STATISTICAL ANALYSIS PLAN

PROTOCOL: PP-001-1001

A safety study of intravitreal PP-001 in patients with chronic, non-infectious uveitis having chronic inflammation

STATISTICAL ANALYSIS PLAN

APPROVAL PAGE

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Contents

Abbreviations

ADR	Adverse Drug Reaction
ADaM	Analysis Data Model
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CS	Clinically Significant
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
HR	Heart Rate
IOP	Intraocular Pressure
ITT	Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
NIU	Non-Infectious Uveitis
PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred Term
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SDMB	Safety and Data Management Board
SDV	Source Data Verified
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event

Revision History

Document Version	Changes Made	Document Date
Draft 0.1	Draft specification based on the following documents: • Study protocol Germany (Version 2.0, 29 November 2016); • eCRF (Version Final 8, 15 March 2017).	11 Apr 2017
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1. Introduction

This document outlines the statistical methods to be implemented in the analysis of the data of Clinical Trial PP-001-1001. The purpose of this plan is to provide general guidelines from which the analysis will proceed. It contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol. Any changes to the protocol or electronic Case Report Form (eCRF) may necessitate updates to the Statistical Analysis Plan (SAP). In case of deviations from this updated SAP, explanations will be provided in the clinical study report.

2. Study Objectives

PP-001 is proposed for development of an intravitreal injection for the treatment of non-infectious uveitis (NIU). This first time in human study will investigate the safety, tolerability and efficacy of single ascending doses of PP-001 using intravitreal injection in male and female patients. The study population will comprise patients with NIU and an otherwise good state of health to ensure homogeneity.
Patients with chronic intraocular inflammation, for whom maximal medical treatment failed or who are unable to tolerate medical treatment because of adverse ocular or systemic effects will be included in this study. The data generated in this study will support the progression of a well-tolerated dose of PP-001, administered by intravitreal injection in patients with NIU.

2.1 Primary objective

To assess the safety and tolerability of ascending doses of PP-001 in patients with chronic, non-infectious uveitis when administered as a single intravitreal injection of 0.3 µg, 0.6 µg and 1.2 µg.

2.2 Secondary objectives

- To assess the improvement of inflammation in patients with chronic, non-infectious uveitis after ascending doses of PP-001 when administered as a single intravitreal injection of 0.3 µg, 0.6 µg and 1.2 µg
- To evaluate the pharmacokinetics of PP-001 in patients with chronic, non-infectious uveitis when administered as a single intravitreal injection of 0.3 µg, 0.6 µg and 1.2 µg

3. Study Design

3.1 General design and plan

In this prospective, multi-centre, open-label, non-randomized, consecutive study eighteen patients at the age of 18 or older will be enrolled and receive a single intravitreal injection of PP-001. Patients must have chronic, posterior uveitis, intermediate uveitis or panuveitis requiring treatment

and have been receiving an adequate therapy of e.g. systemic corticosteroid treatment or immunosuppressive therapy (azathioprine, methotrexate, cyclosporine, mycophenolate, tacrolimus) or any combination thereof. Any systemic therapy at study start should be continued throughout the study. Patients must have best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity of 10 letters or better (approximately 1/35 or 0.032) but equal or less than 50 letters (approximately 20/100 or 0.2) in the study eye for subjects enrolled under Austrian and German protocols, and equal or less than 70 letters (approximately 20/40 or 0.5) in the study eye for subjects enrolled under United Kingdom, Belgium and Netherland protocols.

The study will involve eight inpatient visits (Screening, Baseline, day of injection [Day 0] and Days 2, 7, 14, 21 and 28) and telephone calls on Day 1 and on Day 40 for subjects enrolled under Austrian and German protocols and seven inpatient visits (Screening, Baseline, day of injection [Day 0] and Days 2, 7, 14 and 28) and telephone calls on Day 1 and on Day 40 for subjects enrolled under United Kingdom, Belgium and Netherland protocols.

Patients will be divided into three cohorts of four patients. Patients will receive the following treatments administered as a single intravitreal injection:

- Cohort 1 will receive 0.3 µg of PP-001
- Cohort 2 will receive 0.6 µg of PP-001
- Cohort 3 will receive 1.2 µg of PP-001

The patients within a cohort will be dosed consecutively with a minimum time interval of 7 days between the start of injection of the previous patient and start of injection of the next patient. The results from each dosing day will be reviewed before progressing with the subsequent dosing day. The next cohort will only commence with dosing after the previous cohort has completed all study sessions up to Day 28 and no safety issues have been identified after being reviewed by the safety data management board (SDMB).
After 12 patients have been treated in the three cohorts and after all patients have finished the last follow up an interim analysis by the SDMB will be conducted to identify potential safety issues and to determine the highest tolerable dose. If no safety issue can be identified, then a fourth, higher dose will be given to a cohort of four patients (Cohort 4). The dose for a potential Cohort 4 will be 2.1 µg of PP-001. (Note: Interim analysis and dosing of a fourth cohort will not be performed).
If safety issues are identified in any of Cohorts 2, 3 or 4, two additional patients will receive the next lower dose.

Dosing of further patients will be stopped if the following criterion is observed:

- A moderate or severe AE classified as being possibly, probably or definitively study drug related or potential major safety concerns as identified by the Investigator after consultation with the SDMB are reported in more than 50% of patients in the same cohort.

Dosing will be stopped or the dose decreased if:

- One patient on any dosing day shows a possibly, probably or definitively study-drug related SAE judged by the Investigator after consultation with the SDMB or other potential major safety concerns are identified by the Investigator in agreement with the SDMB.

