit

		Segment 1[a]		Segment 2[l]							Segment 3[l]	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
Physical examination	X	X[j]		X[j]						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
Biochemistry	X	X[j]		X[j]		X		X		X	X	X
Urinalysis	X	X[j]		X[j]		X		X		X	X	X
Fibrinolysis & coagulation panels	X	X[j]		X[j]		X		X		X	X	X
Virology	X	X[j]		X[j]						X	X	X
Retention virology sample		X[j]		X[j]								
Anti-plasminogen antibody		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: PK profile[f]		X	X	X[k]						X		
Clinical assessments[g]		X[j]		X[j]		X		X		X	X	X
Clinical Global Impression		X[j]		X[j]		X		X		X		
Quality of life assessment		X[j]		X[j]		X		X		X		
Chest X-ray		X[j]		X[j]						X		
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
AE assessment		X	X	X		X		X		X	X	X

		Segment 1[a]		Segment 2[l]							Segment 3[l]	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
Subject diary				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 (US subjects only).
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 (US subjects only). See Section 3.2 for details.
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 +/- 2 days.

13. REVISION HISTORY

SAP Version	SAP Version Date	Associated Protocol Version	Reason for Revision
V0.1	26April2016	Amendment 1, 08April2016	Initial draft
V0.2	16Jun2016	Amendment 2, 13Jun2016	2nd draft and addressed comments
V0.3	13Jul2016	Amendment 2, 13Jun2016	Addressed comments with mock TLF reviews
Final 1.0	01Feb2017	Amendment 2, 13Jun2016	Approval for the interim analysis