STATISTICAL ANALYSIS PLAN AMENDMENT 3

Study: TP0001

Product: UCB7665

A MULTICENTER, OPEN-LABEL, MULTIPLE DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFICACY OF UCB7665 IN SUBJECTS WITH PRIMARY IMMUNE THROMBOCYTOPENIA

SAP/Amendment Number	Date
Final SAP	07 Oct 2016
SAP Amendment 1	14 Nov 2017
SAP Amendment 2	14 May 2018
SAP Amendment 3	28 Jan 2019

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LIST OF ABBREVIATIONS

ACP	above cutpoint
ADA	anti-drug antibody
ADaM	analysis data model
AE	adverse event
ALC	absolute lymphocyte count
ALD	above the limit of detection
ALP	alkaline phosphatase
ALQ	above the limit of quantification
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
anti-HCV	hepatitis C virus antibody
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUEC	area under the effect curve
BAFF	B cell activating factor
BCP	below cutpoint
BLQ	below the limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval

CP	confirmed positive
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DEM	data evaluation meeting
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ES	Enrolled Set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EOS	end of study
EW	early withdrawal
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
geoCV	geometric coefficient of variation
geoMean	geometric mean
GGT	gamma glutamyltransferase
GM-CSF	granulocyte-macrophage colony-stimulating factor
[redacted]	[redacted]

H_0	null hypothesis
H_1	alternative hypothesis
HA	high abundance
HbA1c	glycosylated hemoglobin
HBsAg	hepatitis B surface antigen
HCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HLT	high level term
hsCRP	high sensitivity C-reactive protein
ICAM-1	intercellular adhesion molecule-1
ICH	International Council for Harmonisation (formerly referred to as International Conference on Harmonisation)
IFN	interferon
Ig	immunoglobulin
IL	interleukin
INR	international normalized ratio
ITP	primary immune thrombocytopenia
ITP-BAT	ITP-specific Bleeding Assessment Tool
IVIg	intravenous immunoglobulin
IXRS	interactive voice/web response system
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LP	lumbar puncture
MCP	monocyte chemotactic protein

MDC	macrophage-derived chemokine
MedDRA	Medical Dictionary for Regulatory Activities
MIP	macrophage inflammatory protein
MRI	magnetic resonance imaging
n	number of subjects
NCP	not confirmed positive
NFI-MS	Neurological Fatigue Index for Multiple Sclerosis
OD	optical density
PCS	potentially clinically significant
PD	pharmacodynamic
PDILI	potential drug-induced liver injury
PD-PPS	Pharmacodynamic Per Protocol Set
PK	pharmacokinetic
PK-PPS	Pharmacokinetic Per Protocol Set
PPS	Per Protocol Set
PT	preferred term
QWK	every week
QTcF	QT corrected for heart rate using Fridericia's formula
RBC	red blood cells
RMU	relative mass units
RNA	ribonucleic acid
[redacted]	[redacted]
SAP	Statistical Analysis Plan
sc	subcutaneous

SD	standard deviation
SMOG	Skin (S), visible mucosae (M) and organs (O), with gradation of severity
SOC	system organ class
SS	Safety Set
TARC	thymus and activation-related chemokine
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
TFLs	tables, figures and listings
TGFβ	transforming growth factor beta
TNF	tumor necrosis factor
TPO-R	thrombopoietin-receptor
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
WBC	white blood cell
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) amendment is to provide all information that is necessary to perform the required final statistical analysis of study TP0001. It also defines the summary tables, figures and listings (TFLs) to be included in the final clinical study report (CSR) according to the protocol.

This SAP is based upon, and assumes familiarity, with the following documents:

- Final Protocol: 09 November 2015
- Protocol Amendment 0.1 (Moldova): 18 November 2015
- Protocol Amendment 0.2 (Germany): 12 January 2016
- Protocol Amendment 0.3 (Poland): 23 May 2016
- Protocol Amendment 0.4 (Romania): 11 August 2016
- Protocol Amendment 1.0 (Global): 19 May 2016
- Protocol Amendment 1.1 (Moldova): 23 May 2016
- Protocol Amendment 1.3 (Poland): 09 June 2016
- Protocol Amendment 2.0 (Global; not implemented): 21 October 2016
- Protocol Amendment 3.0 (Global): 15 February 2017
- Protocol Amendment 3.1 (Moldova): 08 March 2017
- Protocol Amendment 3.3 (Poland): 07 March 2017
- Protocol Amendment 3.4 (Romania): 10 March 2017
- Protocol Amendment 3.5 (Georgia and Bulgaria): 23 August 2017
- Protocol Amendment 3.6 (Moldova): 07 September 2017

Unless specified below, the study will be analyzed as described in the most recent version of the protocol (European Union Drug Regulating Authorities Clinical Trials [EudraCT]-Number: 2015-003984-12).

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP amendment will be updated accordingly. In addition, if analysis definitions have to be modified or updated prior to database lock, a further SAP amendment will be required.

This SAP amendment 3 is due to various updates and clarifications of the analysis definitions suggested prior to and during the Data Evaluation Meeting 3 part 1 in December 2018.

If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, these changes will be described in the CSR together with the associated rationale. The content of this SAP is compatible with the International Council for Harmonisation (ICH)/Food and Drug Administration (FDA) E9 Guidance documents.