3.2 Visit Schedule and Visit Windows

Assessments and study visits will be performed as listed in the table below:

Phase	Screening	Baseline[i]	Pre injection	Post injection	Telephone call[a]	Safety visits					Telephone call[a]
Day	-14 to -up to dosing	-7 up to dosing	0	0	1	2 +/ -1	7 +/ -1	14 +/- 1	21[l] +/-1	28[h] +/-1	40
Electroretinography		X						X		X	
Fluorescein angiogram	X									X	
Optical coherence tomography		X				X	X	X	X	X	
Best corrected visual acuity (ETDRS)	X	X				X	X	X	X	X	
Visual field (computerized, 30°)		X					X			X	
Visually evoked cortical potential	X									X	
Intraocular pressure	X	X		X[b]		X	X	X	X	X	
Slit lamp examination [c]	X	X	X	X[b]		X	X	X	X	X	
Dilated fundoscopy[d]	X	X		X[b]		X	X	X	X	X	
Study drug injection				X							
Blood sampling for PK analysis	X			X[b,e]		X					
Corneal endothelial microscopy		X					X			X	
Fundus photography		X								X	
Amsler grid		X				X	X	X	X	X	
Urine pregnancy test (only for Austrian protocols) [m]			X						X		
Urine pregnancy test (only for Belgium, United Kingdom and Netherland protocols) [m]			X							X	
Medical and ophthalmic histories	X	X									
Vital signs[f]	X	X	X			X	X	X	X	X	
Twelve-lead electrocardiogram	X									X	
Laboratory assessments	X									X	
Patient-reported outcomes[g]		X								X	
Concomitant medication	X	X	X		X	X	X	X	X	X	
Serious medical events	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X

ETDRS: Early Treatment of Diabetic Retinopathy Study; PK: Pharmacokinetic

a. Standardized questions including (but not limited to): pain, blurred vision, change in visual acuity, redness of the eye

b. Examination will be performed after administration of study drug

c. Conjuctiva, cornea, anterior chamber including grading of cells and haze (Standardization of Uveitis Nomenclature Working Group), lens (Lens opacities classification system II) and vitreal haze (Standardization of Uveitis Nomenclature Working Group)

d. Including slit lamp biomicroscopy of the fundus

e. Day 0 blood sample will be taken 4 h ± 1 h after injection

f. Blood pressure and heart rate

g. National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25), SF36™ Health Survey Version 2 (SF-3 v2) and EuroQol-5 Dimensions Health Questionnaire (EQ-5D)

h: for visit 28 option to perform examinations to 2 consecutive days;

i: in case screening visit and baseline visit are on the same day (-7 up to dosing), examinations scheduled for both visits need only to be performed once and may be used for both study visits;

l: safety visit 21 is applicable only for subjects enrolled under Austrian and German protocols;

m: urine pregnancy test has been performed at different visits, depending on the protocol version. For subjects enrolled under German protocols (versions 2.0, 3.0 and 3.1) no pregnancy testing is done.

3.3 Sample size justification

Eighteen patients will be enrolled in the study. No power calculations will be performed and the sample size is based on the requirements of the study design.

3.4 Randomization and blinding

This is an open-label, non-randomized study. Patients will be assigned to the next available cohort as they are recruited to the study.

3.5 Efficacy endpoints

3.5.1 Primary endpoint

In this study to assess the safety and tolerability of ascending doses of PP-001, safety parameters (i.e., changes in clinical signs and symptoms from ophthalmic exam, and AEs), are the primary endpoints. Detailed ophthalmic examination will be used to determine efficacy and as a safety measure.
The primary efficacy variable is the best corrected visual acuity (ETDRS) change from baseline at day 14 and day 28.

3.5.2 Secondary efficacy endpoints

- Improvement of inflammation or of any other parameter determined at the ophthalmic examination following the injection of PP-001:
    - Vitreous haze, as graded by the ophthalmologist during Slit Lamp examination (classified according to Standardization of Uveitis Nomenclature Working Group). The scale is based on the following unit scale categorized as follows:

0	No inflammation
+0.5	Trace inflammation
+1	Mild blurring of retinal vessels and optic nerve
+1.5	Optic nerve head and posterior retinal view obscuration greater than +1, but less than +2
+2	Moderate blurring of optic nerve head
+3	Marked blurring of optic nerve head
+4	Optic nerve head not visible

    - Electroretinography
    - Fluorescein angiogram

- Optical coherence tomography
- Visual field (computerized, 30°)
- Visually evoked cortical potential
- Intraocular pressure
- Slit lamp examination
- Dilated fundoscopy
- Corneal endothelial microscopy
- Fundus photography
- Amsler grid

3.6 Safety endpoints

The safety endpoints are the following:

- Adverse Events (AEs);
- Vital Signs (blood pressure, heart rate);
- Electrocardiogram (ECG);
- Laboratory parameters (hematology, biochemistry and urinalysis).

3.7 Other endpoints

The other endpoints are the following:

3.7.1 PK parameters

The concentration of PP-001 in plasma at Screening, 4 h ± 1 h after dosing and on Day 2.

3.7.2 Patient Reported Outcomes

Patient-reported outcomes will be assessed by using the following questionnaire:

- Visual Functioning Questionnaire 25 (VFQ-25);
- SF36™ Health Survey Version 2 (SF-36v2);
- EuroQol-5 Dimensions Health Questionnaire (EQ-5D).

4. Statistical Analysis

4.1 General

Descriptive statistics will be provided for all variables in the summary tables by cohorts (PP-001 0.3 µg, 0.6 µg and 1.2 µg) according to the type of variable summarized.
Quantitative variables will be summarised by using n, arithmetic mean, SD, median and range (minimum and maximum).
Categorical variables will be summarised by using frequency distributions and percentages.

Analysis will be performed on the treated eye only assuming that a patient is treated on one eye only.

