DOCUMENT TYPE	ABBREVIATED STATISTICAL ANALYSIS PLAN (SAP)
PROTOCOL TITLE:	A PHASE 2, RANDOMISED, DOUBLE-MASKED, SHAM-CONTROLLED, MULTI-CENTRE STUDY TO EVALUATE THE EFFICACY AND SAFETY OF O**C**R**I**PLASMIN IN INDUCING TOTAL POSTERIOR VIT**R**EOUS DETA**C**HMENT (PVD) IN SUBJECTS WITH NON-PRO**L**IFERATIVE DIAB**E**TIC RETINOPATHY (NPDR) **(CIRCLE)**
PROTOCOL NUMBER:	TG-MV-015
CLINICALTRIALS.GOV IDENTIFIER:	NCT02681809
SAP DATE:	17-JAN-2019

ABBREVIATED STATISTICAL ANALYSIS PLAN FOR FINAL ANALYSIS

PROTOCOL TITLE:	A PHASE 2, RANDOMISED, DOUBLE-MASKED, SHAM-CONTROLLED, MULTI-CENTRE STUDY TO EVALUATE THE EFFICACY AND SAFETY OF O**C**R**I**PLASMIN IN INDUCING TOTAL POSTERIOR VIT**R**EOUS DETA**C**HMENT (PVD) IN SUBJECTS WITH NON-PRO**L**IFERATIVE DIAB**E**TIC RETINOPATHY (NPDR) **(CIRCLE)**
PROTOCOL NUMBER:	TG-MV-015
STUDY PHASE:	PHASE 2
EudraCT NUMBER:	2015-002415-15
IND NUMBER:	126449
SPONSOR:	THROMBOGENICS NV, GASTON GEENSLAAN 1 B-3001 LEUVEN, BELGIUM
FINAL PROTOCOL DATE:	04-SEP-2015
AMENDMENT 1 DATE:	13-OCT-2015
AMENDMENT 2 DATE:	28-OCT-2016

Abbreviated SAP 17Jan2019

CONFIDENTIAL

Table of Contents

1. Background

This document describes the tables and listings generated for the Final Analysis. The final analysis took place after all subjects completed the Month 24 visit (Visit 11). This document is an abbreviated version of the original SAP, which also contained mock-up tables and listings. In addition, information which is considered of intellectual property nature is not included in this abbreviated version of the SAP.

2. Objective

The objective of this document is to define the set of summary tables and individual data listings that will support the writing of the clinical study report.

3. Conventions for Analysis and Computations

All Treated Subjects Analysis Set
A single analysis set will be used. The All Treated Subjects analysis set will include subjects who are randomized and receive the first injection of study treatment. Subjects will be assigned to the treatment they receive at the time of the first injection.

Baseline Value
Baseline value is defined as the last non-missing value prior to administration of the first injection of the study drug.

Change from Baseline
Change from Baseline is calculated as the difference between the value at a considered visit minus the Baseline value. Change from Baseline will be missing if either one of the Baseline Value or the value at the considered visit is missing.

Adverse Events
Adverse events are coded using MedDRA version 18.1.

If a subject has multiple occurrences of an AE after an injection, the subject is presented only once in the respective subject count. Events are counted each time in the event column. Ocular adverse events are those that occur in either eye. Events recorded as OU (both eyes) are counted once for the study eye and once for the non-study eye, and are counted as 2 separate ocular events.

Drug related events are events considered by the Investigator with a reasonable possibility that the study treatment caused the event or events with a missing relationship.

Where severity is missing, the adverse event will be assigned to the ‘severe’ category.

AEs will be attributed to the closest injection prior to the occurrence of the event. AEs with a start date corresponding to the date of one of the injections will be attributed to that particular injection.

Treatment Emergent Adverse Events
Treatment Emergent Adverse Events are adverse events with a start date on or post the date of the first injection, or a missing start date.

Concomittant Interventions/Anti-VEGFs
Concomittant Interventions (including Anti-VEGFs) are interventions with a start date on or post the date of the first injection, or a missing start date.

Imputation of Partially Missing Dates
The conventions for imputing partially missing dates are provided in the appendix of this document.