UCB is the Sponsor and PAREXEL is the Contract Research Organization (CRO) for this study.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary objective of this study is:

- To evaluate the safety and tolerability of UCB7665 administered by subcutaneous (sc) infusion in subjects with primary immune thrombocytopenia (ITP)

2.1.2 Secondary objectives

The secondary objectives of this study are:

- To assess the clinical efficacy of UCB7665 as measured by the change in platelet count
- To assess the pharmacodynamic (PD) effect of UCB7665 as measured by the change in total immunoglobulin (Ig) G (IgG) concentration in serum

2.1.3 Exploratory objectives

The exploratory objectives of this study are:

- [redacted]
- To evaluate the clinical efficacy as measured by the change in ITP bleeding score
- To evaluate the effect of UCB7665 on the concentrations of total protein, albumin, α-globulin and β-globulin, IgG subclasses, IgM, IgA, IgE and serum and plasma complement levels
- To evaluate the emergence of anti-drug antibody (ADA) with respect to immunogenicity and pharmacokinetics (PK)/ pharmacodynamic (PD)
- To evaluate the relationship between changes in platelet count and total IgG, IgG subclasses, ITP-specific autoantibodies
- To assess the plasma concentrations of UCB7665 administered by sc infusion
- To evaluate the genomic components of ITP to understand the molecular etiology, progression, and treatment of the disease, applicable only for subjects consenting to participate in the optional genomic analyses substudy
- [redacted]

2.2 Study variables

2.2.1 Safety variables

2.2.1.1 Primary safety variable

The primary safety variable is:

- Occurrence of treatment-emergent adverse events (TEAEs)

2.2.1.2 Other safety variables

The other safety variables are:

- Vital sign values and change from Baseline (systolic and diastolic blood pressure, temperature, pulse rate respiratory rate and body weight) to each visit in the Dosing Period and in the Observation Period up to Day 85 in Dose Arm 1 (4mg/kg once weekly [QWK]), up to Day 71 in Dose Arm 2 (7mg/kg QWK), up to Day 64 in Dose Arm 3 (10mg/kg QWK) and up to Day 57 in Dose Arms 4 (15mg/kg) and 5 (20mg/kg). Body weight is measured only at Screening and at the corresponding EOS/EW visit as outlined in the protocol
- 12-lead electrocardiogram (ECG) parameters and change from Baseline to each dosing visit in the Dosing Period and to the second and the last visit in the Observation Period as outlined in the protocol
- Laboratory values and change from Baseline (hematology including coagulation parameters, clinical chemistry, and urinalysis) to each visit in the Dosing Period and in the Observation Period up to the corresponding EOS/EW visit as outlined in the protocol
- Values and change from Baseline in concentrations of total protein, albumin, α-globulin, and β-globulin to each visit in the Dosing Period and in the Observation Period up to the corresponding EOS/EW visit as outlined in the protocol
- TEAEs leading to withdrawal of UCB7665
- Change from Baseline in serum biomarkers [redacted] to each visit in the Dosing Period and up to the last visit prior to the corresponding EOS visit as outlined in the protocol

2.2.2 Efficacy variables

The efficacy variables are as follows where all variables relating to platelets refer to those measured by ACM Global Central Laboratory:

- Response during the study: platelet count $\geq 30 \times 10^9$/L and at least 2-fold increase from the Baseline count
- Complete Response during the study: platelet count $\geq 100 \times 10^9$/L
- Platelet count $\geq 50 \times 10^9$/L during the study
- Response by visit
- Complete Response by visit
- Platelet count $\geq 50 \times 10^9$/L by visit

- The maximum value and maximum increase from Baseline in platelet count during the study
- Value and change from Baseline in platelet count over time
- Baseline-corrected area under the effect curve (AUEC) for platelet count calculated from Baseline to the end of study visit (Day 85 in the Observation Period in Dose Arm 1, Day 71 in the Observation Period in Dose Arm 2, Day 64 in the Observation Period in Dose Arm 3 and Day 57 in Observation Period in Dose Arms 4 and 5)
- Time to Response: time from starting treatment to achievement of Response
- Time to Complete Response: time from starting treatment to achievement of Complete Response
- Time to achieving platelet count $\geq 50x10^9/L$
- Duration of Response: measured from achievement of Response to loss of Response (loss of Response defined as platelet count $<30x10^9/L$ or less than 2-fold increase of Baseline platelet count)
- Duration of Complete Response: measured from achievement of Complete Response to loss of Complete Response (loss of Complete Response defined as platelet count $<100x10^9/L$)
- Duration of platelet count $\geq 50x10^9/L$: measured from achievement of platelet count $\geq 50x10^9/L$ to reduction of platelet count $<50x10^9/L$
- Clinical Response: confirmation of platelet count $\geq 30x10^9/L$ and at least 2-fold increase from the Baseline value and absence of bleeding
- Time to Clinical Response: time from starting treatment to achievement of Clinical Response
- Duration of Clinical Response: measured from achievement of Clinical Response to loss of Clinical Response (loss of Clinical Response defined as platelet count $<30x10^9/L$ or less than 2-fold increase from Baseline platelet count or presence of bleeding)
- Complete Clinical Response: confirmation of platelet count $\geq 100x10^9/L$ and absence of bleeding
- Time to Complete Clinical Response: time from starting treatment to achievement of Complete Clinical Response
- Duration of Complete Clinical Response: measured from achievement of Complete Clinical Response to loss of Complete Clinical Response (loss of Complete Clinical Response defined as platelet count $<100x10^9/L$ or presence of bleeding)
- No Clinical Response: confirmation of platelet count $<30x10^9/L$ and less than 2-fold increase from Baseline or presence of bleeding
- Assessment of ITP bleeding score over time at Baseline and at each dosing visit in the Dosing Period and to Day 36, Day 50, Day 64 and Day 85 in the Observation Period in Dose Arm 1, to Day 22, Day 36, Day 50 and Day 71 in the Observation Period in Dose Arm 2, to Day 15, Day 29, Day 43 and Day 64 in the Observation Period in Dose Arm 3 and to Day 8, Day 22, Day 36 and Day 57 in the Observation Period in Dose Arms 4 and 5