The baseline used in the analysis for each variable is reported in the table below:

Endpoint	**Baseline**
Electroretinography	Baseline (Day -7 up to dosing)
Fluorescein angiogram	Screening (Day -14 up to dosing)
Optical coherence tomography	Baseline (Day -7 up to dosing)
ETDRS	Baseline (Day -7 up to dosing)
Visual field	Baseline (Day -7 up to dosing)
Visually evoked cortical potential	Screening (Day -14 up to dosing)
Intraocular pressure	Baseline (Day -7 up to dosing)
Slit lamp examination	Baseline (Day -7 up to dosing)
Dilated fundoscopy	Baseline (Day -7 up to dosing)
Corneal endothelial microscopy	Baseline (Day -7 up to dosing)
Fundus photography	Baseline (Day -7 up to dosing)
Amsler grid	Baseline (Day -7 up to dosing)
Patient-reported outcomes	Baseline (Day -7 up to dosing)
Vital signs	Baseline (Day -7 up to dosing)
Laboratory assessments	Screening (Day -14 up to dosing)

All endpoints data collected in the eCRF will be presented in the listings. PK endpoints will be listed as well.

No multiplicity adjustment will be implemented.

4.2 Analysis sets

4.2.1 Per-Protocol Analysis Set

The PP set will include all Safety Set patients who have no major protocol deviations, and who complete the study up to the end of the post-study assessments (including telephone call days).

4.2.2 Safety Analysis Set

The Safety set will include all patients who receive at least one injection of study drug. All analyses will be conducted in this population.

4.2.3 Pharmacokinetic Analysis Set

The PK set will include all Safety Set patients who have at least one evaluable pharmacokinetic sample.

4.2.4 Incorrect treatment allocations

Not applicable.

4.3 Sub-group analyses

Not foreseen.

4.4 Covariates

Not foreseen.

4.5 Pooling of sites

Not foreseen.

4.6 Interim analyses

No interim analyses will be performed.

4.7 Handling of missing and incomplete data

Missing values will not be imputed. The number of patients with missing data will be presented under the "Missing" category, if present.
Only the non-missing values will be evaluated for computing summary statistics.

4.8 Changes in the planned analysis

The following change was implemented in this SAP with respect to the analyses planned in the protocol:

- As agreed with the Sponsor, the Intent-to-Treat Analysis set will not be used for the analysis and only the Safety set will be used for the primary analysis instead. Moreover, also the Per Protocol set definition have been updated accordingly.
- As agreed with the Sponsor, vitreous haze will not be considered as the primary endpoint but as secondary endpoint and the best corrected visual acuity (ETDRS) change from baseline at day 14 and day 28 will be considered as the primary endpoint instead.
- Any reference to dose 2.1 µg treatment group (cohort 4) has been removed from the analysis since it has been decided to close the study at cohort 3.
- No interim analyses will be performed.

4.9 Data Review Meeting

Major protocol violations will be identified by the Sponsor and provided to CROS NT in order to create the PP set.

4.10 Software

All statistical analyses and data processing will be performed using Statistical Analysis Systems (SAS®) Software (release 9.4) on a Windows 7 operating system.

5. Evaluation of Demographic and Baseline Characteristics

5.1 Subject enrolment and disposition

Statistical analysis
Disposition of patients will be presented by cohort and overall for all the patients..
The number of patients included in each of the Safety, PP and PK sets will be summarised for each cohort.

5.2 Protocol violations

Definitions and data conventions
All the protocol violations will be discussed case by case by the clinical team and the list of major and minor violators will be provided to CROS NT.

Statistical analysis
Major and minor protocol violations will be listed only.

5.3 Study discontinuations

Definitions and data conventions
Date of first study drug intake
The date of first study drug intake is assumed to be the date of the 1st injection at Day 0.

Completer/discontinued Patient
A Patient will be considered a completer if the answer to the question “Did the subject complete the study?” is equal to “Yes”.

A Patient will be considered as discontinued if the answer to the question “Did the subject complete the study?” is equal to “No”.

Statistical analysis
Patients who discontinued from the study prematurely will also be presented with a breakdown of the reasons for discontinuation by cohort and overall for the Safety set.

5.4 Demographics and baseline characteristics

Definitions and data conventions

Age

If the date of birth is not missing, age will be calculated using the following rules:

- If month of screening date is greater than month of date of birth or (month of screening date is equal to month of date of birth and day of screening date is greater than or equal to day of date of birth), then:

Age (years) = year (screening date) – year (date of birth)

- Otherwise:

Age (years) = year (screening date) – year (date of birth) - 1

In order to determinate the age of patient, the following rules will be applied for the partial date of birth:

- if only the day is missing, the 15th of the month will be assumed;
- if the day and the month are missing, 30th June will be assumed.

Body Mass Index (BMI) (kg/m2)

BMI will be calculated using the following formula:

$$\text{BMI} = \frac{\text{Body weigh t}\left(\text{kg}\right)}{\text{height }\left(\text{m}\right)^2}$$

Statistical analysis

The baseline demographic characteristics will be summarised for the single cohorts and overall by means of descriptive statistics.

The following characteristics will be provided for the Safety set:

- Age (years)
- Sex (male/female)
- Ethnicity (Hispanic or Latino/ Not Hispanic or Latino)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Smoking Status (Non-smoker, Ex-smoker, Current smoker)

5.5 Medical and ophthalmic history

Definitions and data conventions

Past disease

A disease is considered as past disease if it is not ongoing at screening visit ("ongoing" box is not ticked).

Concomitant disease
A disease is considered as concomitant disease if it is ongoing at screening visit ("ongoing" box is ticked).

Statistical analysis
Past disease and concomitant diseases will be coded using Medical Dictionary for regulatory activities (MedDRA) dictionary (version 19.0) and frequency distributions and percentages will be summarised by sequence for the Safety set by System Organ Class (SOC) and Preferred Term (PT). Counts will be given for both SOC and PT by subject. Subjects experiencing more than one past/concomitant disease event will be counted only once within each SOC and PT.

5.6 Prior and concomitant medications

Definitions and data conventions
The following categories of medications will be identified:

- previous medication (stop date ≤ date of first study medication intake);
- concomitant medication (stop date > date of first study medication intake or stop date ongoing/missing).