Age Computation
The Date of Birth (DOB) will be imputed to 01JULYYYY where YYYY correspond to the year of birth. The following SAS code will be used for calculating age.

floor((intck('month',DOB,first injection date) - (day(first injection date) < day(DOB))) / 12)

By Visit Layout
In tables summarizing data 'By Visit', post-injection 2 and 3 visits will be presented on 2 rows. The first row will be labelled 'Day/Month xx, Post-Injection 2/3' and will present data of subjects with 2 or 3 injections, respectively. The second row will be labelled 'Day/Month xx, Missing Repeat Injection(s)' and will present data of subjects who did not receive the complete set of repeat injections.

Early Termination Visit
The Early Termination visit corresponds to the last visit attended by subjects who discontinue from the study. Early Termination visits will be re-coded when possible. The related data will be summarized in the corresponding re-coded visit and in a visit named '*Early Termination*'. For example, if a subject discontinues with its last visit being the Day 28 visit, then the corresponding data will appear in the line '*Day 28, Post-Injection 1*' and in the line '*Early Termination*' of the summary tables.

Unscheduled Visit
Unscheduled visits will not appear in the summary tables, but in the listings.

Summary Statistics
Descriptive statistics for continuous variables and calculated change from baseline variables will include:

- number of subjects with available data
- mean and standard deviation
- median
- minimum and maximum

- 95% CI for mean, where indicated.

Categorical data and shift from baseline will be summarized by presenting:

- count
- percentage (where the denominator is based on the total number of subjects in the treatment group or overall, unless otherwise stated in the table footnotes)
- 95% CI for the proportion (Clopper-Pearson method), where indicated.

Protocol Deviations
Deviations from the protocol will be documented on an ongoing basis by the study monitors and project managers throughout the study. Protocol deviations are recorded outside the clinical database and will be reviewed by ThromboGenics during the course of the study, prior to database lock.

Missing Data
Missing data will not be replaced (unless otherwise specified), and data analysis will be performed based on the observed cases (OC) principle.

Subgroup Analysis
No subgroup analyses, nor analysis per center, will be performed.

Sensitivity Analysis
No sensitivity analyses will be performed.

Changes in Planned Analyses from the Protocol
The early stopping of the subject enrolment has led to the following changes to the analyses planned in the protocol.

A single analysis dataset will be used instead of the 3 listed in the protocol.

The first and third quartiles, and 5th and 95th percentiles will not be included in the summary statistics of continuous variables.

No statistical testing will be performed.

The last-observation-carried-forward method for data imputation will not be used, and no sensitivity analysis will be performed.

The stratification variable, NPDR severity, will not be taken into account in any summary statistics.

The following exploratory endpoints will not be summarized:

- A ≥ 2-step progression on the ETDRS Severity Scale from baseline, at Month 15 and at Month 24, based on 7-standard field stereo colour fundus photography, as assessed by the masked CRC

- Improvement of ≥ 2 steps on the ETDRS Severity Scale from baseline, at Month 15 and at Month 24, based on 7-standard field stereo colour fundus photography, as assessed by the masked CRC
- Neovascularisation as compared to baseline, at Month 15 and at Month 24, based on 7 standard field stereo colour fundus photography, as assessed by the masked CRC
- Vitreous / pre-retinal haemorrhage by Month 24, based on 7-standard field stereo colour fundus photography, as assessed by the masked CRC
- Development of iris neovascularisation as compared to baseline, at each study visit, based on slit lamp examination

4. Appendix

4.1. Conventions for Imputing Partially Missing and Missing Dates

Partially missing and missing dates will be imputed using the following rules when used for calculating day intervals (actual data will be presented in the listings).

For **start** dates, the following rules will be used:

- Missing day and month/year present: if the month and year are the same as the month and year of the first injection then impute with the date of the first injection; otherwise, impute with the first day of the month
- Missing day and month, and year present: if the year is the same as the year of the first injection then impute with the date of the first injection; otherwise, impute with the first day of the year
- If missing date, then no imputation

For **end** dates, the following rules will be used:

- Missing day and month/year present: if the month and year are the same as the month and year of the first injection then impute with the date of the first injection; otherwise, impute with the last day of the month
- Missing day and month, and year present: if the year is the same as the year of the first injection then impute with the date of the first injection; otherwise, impute with the last day of the year
- If missing date, then no imputation