- Value and change from Baseline in Neurological Fatigue Index for Multiple Sclerosis (NFI-MS) summary score to Day 36, Day 50, Day 64 and Day 85 in the Observation Period in Dose Arm 1, to Day 22, Day 36, Day 50 and Day 71 in the Observation Period in Dose Arm 2, to Day 15, Day 29, Day 43 and Day 64 in the Observation Period in Dose Arm 3 and to Day 8, Day 22, Day 36 and Day 57 in the Observation Period in Dose Arm 4 and 5

2.2.3 Pharmacokinetic and pharmacodynamic variables

2.2.3.1 Pharmacokinetic variable

The PK variable is:

- Plasma concentration of UCB7665 over time, at each visit during the Dosing Period and 3 and 7 days following the last dose of UCB7665 in each dose arm
- Additional blood samples for the optional PK/PD substudy (early blood sampling) will be drawn at Visit 2 (predose and 4 hours after end of infusion on Day 1), Visit 2a (24 and 36 [optional] hours after the start of Day 1 UCB7665 infusion) and Visit 2b (48 hours after the start of Day 1 UCB7665 infusion).

2.2.3.2 Pharmacodynamic variables

The PD variables are:

- Minimum value and maximum decrease from Baseline in total IgG concentration (absolute and percentage) measured by ACM Global Central Laboratory
- Value and change from Baseline (absolute and percentage) in total IgG concentrations (measured by ACM Global Central Laboratory) to each visit in the Dosing Period and in the Observation Period up to Day 85 in Dose Arm 1, up to Day 71 in Dose Arm 2, up to Day 64 in Dose Arm 3 and up to Day 57 in Dose Arms 4 and 5
- ITP-specific autoantibodies in serum [redacted] over time, measured at Day 1, Day 36 and Day 85 in Dose Arm 1, at Day 1, Day 22 and Day 71 in Dose Arm 2, at Day 1, Day 15, and Day 64 in Dose Arm 3 and at Day 1, Day 8 and Day 57 in Dose Arms 4 and 5
- Change from Baseline in IgG subclass concentrations (measured by ACM Global Central Laboratory) to each visit in the Dosing Period and in the Observation Period up to Day 85 in Dose Arm 1 and up to Day 71 in Dose Arm 2, up to Day 64 in Dose Arm 3 and up to Day 57 in Dose Arms 4 and 5

2.2.4 Other immunological variables

Other immunological variables are:

- Change from Baseline in serum immunoglobulin concentrations (total IgA, IgE, and IgM) to the last visit in the Dosing Period and to Day 36 and Day 71 in the Observation Period in Dose Arm 1, to Day 22 and Day 57 in the Observation Period in Dose Arm 2, to Day 15 and Day 50 in the Observation Period in Dose Arm 3 and to Day 8 and Day 43 in the Observation Period in Dose Arms 4 and 5
- Change from Baseline in serum (C3 and C4) and plasma (C3a and C5a) complement levels to Day 15 (Dosing Period) and to Day 32 and Day 57 in the Observation Period in Dose

Arm 1, to Day 15 (Dosing Period) and to Day 18 and Day 43 in the Observation Period in Dose Arm 2, to Day 11 and Day 36 in Observation Period in Dose Arm 3 and to Day 4 and Day 29 in Observation Period in Dose Arms 4 and 5

- Change from Baseline in exploratory biomarkers relating to mechanism of action, disease activity, treatment response, and clinical outcome
- Value and change from Baseline in ADA relative mass units (RMU) to each visit in the Dosing Period and to Day 32, Day 36, Day 43, Day 57, Day 71 and Day 85 in the Observation Period in Dose Arm 1, and to Day 18, Day 22, Day 29, Day 43, Day 57 and Day 71 in the Observation Period in Dose Arm 2, to Day 11, Day 15, Day 22, Day 36, Day 50 and Day 64 in Dose Arm 3 and to Day 4, Day 8, Day 15, Day 29, Day 43 and Day 57 in Dose Arms 4 and 5
- Anti-drug antibody screening status (positive/negative) at each of the visits described above. For ADA screening positive results the confirmatory ADA result will be reported as either confirmed positive (CP) or not confirmed positive (NCP).
- Change from Baseline in cytokines over time. Cytokines will be measured at all visits in all dose arms for subjects who experience infusion reactions only. Further description of the cytokines variables can be found in Appendix 13.4. Additional exploratory biomarkers may be investigated if needed using the samples already available.
- Change from Baseline in serum B cell activating factor (BAFF) levels to each dosing visit in the Dosing Period and to Day 43 and Day 71 in the Observation Period in Dose Arm 1, to Day 29 and Day 57 in the Observation Period in Dose Arm 2, to Day 22 and Day 50 in the Observation Period in Dose Arm 3 and to Day 15 and Day 43 in the Observation Period in Dose Arms 4 and 5
- Change from Baseline in B- and T-lymphocyte concentrations to each visit in the Dosing Period and in the Observation Period up to Day 85 in Dose Arm 1, up to Day 71 in Dose Arm 2, up to Day 64 in Dose Arm 3 and up to Day 57 in Dose Arms 4 and 5

2.3 Study design and conduct

This is a Phase 2, multicenter, open-label, multiple-dose, multiple-arm study to evaluate the safety, tolerability, and efficacy of UCB7665 in subjects with primary persistent or chronic ITP. The 5 dose arms will be as follows:

- Dose Arm 1 (15 subjects): UCB7665 4mg/kg sc (5 doses at an interval of 1 week)
- Dose Arm 2 (15 subjects): UCB7665 7mg/kg sc (3 doses at an interval of 1 week)
- Dose Arm 3 (6 to 12 subjects): UCB7665 10mg/kg sc (2 doses at intervals of 1 week)
- Dose Arm 4 (6 to 12 subjects): UCB7665 15mg/kg sc (1 dose)
- Dose Arm 5 (6 to 12 subjects): UCB7665 20mg/kg sc (1 dose)

The maximum duration of the study per subject is approximately 16 weeks, consisting of a Screening Period (1 to 28 days), a Dosing Period of 1 to 4 weeks, and an Observation Period of 8 weeks.