In case of missing or incomplete dates/times not directly allowing allocation to any of the two categories of medications, a worst-case allocation will be done according to the available parts of the start and the end dates. The medication will be allocated to the first category allowed by the available data, according to the following order:

- concomitant medication;
- previous medication.

Statistical analysis
Previous and Concomitant medications
Medications will be coded using WHO Drug Dictionary (WHO-DD), version 2016Q1 (1st Quarter of 2016), and the following Anatomical Therapeutic Chemical Classification (ATC) codes:

- Anatomical Main Group (ATC 1st level code);
- Chemical subgroup (ATC 4th level code);
- Preferred name.

Previous and concomitant medications will be summarized separately for Safety set by anatomical main group, chemical subgroup and preferred name by cohort.
Subjects experiencing more than one previous (or concomitant) medication within the same anatomical main group, chemical subgroup and preferred name will be counted only once.

5.7 Other baseline characteristics

Not foreseen.

6. Evaluation of Treatment Compliance and Exposure

6.1 Compliance to study drug and treatment

Not foreseen.

6.2 Exposure to study drug

Not foreseen.

6.3 Evaluation of pharmacokinetics

The concentration of PP-001 in plasma will be measured in blood samples taken at Screening, 4 h ± 1 h after dosing and on Day 2. Analysis will be performed on the PK set.

7. Evaluation of Efficacy

All efficacy endpoints will be presented in terms of descriptive statistics by cohort for the Safety set.

7.1 Analysis of primary endpoint

Definitions and data conventions
The primary efficacy variable is the best corrected visual acuity (ETDRS) change from baseline at day 14 and day 28.

Primary efficacy analysis
Analysis will be performed on Safety and PP sets.
The best corrected visual acuity (ETDRS)will be summarized by visits and cohort together with the change from baseline at each post-baseline visit by means of descriptive statistics.

7.2 Analysis of secondary efficacy endpoints

Definitions and data conventions
The following detailed ophthalmic examination will be used to determine efficacy:

Vitreous haze

- as graded by the ophthalmologist during Slit Lamp examination (classified according to Standardization of Uveitis Nomenclature Working Group)

Electroretinography

- Investigator's assessment

Fluorescein Angiogram
- Investigator's assessment
- Hypofluorescence
- Hyperfluorescence

Optical Coherence Tomography
- Retinal thickness
- Cystoid spaces
- Subretinal Fluid
- Vitreoretinal interface abnormalities

Visual Field Measurement
- Mean deviation
- Pattern standard deviation
- Short-term fluctuation
- Corrected pattern standard deviation
- Investigator's assessment

Visually Evoked Cortical Potential
- Investigator's assessment

Intraocular Pressure
- mmHg
- Investigator's assessment

Slit Lamp Examination
- Lid
- Conjunctiva
- Cornea
- Anterior chamber
- Iris
- Lens
- Macula
- Optic nerve
- Vitreous haze

Dilated Fundoscopy
- Retinal Oedema
- Infiltration
- Vasculitis
- Retinal Ischemia
- Epiretinal Gliosis
- Vascular occlusion
- Hyperpigmentation
- Hypopigmentation
- Choroid Atropy

Corneal endothelial microscopy
- Average cell area
- Cell density
- Investigator's assessment

Fundus photography
- Investigator's assessment

Amsler grid
- Investigator's assessment

Statistical analysis
Descriptive statistics will be presented by visit and for each cohort on the Safety set.

7.3 Analysis of other efficacy endpoints

Definitions and data conventions

National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25)
Visual functioning is assessed using the 25-item NEI-VFQ. The questionnaire contains 25 vision-targeted questions (grouped into 11 subscales) plus one single-item question related to general health (Question 1). The responses to the 25 vision-related questions are used to generate 12 subscale scores, and 11 of them are then averaged to produce an overall composite score to be used for analysis. Averaging the subscale scores gives equal weight to each subscale, whereas averaging the scores of the individual questions would give more weight to the subscales containing more questions.

The three-step process for deriving the overall NEI-VFQ composite score is explained in the VFQ-25 Manual "The National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25)" (Version 2000), and the details of the algorithm are given below.

Step 1

The categorical responses to the survey are assigned numeric values as dictated by the design of the questionnaire, which is available online from the National Eye Institute (2000).

The numeric values are then re-coded to a scale between 0 and 100; such that a higher score represents better eye functioning. The re-coding rules are given in the table below.

Question Numbers	Original Response Category[a]	Re-coded Value
1	1	0
	2	25
	3	50
	3.5	75
	4	100
3, 4, 15c[b], 17, 18, 19	1	100
	2	75
	3	50
	4	25
	5	0
2	1	0
	2	20
	3	40
	4	60

Question Numbers	Original Response Category[a]	Re-coded Value
	5	80
	6	100
5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 16a	1	100
	2	75
	3	50
	4	25
	5	0
	6	*
20, 21, 22, 23, 24, 25	1	0
	2	25
	3	50
	3.5	75
	4	100

[a] Pre-coded response choices as printed in the questionnaire.

[b] Question 15c has 4 responses levels (1 to 4), but is expanded to 5 levels using Question 15b:
If 15b = 1, then 15c should be recoded to 0.
If 15b = 2, then 15c should be recoded to missing.
If 15b = 3, then 15c should be recoded to missing.

* Response choice 6 indicates that the person does not perform the activity because of non-vision related problems. If this choice is selected, the item is coded as missing.

Step 2

The re-coded scores are grouped into 12 categories as shown in the table below, and the mean of the non-missing values in each category represents the subscale score for that category.

Scale	Number of Questions	Question Numbers to be Averaged for Subscale Score (after re-coding)
General Health	1	1
General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance Activities	3	8, 9, 14
Vision-Specific:		
Social Functioning	2	11, 13
Mental Health	4	3, 21, 22, 25
Role Difficulties	2	17, 18
Dependency	3	20, 23, 24
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

Step 3

The overall composite score is calculated as the mean of 11 subscale scores that were derived in *Step 2,* excluding the "General Health" subscale score. If not all subscale scores are calculated due to missing values, the mean of the available subscale scores will be taken.

SF36™ Health Survey Version 2 (SF-36v2)

The SF-36 is a multi-purpose, short-form health survey with only 36 questions yielding 8 health domain scales and 2 psychometrically based physical and mental component summary measures. The standard form of the SF-36v2 will be used. The question number 2 will not be used to score any of the 8 health domain scales or 2 summary measures because it is not applicable.

The 8 health domain scales are referred to as the 'Physical Functioning (PF)', 'Role- Physical (RP)', 'Bodily Pain (BP)', 'General Health (GH)', 'Vitality (VT)', 'Social Functioning (SF)', 'Role-Emotional (RE)', and 'Mental Health (MH)' scales. The 2 summary measures are referred to as the physical component score (PCS) and mental component score (MCS).

The methods of SF-36v2 scoring, handling of missing values, z- and T-score transformations are provided below.

Each item on the 36-item short-form health survey will be answered by the patients (on scales of 1 to 3, 1 to 5, or 1 to 6). Some of those answers will then be re-coded so that across all questions, a higher score will indicate a better health state. Questions 3a-3j, ,9a, 9d, 9e, 9h, 11b, 11d will be scored as recorded; the other questions will have the scores transformed as shown in the **Table 1**.

The raw score for the following 8 scales will be calculated by summing the scores (either original or re-coded depending on the question) for the set of questions listed in **Table 2** if all of the questions within that scale are answered. If < 50% of the questions within a scale is answered, then the raw score will not be calculated.

Table 1

SF-36v2: Re-code						
Question	**Original code and re-code response**					
Question number: 1						
Original response	5	4	3	2	1	
Re-coded response	5	4.4	3.4	2	1	
Questions numbers: 6						
Original response	1	2	3	4	5	
Re-coded response	5	4	3	2	1	
Questions numbers: 4a-4d, 5a-5c, 9b, 9c, 9f, 9g, 9i, 10, 11a, 11c						
Original response	5	4	3	2	1	
Re-coded response	1	2	3	4	5	
Question number: 7						
Original response	1	2	3	4	5	6
Re-coded response	6	5.4	4.2	3.1	2.2	1
Question number: 8 (if question number 7 is answered)						
Original response to #8	1	1	2	3	4	5
Original response to #7	1	2-6	1-6	1-6	1-6	1-6
Re-coded response	6	5	4	3	2	1

SF-36v2: Re-code						
Question	**Original code and re-code response**					
Question number: 8 (if question number 7 is NOT answered)						
Original response	1	2	3	4	5	
Re-coded response	6	4.75	3.5	2.25	1	

Table 2

SF-36v2: Scales	
Scales	**Questions**
Physical functioning (PF)	3a to 3j
Role – physical (RP)	4a to 4d
Bodily pain (BP)	7, 8
General health (GH)	1, 11a to 11d
Vitality (VT)	9a, 9e, 9g, 9i
Social functioning (SF)	6, 10
Role - emotional (RE)	5a to 5c
Mental health (MH)	9b, 9c, 9d, 9f, 9h

If ≥ 50% but not all of the questions are answered on a domain, first the non-missing questions are recoded (if necessary) and then summed. An average score is calculated for those non-missing scores and that average score is filled in as the score to be used for the value of the missing questions. The raw score is then calculated as the sum of all the question scores. For example, for the VT scale, if questions 9a, 9e, and 9g are answered but question 9i is missing, the algorithm will proceed as shown in **Table 3** from left to right:

Table 3

SF-36v2: Algorithm for unanswered questions					
Question	**Patient recorded response**	**Response after re-coding**		**Average is filled in for missing responses**	
9a	1	5	Average of non-missing scores = (5+3+5)/3 = 4.33333.	5	Raw score = 5+3+5+4.3333… = 17.33333…
9e	3	3		3	
9g	5	5		5	
9i	Missing	Missing		4.33333…	

After the raw score is calculated, the raw score is then converted into a transformed scale score (on a scale of 0 to 100) using the following transformation:

$$\text{Transformed scale score} = \frac{\text{Total raw score - Lowest possible raw score}}{\text{Possible raw score range}} \times 100$$

The transformed scale scores will then be standardised using the following formula for the z-score transformation:

$$\text{z-score} = \frac{\text{Transformed scale score - Mean of General US population}}{\text{Standard deviation of General US population}}$$

For example, a VT total raw score of 17.33333 would be transformed as follows:

$$\text{VT transformed scale score} = \frac{17.33333 - 4}{16} \times 100 = 83.3333125$$

As shown in Table 4, the lowest possible VT score equals 4 and the possible VT total raw score range equals 16. This transformation converts the lowest and highest possible raw scores to 0 and 100, respectively. Scores between these values represent the percentage of the total possible score achieved.

When based on the 1998 US general population, the VT z-score is as follows:

$$\text{VT z-score} = \frac{83.3333125 - 58.41968}{20.87823}$$

The lowest possible raw score, possible raw score range, mean and standard deviation for each scale are shown in **Table 4**.