A data monitoring committee (DMC) will monitor emergent safety data during the study. The first 6 subjects in the study will receive UCB7665 4mg/kg. These subjects in Dose Arm 1 will not be randomized. While recruitment is still ongoing safety data for the first 3 subjects up to 7 days after the final dose of the third subject in Dose Arm 1 will be reviewed by the DMC.

During a second DMC meeting, all available safety data up to the cut off date defined as 7 days after the final dose of the sixth subject in Dose Arm 1 will be reviewed. During these reviews recruitment in the dose arm will not be stopped. Following this review, the DMC will make a decision on whether to open Dose Arm 2 for enrollment. Once the DMC has advocated the initiation of Dose Arm 2, the subsequent subjects will be randomly assigned in 1:1 ratio to either Dose Arm 1 or Dose Arm 2 using an interactive voice/web response system (IXRS). Once 15 subjects are enrolled in Dose Arm 1, the remaining subjects will enrolled in Dose Arm 2.

After the safety data review of at least 6 subjects in Dose Arm 2 is done, the DMC will make a recommendation on whether to open Dose Arm 3 for enrollment. Once the DMC has advocated the initiation of Dose Arm 3 and the enrollment of 15 subjects in Dose Arm 2 has been completed, the subsequent subjects will be assigned to Dose Arm 3 only. After every third subject has been enrolled, the DMC will review all available safety data up to cut off date defined as 7 days after the dosing. Depending on the emerging safety data of 6 subjects in Dose Arm 3, the DMC will recommend whether to open Dose Arm 4 for enrollment or to include additional subjects in Dose Arm 3. A maximum of 12 subjects may be enrolled in Dose Arm 3.

Once the DMC has advocated the initiation of Dose Arm 4, the enrollment of Dose Arm 3 will be closed and all subsequent subjects will be assigned to Dose Arm 4. After every third subject is enrolled, the DMC will review all available safety data up to the cutoff date defined as 7 days after the dosing. Depending on the emerging safety data of 6 subjects in Dose Arm 4, the DMC will recommend to include additional subjects in Dose Arm 4 or not. A maximum of 12 subjects may be enrolled in Dose Arm 4. The DMC will recommend to open Dose Arm 5 for enrollment in a subsequent meeting, if applicable.

Once the DMC has advocated the initiation of Dose Arm 5, the enrollment of Dose Arm 4 will be closed and all subsequent subjects will be assigned to Dose Arm 5. After every third subject is enrolled, the DMC will review all available safety data up to the cutoff date defined as 7 days after the dosing. Depending on the emerging safety data of 6 subjects in Dose Arm 5, the DMC will recommend to include additional subjects in Dose Arm 5. A maximum of 12 subjects may be enrolled in Dose Arm 5.

At least 11 interim analyses will be performed. Based on the interim analyses the DMC will assess the safety of UCB7665, determine whether to initiate subsequent dose arms and may decide to adapt the dose regimen. The analyses and TFLs required for the interim analyses are described in a separate interim SAP.

During this study, subjects will also have the option of providing additional informed consent for exploratory deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) analyses. Participation in this additional portion of the study is optional and does not preclude subject's eligibility for participation in the main study. The additional genomic samples must not be collected if the subject has not consented to participate in this exploratory genomic substudy. Any results from this analysis will be reported separately and will not form a part of the main CSR. Thus, these analyses are not described further in this SAP.

During this study, subjects from Bulgaria, Georgia and Moldova who are enrolled in Dose Arm 3, 4 or 5, will also have the option of providing additional informed consent for a PK/PD substudy (early blood sampling) at selected study sites. Participation in this additional portion of the study is optional and does not preclude subject's eligibility for participation in the main study. The additional PK/PD blood samples must not be collected if the subject has not consented to participate in this exploratory substudy.

2.4 Determination of sample size

The sample size of 15 subjects in Dose Arms 1 and 2, is mainly based on the efficacy objective of the study. In addition, the inclusion of 15 subjects in Dose Arms 1 and 2 will ensure that sufficient data are available to form conclusions about the safety of administering UCB7665. Based on the safety data from Dose Arms 1 and 2, the sample size of 6 to 12 subjects in Dose Arms 3, 4 and 5 were judged to be sufficient in order to explore subjects' safety and IgG reductions under different dose regimens and is not based on a formal sample size calculation.

For Dose Arms 1 and 2 an approximate sample size calculation for the efficacy variable "maximum increase from Baseline in platelet count" shows that 15 subjects would be sufficient to show a change from Baseline with 1-sided testing at 5% and power of 80%. The anticipated change is based on an assumed Baseline average of $25x10^9$/L and a clinically meaningful maximum value of $100x10^9$/L. The calculation made use of platelet count data presented in a publication by Robak (Robak et al, 2009), but it is approximate as maximum changes from Baseline for individual subjects were not available, necessitating the use of the maximum average platelet count instead. The standard deviation (SD) is taken from visual inspection.

With 15 subjects, the responder endpoints will confirm a true 50% response rate, in excess of the maximum 15% anticipated with no treatment benefit, with power in excess of 80%.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical evaluation will be performed by PAREXEL. The datasets will follow the UCB analysis data model (ADaM) specifications.

All analyses will be performed using SAS version 9.3 or higher (SAS Institute, Cary, North Carolina, United States of America). Continuous variables will be summarized by visit (where applicable) including number of subjects (n), arithmetic mean, SD, median, minimum and maximum. Categorical variables will be summarized by visit (where applicable) with frequency counts and percentages with 95% confidence intervals (CI) where stated. Geometric coefficient of variation (geoCV), geometric mean (geoMean) and 95% CI for the geoMean will also be presented in the descriptive statistics for the PK concentration data.

When reporting relative frequencies or other percentage values, the following rules apply:

- For values where all subjects fulfill certain criteria, the percentage value will be displayed as 100
- For values where the absolute frequency is zero, there will be no percentage displayed at all
- All other percentage displays will use 1 decimal place

Percentages displayed based on continuous data (eg, percentage changes from baseline) will be displayed to 1 decimal place.

When reporting descriptive statistics, the following rules will apply in general:

- n will be an integer
- Mean (arithmetic and geometric), SD and median will use 1 decimal place more than the original data
- Minimum and maximum will be reported using the same number of decimal places as the original value
- If no subjects have data at a given timepoint, for example, then only n=0 will be presented. If n<3, present the n, minimum and maximum only. If n=3, present the n, mean, median, minimum and maximum only. The other descriptive statistics will be left blank.

When reporting descriptive statistics for PK data, the following rules will apply with regard to rounding and precision:

- Individual values for PK concentration data will be reported to the same level of precision as received from the bioanalytical laboratory
- Descriptive statistics for PK concentration data will be reported to the same level of precision as the individual data for the minimum and maximum, and to 1 additional significant figure for the mean (arithmetic and geometric), median, SD and 95% CI for the geoMean
- Geometric CV will be reported as a percentage to 1 decimal place

All statistical tests will be carried out 1-tailed at the 5% level of significance unless otherwise stated. P-values will be presented to 4 decimal places; p-values less than 0.0001 will be presented as "<0.0001" and p-values greater than 0.9999 will be presented as ">0.9999". All statistical output will be presented in statistical appendices where appropriate.

Analyses will be performed by dose arm for all efficacy, immunological, PK, PD and safety data, with the exception of adverse event (AE) data which will be presented by dose arm and overall (Section 13.6).

In the event that the number of planned infusions in the dose arms are modified following review by the DMC, the data will be summarized based on the actual dose arms completing the study. For example, if the 5x4 mg/kg QWK dose arm is modified such that some subjects receive only 4 infusions, then the data will be summarized separately for this new dose regimen.

In the TFLs the dose arms will be displayed as follows where applicable:

- UCB7665 5x4mg/kg
- UCB7665 3x7mg/kg
- UCB7665 2x10mg/kg
- UCB7665 1x15mg/kg
- UCB7665 1x20mg/kg

If additional dose arms are initiated during the study these will be displayed similarly. For example, if the 5x4 mg/kg QWK dose arm is modified such that some subjects receive only 4 infusions this dose arm will be displayed as UCB7665 4x4mg/kg QWK in the TFLs.

Data listings containing all documented data and all derived data will be generated.

3.2 General study level definitions

3.2.1 Analysis timepoints

3.2.1.1 Relative day

Relative day for an event will be derived with the date of the first infusion of UCB7665 as reference.

Relative days for an event of measurement occurring before the date of first infusion are calculated as follows:

Relative Day = [(Event Date – Date of First Infusion)]

The relative day for an event or measurement occurring on or after the reference date to the date of the last infusion is calculated as follows:

Relative Day = [(Event Date - Date of First Infusion) + 1]

For events or measurements occurring after the date of the last infusion, relative day will be prefixed with '+' in the data listings and will be calculated as follows:

Relative Day = + [(Event Date – Date of Last Infusion)]

There is no relative Day 0. Relative day is not calculated for partial dates in cases where relative day is shown in a subject data listing. In such cases, relative day should be presented as '-' in the subject data listings.

3.2.1.2 Study periods

For each subject the duration of the study is approximately 16 weeks.

- Screening Period: 1 to 28 days
- Dosing Period: 1 to 4 weeks; during the Dosing Period subjects will receive weekly doses of UCB7665 (5 doses of 4mg/kg [QWK] in Dose Arm 1, 3 doses of 7mg/kg [QWK] in Dose Arm 2, 2 doses of 10mg/kg [QWK] in Dose Arm 3, 1 dose of 15mg/kg in Dose Arm 4 and 1 dose of 20mg/kg in Dose Arm 5). The dose regimen may be adapted following review by the DMC
- Observation Period: 8 weeks; a visit will be scheduled 3 days after the final dose (or only dose administration for Dose Arms 4 and 5) and weekly thereafter to collect safety and efficacy data

The end of the study is defined as the date of the last visit of the last subject in the study.

3.3 Definition of Baseline values

Baseline will be the last available predose value prior to the first infusion of UCB7665, or if missing, the latest non missing value prior to Baseline (screening value or unscheduled visit value).

Measurement-specific Baseline timepoints (based on the scheduled or unscheduled measurements) are presented in Table 3–1.