Table 4

Lowest possible raw score and range, and means and standard deviations for deriving the z-scores for the scales of the SF-36v2 ACUTE form

Scale	Lowest possible raw score	Possible raw score range	Mean	Standard deviation
PF	10	20	82.62455	24.43176
RP	4	16	82.65109	26.19282
BP	2	10	73.86999	24.00884
GH	5	20	70.78372	21.28902
VT	4	16	58.41968	20.87823
SF	2	8	85.11568	23.24464
RE	3	12	87.50009	22.01216
MH	5	20	75.76034	18.04746

The physical and mental component raw scores are composed of a combination of the 8 domain z-scores and these will be calculated based on each domain scale z-score multiplied by a constant provided in **Table 5**, and then add the 8 scales together.
To illustrate, a portion of the formula for aggregating scales when estimating an aggregate physical and mental component score are as follows:
Aggregate PCS = (PF z-score x 0.42402) + . . . + (GH z-score x -0.22069)
Aggregate MCS = (PF z-score x –0.22999) + . . . + (MH z-score x 0.48581)
Note: if any of the 8 domain z-score is missing the aggregate PCS and MCS will be missing.

The T-scores for the 8 scale scores will be calculated by multiplying the scale z-scores by 10 and adding 50.
To illustrate, a portion of the formula for transforming domain scale z-scores to T-scores:
PF T-score = 50 + (PF z-score x 10)
MH T-score = 50 + (MH z-score x 10)

The physical and mental component T-scores will then be calculated by multiplying the component raw scores by 10 and adding 50.
The formulas for computing the norm-based T-score for each component summary measure are:
PCS T-score = 50 + (Aggregate physical component score x 10)
MCS T-score = 50 + (Aggregate mental component score x 10)

Table 5

SF-36v2: Scale constants used to calculate component scores		
Scale	**Physical health component**	**Mental health component**
PF	0.42402	-0.22999
RP	0.35119	-0.12329
BP	0.31754	-0.09731
GH	0.24954	-0.01571
VT	0.02877	0.23534
SF	-0.00753	0.26876
RE	-0.19206	0.43407
MH	-0.22069	0.48581

The responses to the SF-36v2 at Visit 9 (Day 28) will also be categorized as improved, worsened and stable based on the changes from baseline in T-score. The criteria for a MCID (Ware et al, 2007) will be used to assign a visit response for each score (see **Table 6**). The T-scores will be based on the 1998 US general population survey as reported in Ware et al, 2007. At follow up visit, the criteria that will be used to assign a visit response to the changes from baseline will be based on the MCIDs shown in **Table 6**.

Only patients with a non-missing score at both baseline and at Visit 9 (Day 28) will be considered eligible for categorization.

Table 6

Response Categories			
	Visit response		
Score	**Improved**	**Worsened**	**Stable**
PCS	≥ + 3.1	≤ - 3.1	Otherwise
MCS	≥ + 3.8	≤ - 3.8	Otherwise
PF	≥ + 3.5	≤ - 3.5	Otherwise
RP	≥ + 3.2	≤ - 3.2	Otherwise
BP	≥ + 4.5	≤ - 4.5	Otherwise
GH	≥ + 5.7	≤ - 5.7	Otherwise
VT	≥ + 5.5	≤ - 5.5	Otherwise
SF	≥ + 5.0	≤ - 5.0	Otherwise
RE	≥ + 3.8	≤ - 3.8	Otherwise
MH	≥ + 5.5	≤ - 5.5	Otherwise

EuroQol-5 Dimensions Health Questionnaire (EQ-5D)

The EuroQol EQ-5D-5L consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which is recorded on a 5 point scale (1 to 5). The first response choice ("no problems") is coded as a 1; the second ("slight problems") is coded as a 2; the third ("moderate problems") is coded as a 3; the forth ("severe problems") is coded as a 4; the fifth ("extreme problems") is coded as a 5 as indicated on the questionnaire. Values recorded in the eCRF will not be recoded.

Each combination of dimensions scores for a single subject is concatenated together to form the Health State (e.g. a string variable '11233' for the scores in mobility=1, self-care=1, usual activities=2, pain/discomfort=3, and anxiety/depression=3).

The five dimensions will also be converted into a Health State Index on a scale of approximately 0 to 1, where scores close to 0 represent a health state of death and a score of 1 represents full quality of life. The conversion between the ordinal scores to an index will be carried out using UK weighting and using SAS programs supplied by EUROQOL.

A higher score indicates a more preferred health status. For the precision of TLFs the actual derived value will be used in all summary statistic calculations but will be listed to two decimal places. Summary statistics will be rounded based on the same decimal precisions.

The final EQ-5D question (the 'Scored Health Today') asks respondents to rate their present health status on a vertical 0 to 100 visual analogue scale of 20 cm, with 0 labelled as "Worst imaginable health state" and 100 labelled as "Best imaginable health state." The scale is marked in increments of "10," with values labelled at each decile.

Statistical analysis
The EuroQol-5 Questionnaire (EQ-5D-5L) Health State Index as the Scored Health, NEI-VFQ overall composite score and SF-36v2 scores as measured at baseline and Visit 9 (Day 28), will be summarised using descriptive statistics, and the change in score from the baseline visit will be calculated for each patient.

7.4 Evaluation of pharmacodynamics

Statistical analysis
The PK parameters will be listed only.

8. Evaluation of Safety

8.1 Adverse events

Definitions and data conventions
Pre-treatment adverse events
An AE will be classified as pre-treatment AE if it starts before the date/time of first study medication intake (AE onset date/time < date/time of first study medication intake).

Treatment-emergent adverse event (TEAE)
An AE will be classified as a TEAE if it starts on or after the date/time of first study medication intake (AE onset date/time ≥ date/time of first study medication intake).
In case of missing or incomplete dates/times not allowing a direct allocation to any of the two categories of AEs, a worst-case allocation will be done according to the available parts of the onset and the end dates/times. The AE will be allocated to the first category allowed by the available data, according to the following order:

- TEAE
- Pre-treatment.

Serious adverse event (SAE)
A SAE is an AE judged as serious.

Adverse drug reaction (ADR)
An ADR is an AE judged as “Possibly Related”, “Probably Related” or “Definitely Related”.

Adverse event leading to discontinuation
An AE leading to discontinuation is an AE with action taken equal to “Study drug withdrawn and /or patient withdrawn from the study”.