Table 3–1: Definition of Baseline

Measurement	Definition of Baseline
Safety data: • Clinical chemistry (including proteins) • Hematology (including platelets measured locally) • Coagulation • Urinalysis • Vital signs • 12-lead ECG • Serum safety biomarkers [redacted]	• Predose Day 1 or if missing the latest non missing value prior to Day 1
Efficacy variables: • Platelets (measured by ACM Global Central Laboratory) • ITP bleeding scale • NFI-MS	• Platelets: Predose Day 1 or if missing the latest non missing value prior to Day 1 • ITP bleeding scale: Predose Day 1 or if missing the latest non missing value prior to Day 1 • NFI-MS: Predose Day 1
Pharmacodynamic variables: • Total IgG • IgG subclasses • • ITP-specific autoantibodies in serum [redacted]	• Total IgG: Predose Day 1 or if missing the latest non missing value prior to Day 1 • IgG subclasses: Predose Day 1 or if missing the latest non missing value prior to Day 1 • ITP-specific autoantibodies: Predose Day 1
Immunological variables: • Immunoglobulins (IgA, IgE and IgM) • B- and T-lymphocytes • Serum (C3 and C4) and plasma complement (C3a and C5a) • ADA • Serum BAFF • Cytokines, if applicable (as outlined in the protocol)	• Predose Day 1 (except B- and T-lymphocytes) • B- and T-lymphocytes: Predose Day 1 or if missing the latest non missing value prior to Day 1

ADA=anti-drug antibody; BAFF= B cell activating factor; ECG=electrocardiogram; Ig=immunoglobulin; ITP=primary immune thrombocytopenia; NFI-MS= Neurological Fatigue Index for Multiple Sclerosis; [redacted]

If a measurement is repeated at Baseline and is obtained prior to receiving the first dose of UCB7665, then the last available measurement will be used as the Baseline value.

For the platelet count performed at Screening (measured by ACM Global Central Laboratory only), 2 separate blood samples will be obtained on the same day. If the latest non missing value prior to Baseline is to be used as Baseline (i.e., predose Day 1 is missing), the highest value for the platelet count obtained from the last 2 non missing measurements prior to Baseline will be used as the Baseline.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary efficacy, key safety, or PK/PD outcomes (if applicable) for an individual subject. The criteria for identifying such protocol deviations will be defined within the important protocol deviation specifications which is part of the data cleaning plan. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important protocol deviations will be discussed and documented at the data evaluation meeting (DEM) together with any decisions regarding exclusion from analysis sets.

3.5 Analysis sets

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects who have given informed consent. This will include screening failures. Screening failures will be labeled as 'not treated' in any outputs based on the ES.

3.5.2 Safety Set

The Safety Set (SS) will consist of all subjects who have received at least 1 infusion (full or partial infusion) of UCB7665 and will be used for the analysis of safety data.

3.5.3 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects who have received at least 1 infusion (full infusion) of UCB7665 and, in addition, have a Baseline and at least 1 post-Baseline measurement for platelet count (measured by ACM Global Central Laboratory).

The analysis of the PD (excluding total IgG and IgG subclasses), efficacy and immunologic variables will be performed on the FAS. Efficacy analyses will be repeated for the pharmacodynamics per protocol set (PD-PPS) where stated in the SAP.

Platelet data for subjects who have taken rescue medications (based on medical review and defined in Section 8.1.4) will only be utilized in the summary tables up to the start of these rescue medications.

3.5.4 Per Protocol Set

The Per Protocol Set (PPS) is a subset of the FAS, consisting of those subjects who had received all foreseen sc infusions, had a platelet count measurement (measured by ACM Global Central Laboratory) during the Observation Period, and no important protocol deviations that may potentially affect the platelet count as confirmed during a pre-analysis review of the data prior to database lock. Protocol deviations may not necessarily lead to total exclusion of a subject from the PPS but may lead to exclusion of specific data and/or timepoints from the analysis.

Platelet data for subjects who have taken prohibited medications potentially affecting platelet counts such as IV corticosteroids, TPO-Rs, Oral corticosteroids, immunosuppressants (based on medical review) will only be utilised in the summary tables, up to the start date of these prohibited medications.

3.5.5 Pharmacokinetic Per Protocol Set

The Pharmacokinetic Per Protocol Set (PK-PPS) is a subset of the FAS, consisting of those subjects who had no important protocol deviations potentially affecting the plasma concentration of UCB7665, as confirmed during a pre-analysis review of the data prior to database lock.

3.5.6 Pharmacodynamic Per Protocol Set

The Pharmacodynamic Per Protocol Set (PD-PPS) is a subset of the FAS, consisting of those subjects who had no important protocol deviations potentially affecting the serum concentration of total IgG, as confirmed during a pre-analysis review of the data prior to database lock. Protocol deviations may not necessarily lead to total exclusion of a subject from the PD-PPS but may lead to exclusion of specific data.

The PD-PPS will be used for the analysis of the total IgG and IgG subclasses.

3.6 Treatment assignment and treatment groups

Treatment (dose arm) assignment for the SS, FAS, PK-PPS, PD-PPS and the PPS will be according to the planned treatment regimen (reflecting the potential DMC decisions).

In the event that the number of planned infusions in the dose arms are modified following review by the DMC, the data will be summarized based on the actual dose arms completing the study. For example, if the weekly 5x4mg/kg QWK dose arm is modified such that some subjects receive only 4 infusions, then the data will be summarized separately for this new dose regimen.

Analyses will be performed by dose arm, unless otherwise stated.

3.7 Center pooling strategy

The clinical study will be conducted in multiple centers in Europe and Australia. The data from different sites will be pooled for all analyses. There will be no analyses by site or country performed.

3.8 Coding dictionaries

Adverse events and medical history will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA®).

Medications will be coded according to the World Health Organization Drug Dictionary (WHODD [September 2015]). Medical procedures will not be coded.

3.9 Changes to protocol-defined analyses

The protocol stated that changes from Baseline would be evaluated for the ITP-specific autoantibodies. However, as these data are semi-quantitative, changes from Baseline are not considered an appropriate way to present the results and would not provide any additional information. Thus, only absolute values over time will be reported.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

There will be no adjustment for covariates.

4.2 Handling of dropouts or missing data

In general, there will be no imputation of missing data unless otherwise stated below.

4.2.1 Efficacy data

There will be no imputation of missing platelet data (measured by ACM Global Central Laboratory) or missing data for the ITP bleeding score. Missing data for the calculation of the NFI-MS summary score will be handled as described in Section 13.2.

4.2.2 Safety laboratory data

Measurements below the limit of quantification (BLQ) will be imputed with half of the lower limit of quantification (LLOQ) for the purpose of calculating change from Baseline and for descriptive statistics. Measurements above the limit of quantification (ALQ), if applicable, will be imputed to the upper quantification limit.

These rules will be applied to all safety laboratory data including coagulation parameters, clinical chemistry and urinalysis.

4.2.3 Pharmacodynamic data

Measurements BLQ are not anticipated in the PD data (total IgG [measured by ACM Global Central Laboratory] and IgG subclasses). In the event that any BLQ measurements are received, these will be discussed at the DEM.

For the ITP-specific autoantibodies any measurements that are above the limit of detection (ALD) will be imputed with the value of the upper quantification limit for the calculation of summary statistics.

4.2.4 Immunological data

The rules for handling BLQ or ALQ measurements for all immunological data (including IgA, IgE, IgM, B- and T-lymphocytes, serum and plasma complement, serum biomarkers (including BAFF), ADA and cytokines) will be as described in Section 4.2.2.

For all immunological data, measurements that are BLQ will be imputed with LLOQ/2 for individual plots.

4.2.5 UCB7665 concentration data

Measurements that are BLQ will be imputed with LLOQ/2 for the purpose of calculating the geoMean and its 95% CI, the geoCV, the arithmetic mean, and SD for summaries and figures.

For the individual figures, any concentrations that are BLQ will be imputed with LLOQ/2, with the exception of predose BLQ measurements on Day 1, which will be imputed with zero for linear scale plots.

Additional rules for PK data summaries are provided in Section 9.1.

4.2.6 Electrocardiogram data

For the ECG data, all calculations of changes from Baseline and descriptive statistics will be based on the mean of the triplicate assessments at each visit. In the event that there are not 3 available measurements at a given visit, the mean will be calculated based on the number of measurements for which data is provided (variables analyzed will be those described in Section 10.4.2).

4.2.7 Dates and times

Partial dates may be imputed for the following reasons:

- Classification of AEs as treatment-emergent
- Classification of medications as past, prior or concomitant

Imputed dates will not be shown in the listings; all dates will be displayed as reported in the database.

The following rules will be applied for partial start dates:

- If only the month and year are specified and the month and year of first dosing is not the same as the month and year of the start date then use the 1st of the month, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month). If time is missing this will be imputed as 00:00 h;
- If only the month and year are specified and the month and year of first dosing is the same as the month and year of the start date, then use the date of first dosing. If this results in an imputed start date that is after the specified end date, then use the 1st of the month, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month). If the imputed date is the date of first dosing then time will be imputed as the start time of the infusion (i.e., event will be regarded as treatment-emergent);
- If only the year is specified, and the year of dosing is not the same as the year of the start date then use January 01 of the year of the start date. If time is missing this will be imputed as 00:00 h;
- If only the year is specified, and the year of dosing is the same as the year of the start date, then use the date of dosing. If this results in an imputed start date that is after the specified end date, then use January 01 of the year of start date, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use January 01). If the imputed date is the date of first dosing then time will be imputed as the start time of the infusion (i.e., event will be regarded as treatment-emergent);
- If the start date is completely unknown, then use the date of first dosing. If this results in an imputed start date that is after the specified end date, then use January 01 of the year of the end date, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use January 01). If the imputed date is the date of first dosing then time will be imputed as the start time of the infusion (i.e., event will be regarded as treatment-emergent).

Start and end time is not recorded for concomitant medications, thus no imputations for missing times will be performed. Any medication with a start date on the first dosing date, will be assumed to be concomitant.

The following rules will be applied for partial stop dates:

- If only the month and year are specified, then use the last day of the month;
- If only the year is specified, then use December 31 of the known year;
- If the stop date is completely unknown, do not impute the stop date, except for ITP medications where end date is missing and ongoing is ticked as 'no', which will be imputed as "Past" medications.

Missing or partially missing date and/or times will be imputed as described in Table 4–1 for the calculation of duration of each AE. Adverse event duration is computed and reported in day and time format: xx d hh:mm.

Table 4–1: Calculation rules for duration of adverse events

Data availability	Onset date/time	Outcome date/time	Calculation rules
Complete data	D1/T1	D2/T2	Duration = [(D2 – D1)*24 + (T2 – T1)]/24 d
End time missing	D1/T1	D2/--	End time is substituted by time 23:59h (=23.98 in decimal format) Duration = <[(D2 – D1)*24 + (23.98 – T1)]/24 d
Start time missing	D1/--	D2/T2	Onset time is substituted by time 00:00h. Duration = <[(D2 – D1)*24 + T2]/24 d
Start and end time missing	D1/--	D2/--	Duration = <D2 – D1 + 1
Start day and time missing	--/--	D2/T2	Duration = <[(D2 – D0)*24 + (T2 – T0)]/24 d For a subject in the SS, D0 and T0 are the date and time of first administration of UCB7665 and for screen failures, D0 is the date of the screening visit and T0 = 00:00h
End day and time missing	D1/T1	--/--	For ongoing AE: Duration = >Discharge day – D1 d For resolved AE: Duration = <Discharge day – D1 d Where discharge refers to the date of the end of study visit or the date of discontinuation for subjects that were withdrawn. For any AEs with known start date/time after the date of discontinuation, the date of last contact will be used as the discharge day.