Adverse event leading to death
An AE leading to death is an AE with outcome equal to “Fatal”.

Count of adverse events
Two AEs with the same Preferred Term (PT) and classified in the same category (pre-treatment AE or TEAE) will be considered as two different events when calculating the "number of events" in the tables.

Statistical analysis
Pre-treatment AEs and TEAEs will be presented separately. Pre-treatment AEs will be presented in the listings only.
The number of treatment-emergent AEs, SAEs, ADRs, serious ADRs, severe AEs, AEs leading to discontinuation and AEs leading to death, and the number and the percentage of patients experiencing treatment-emergent AEs, SAEs, ADRs, serious ADRs, severe AEs, AEs leading to discontinuation and AEs leading to death will be summarised by cohort.
AEs will be coded using the MedDRA dictionary (version 19.0). The SOCs and PTs will be used for tabulation. The number of AEs and the number and the percentage of patients with at least one AE will be presented by SOC and PT for treatment-emergent AEs, SAEs, ADRs, AEs leading to discontinuation and AEs leading to death by cohort.

8.2 Clinical laboratory evaluation

Statistical analysis
Hemathology, biochemistry parameters and their change from screening will be summarised by cohort at each available visit by means of descriptive statistics.
Shift tables presenting the number and the percentage of patients in each bivariate category (screening visit versus Visit 9) with regards to Investigator's interpretation (Normal, NCS, CS) will be presented by cohort for all laboratory parameters.
Urinalysis parameters will be listed only.

8.3 Vital signs

Statistical analysis
Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Heart Rate (beats/min) and their change from baseline will be summarised by cohort at each available visit by means of descriptive statistics.

8.4 ECGs

Statistical analysis
Heart rate (beats/min), PR interval (msec), QRS Duration (msec), QTc interval (msec), QTcf (msec) and the Investigator's interpretation (Normal, NCS, CS) will be listed only.

8.5 Physical examination

Statistical analysis
Physical examination will be listed only.

8.6 Other safety evaluations

Not foreseen.

9. Tables, Figures and Listings

9.1 Programs and tables quality control

The statistician-programmer of the tables, listings and figures will carefully review the programs and will verify that no error message is highlighted in the 'LOG' file.
Moreover, a second statistician-programmer will verify the internal consistency of each table by checking the results using different SAS programs.

The following level of validation will be implemented:

- Validation of statistical datasets: via validation of the final output (tables)
- Validation of statistical output:
  - tables: independent programming, with a comparison of the results against the initial output;
  - listings: peer review.

9.2 Programming conventions

All tables/figures/listings will be presented in landscape format.
The standard font size is 9 points Arial for all tables. Listings will be presented with an 8 or 7 points Arial.

Titles will be center-aligned; footnotes will be left-aligned.
Each table/figure/listing will have 2 titles:

- The 1st title will be the table/figure/listing number with the description of the table/figure/listing;
- The 2nd title will be a description of the study set presented in the table/figure/listing.

Some tables will have a third title (before 2nd title) with a description of the statistical method used in those tables.

Any footnote added to explain the table/listing/figure contents will be presented in the following format:
Note 1: Percentages are calculated on the number of patients (N).
Note 2: A serious adverse event is an ....
Note 3: …….

The last two footnotes of each table/figure will be footers indicating:

- the reference listing of the data;
- the program name, the date and time of generation and the SAS® version used.

The last footnote of each listing will be a footer indicating the program name, the date and time of generation and the SAS® version used.

Unless otherwise stated, listings will be presented by the only treatment and sorted by the patient number.

All the listings will be based on the Safety set, except stated otherwise.

The derived variables will be identified in the listings with a flag (*).

In general, dates will be presented on listings in the format ddmmmyyyy (date9.) and time in the format hh:mm (time5.). In case of partial dates or times, missing information will be replaced by dashes. Numeric variables will be listed generally with the same number of decimal places as in the actual data.

The following rules on decimal places will be considered in the listings for the derived variables (in the analyses approximations will not be performed):

- Age (years): 0 decimal place;
- BMI (kg/m^2): 1 decimal place;
- change from baseline: same as the variable considered.

The following rules on decimal places will be considered for the results of the analyses (if the analyses are performed on derived variables, the level of precision of the actual data is derived from the previous list):

- Min, max: same as actual data;
- Mean and its confidence limits (unadjusted and adjusted), SD, median: actual data + 1 decimal;
- Percentage: 1 decimal place;
- P-value: 3 decimal places.

9.3 Tables

The list of tables is provided here below:

TABLE	TITLE
TABLE 14.1.1	SUBJECT DISPOSITION / SUMMARY OF ALL SUBJECTS
TABLE 14.1.2.1	PRIMARY REASONS FOR DISCONTINUATION FROM STUDY / SAFETY SET
TABLE 14.1.3.1	ANALYSIS SETS / SAFETY SET
TABLE 14.1.4.1	DEMOGRAPHIC CHARACTERISTICS / SAFETY SET
TABLE 14.1.5.1	MEDICAL AND OPHTHALMIC HISTORY: PAST DISEASES / SAFETY SET
TABLE 14.1.5.2	MEDICAL AND OPHTHALMIC HISTORY: CONCOMITANT DISEASES / / SAFETY SET
TABLE 14.1.6.1	PREVIOUS MEDICATIONS / SAFETY SET
TABLE 14.1.6.2	CONCOMITANT MEDICATIONS / SAFETY SET
TABLE 14.2.2.1	ETDRS SCORES DURING THE STUDY AND CHANGE FROM BASELINE / SAFETY SET
TABLE 14.2.2.2	ETDRS SCORES DURING THE STUDY AND CHANGE FROM BASELINE / PP SET

TABLE	TITLE
TABLE 14.2.3.1	SLIT LAMP EXAMINATION DURING STUDY / SAFETY SET
TABLE 14.2.4.1	FLUORESCEIN ANGIOGRAM, ETDRS, VISUALLY EVOKED CORTICAL POTENTIAL, INTRAOCULAR PRESSURE AND DILATED FUNDOSCOPY DURING STUDY / SAFETY SET
TABLE 14.2.5.1	ELECTRORETINOGRAPHY, OPTICAL COHERENCE TOMOGRAPHY, VISUAL FIELD, CORNEAL ENDOTHELIAL MICROSCOPY, FUNDUS PHOTOGRAPHY AND AMSLER GRID DURING STUDY / SAFETY SET
TABLE 14.2.6	PATIENT- REPORTED OUTCOMES DURING THE STUDY AND CHANGE FROM BASELINE / SAFETY SET
TABLE 14.3.1.1	SUMMARY OF TREATMENT EMERGENT ADVERSE EVENTS / SAFETY SET
TABLE 14.3.1.2	TREATMENT EMERGENT ADVERSE EVENTS BY SYSTEM ORGAN CLASS AND PREFERRED TERM / SAFETY SET
TABLE 14.3.1.3	TREATMENT EMERGENT SERIOUS ADVERSE EVENTS BY SYSTEM ORGAN CLASS AND PREFERRED TERM / SAFETY SET
TABLE 14.3.1.4	TREATMENT EMERGENT ADVERSE DRUG REACTIONS BY SYSTEM ORGAN CLASS AND PREFERRED TERM / SAFETY SET
TABLE 14.3.1.5	TREATMENT EMERGENT ADVERSE EVENTS LEADING TO DISCONTINUATION BY SYSTEM ORGAN CLASS AND PREFERRED TERM / SAFETY SET
TABLE 14.3.1.6	TREATMENT EMERGENT ADVERSE EVENTS LEADING TO DEATH BY SYSTEM ORGAN CLASS AND PREFERRED TERM / SAFETY SET
TABLE 14.3.2.1	HAEMATOLOGY RESULTS DURING THE STUDY AND CHANGE FROM SCREENING / SAFETY SET
TABLE 14.3.2.2	BIOCHEMISTRY RESULTS DURING THE STUDY AND CHANGE FROM SCREENING / SAFETY SET
TABLE 14.3.2.3	HAEMATOLOGY RESULTS: SHIFTS FROM SCREENING TO VISIT9 / SAFETY SET
TABLE 14.3.2.4	BIOCHEMISTRY RESULTS: SHIFTS FROM SCREENING TO VISIT9 / SAFETY SET
TABLE 14.3.3.1	VITAL SIGNS DURING THE STUDY AND CHANGE FROM BASELINE / SAFETY SET

9.4 Figures

Figures not foreseen.

9.5 Listings

The list of listings is provided here below:

LISTING	TITLE
LISTING 16.2.1.1	DISPOSITION OF SUBJECTS / ALL SUBJECTS
LISTING 16.2.1.2	STUDY TERMINATION / SAFETY SET
LISTING 16.2.2.1	PROTOCOL DEVIATIONS / SAFETY SET
LISTING 16.2.2.2	VIOLATIONS OF INCLUSION/EXCLUSION CRITERIA / SAFETY SET
LISTING 16.2.3.1	ANALYSIS SETS / SAFETY SET
LISTING 16.2.4.1	DEMOGRAPHIC CHARACTERISTICS / SAFETY SET

LISTING	TITLE
LISTING 16.2.4.2	MEDICAL AND OPHTHALMIC HISTORIES / SAFETY SET
LISTING 16.2.4.3	MEDICATIONS / SAFETY SET
LISTING 16.2.5.1	STUDY DRUG ADMINISTRATION / SAFETY SET
LISTING 16.2.6.1	ETDRS / SAFETY SET
LISTING 16.2.6.2	SLIT LAMP EXAMINATION / SAFETY SET
LISTING 16.2.6.3	FLUORESCEIN ANGIOGRAM, ETDRS, VISUALLY EVOKED CORTICAL POTENTIAL, INTRAOCULAR PRESSURE AND DILATED FUNDOSCOPY / SAFETY SET
LISTING 16.2.6.4	ELECTRORETINOGRAPHY, OPTICAL COHERENCE TOMOGRAPHY, VISUAL FIELD, CORNEAL ENDOTHELIAL MICROSCOPY, FUNDUS PHOTOGRAPHY AND AMSLER GRID / SAFETY SET
LISTING 16.2.6.5	PATIENT REPORTED OUTCOMES / SAFETY SET
LISTING 16.2.7.1	ADVERSE EVENTS / SAFETY SET
LISTING 16.2.8.1	LABORATORY PARAMETERS: HAEMATOLOGY / SAFETY SET
LISTING 16.2.8.2	LABORATORY PARAMETERS: BIOCHEMISTRY / SAFETY SET
LISTING 16.2.8.3	LABORATORY PARAMETERS: URINALYSIS / SAFETY SET
LISTING 16.2.8.4	URINE PREGNANCY TEST / SAFETY SET
LISTING 16.2.8.5	VITAL SIGNS / SAFETY SET
LISTING 16.2.8.6	12-LEAD ECG RESULTS / SAFETY SET
LISTING 16.2.8.7	ABNORMAL PHYSICAL EXAMINATION / SAFETY SET
LISTING 16.2.8.8	PK / PK SET

10. Literature

- CROS NT Standard Operating Procedure SOP ST03/V01 “Statistical Analysis Plans”;
- European Medicines Agency (EMA), International Conference on Harmonisation (ICH) E3 Harmonised Guideline (1996) “Structure and Content of Clinical Study Reports”;
- EMA, ICH E9 Harmonised Guideline (1998) “Statistical Principles for Clinical Trials”.

11. Appendices

11.1 Table shells

See AppendixI_PP001-1001_200217(Final_3.0)

11.2 Listing shells

See AppendixI_PP001-1001_200217 (Final_3.0)