Table 4–1: Calculation rules for duration of adverse events

Data availability	Onset date/time	Outcome date/time	Calculation rules
Start and end date missing	--/--	--/--	For ongoing AE: Duration = >Discharge day – D0 d For resolved AE: Duration = <Discharge day – D0 d For a subject in the SS, D0 and T0 are the date and time of first administration of UCB7665 and for screen failures, D0 is the date of the screening visit and T0 = 00:00h. Discharge refers to the date of the end of study visit or the date of discontinuation for subjects that were withdrawn. For any AEs with known start date/time after the date of discontinuation, the date of last contact will be used as the discharge day.

4.3 Handling of repeated and unscheduled measurements

All repeated and unscheduled measurements will be presented in the listings, where applicable. The following general rules will apply to all repeated and unscheduled measurements:

- For repeated and unscheduled measurements obtained prior to the first dose of UCB7665 the latest value (which may be scheduled or unscheduled) will be used in the calculation of descriptive statistics;
- For repeated and unscheduled measurements obtained at the designated Baseline visit, the latest value (which may be scheduled or unscheduled) will be defined as the Baseline provided that this occurred prior to the first dose of UCB7665;
- For repeated measurements obtained at any timepoint after the first dose of UCB7665, the first value of any repeated measurements will be used in the calculation of changes from Baseline and for the descriptive statistics. Unscheduled and repeated measurements will not be included in the descriptive statistics at timepoints after the first dose of UCB7665, however they may be included in any summaries for abnormal measurements.

The above rules are not applicable for the determination of the response variables for the platelet measurements; both scheduled and unscheduled measurements may be used in the calculation of response, time to response and duration of response (Section 8.1.1).

4.4 Interim analyses and data monitoring

For the sequential adaptive design in this study, at least 11 interim analyses will be performed. Safety data from the interim analyses will be reviewed by the DMC to monitor the safety, to adapt the dose regimen, and to decide when and if the UCB7665 7mg/kg weekly group (Dose Arm 2), UCB7665 10mg/kg weekly group (Dose Arm 3), UCB7665 15mg/kg group (Dose Arm

4) and UCB7665 20mg/kg group (Dose Arm 5) should be opened, as well as whether the doses in any of the treatment groups should be modified.

A detailed description of the DMC composition, processes and responsibilities will be provided in a separate DMC Charter. The data required for review as well as the timing of each interim analysis is described in a separate interim SAP and includes all data specified in the DMC Charter, which is available at the time. For the interim analyses the data, subject to analysis, should be as clean as possible; however, the database will not be locked and a snapshot will be taken.

4.5 Multicenter studies

Individual center results will not be displayed.

4.6 Multiple comparisons/multiplicity

Not applicable.

4.7 Active-control studies intended to show equivalence

Not applicable.

4.8 Examination of subgroups

The following subgroups will be defined within each dose arm:

- Concomitant corticosteroid medication: Yes/No

  Concomitant medication is defined in Section 6.4.4. The list of applicable Anatomical Therapeutic Chemical (ATC) codes to be utilized as corticosteroids is provided in Section 13.1.

- Responder at the end of past ITP therapy: No/Yes/Unknown

  Responder categories will be defined utilizing the value (either Yes or No) for the last reported ITP therapy for each patient. If this value is unknown, the second-last reported ITP therapy value will be used, then the third-last, and so on, until a known response is provided. The Unknown responder category will only be considered in cases where the investigator has never reported a category (Yes or No) for any of the past ITP therapies. For the 'Response' definition, the CRF entries will be utilized.

  The past ITP therapy is defined as procedure history related to ITP or past medication related to ITP, where past medication is defined in Section 6.4.1. For 'related to ITP' CRF entries will be utilized.

  The corticosteroid medication given more than 3 months prior to screening was routinely not recorded and cannot be considered. Thus, some patients with an unknown response might have had a known response.

- Past intravenous immunoglobulin (IVIg) medication: Yes/No

  Past medication is defined in Section 6.4.1. The ATC Therapeutic Subgroup code (Level 2) 'IMMUNE SERA AND IMMUNOGLOBULINS' will be utilized.

- Number of past ITP therapies: ≤2/>2

The past ITP therapy is defined as procedure history related to ITP or past medication related to ITP, where past medication is defined in Section 6.4.1. For 'related to ITP' CRF entries will be utilized.

The corticosteroid medication given more than 3 months prior to screening was routinely not recorded and cannot be considered. Thus, some patients might have had 1 more past ITP therapy than utilized for subgroup determination.

The descriptive summaries for platelets and total IgG will be presented for the subgroups above.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The number of subjects who were enrolled, dosed, subjects included in each analysis set, and subjects who completed or prematurely discontinued the study, as well as the reason for discontinuation, will be presented by dose arm and overall. Screen failure reasons will be summarized, based on the ES.

In addition, the following listings will be presented by dose arm:

- Subject disposition (ES)
- Study discontinuation (SS)
- Visit dates (SS)
- Subject analysis sets (ES)

The listing of subject disposition will include the date of informed consent, date of genomic consent (if applicable), date of randomization (if applicable), date and time of first and last dose of UCB7665 (if applicable), date of premature termination and primary reason (if applicable) and date of final contact.

The listing of study discontinuation will include the reason for discontinuation and the number of days on UCB7665.

The number of days on UCB7665 will be calculated as follows:

Number of days on UCB7665= [(Date of Last Dose Received) – (Date of First Dose Received)] + 1

5.2 Protocol deviations

Important protocol deviations will be identified and classified by the deviation types identified in the important protocol deviations document. A listing of all important protocol deviations identified at the DEM will be presented for all subjects in the SS, and will include the deviation type and description. The number and percentage of subjects in the SS with important protocol deviations will be summarized by dose arm and overall. The denominator for percentages will be the number of subjects in the SS.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

A by-subject listing of Baseline demographics will be presented by dose arm for the ES. This will include the year of birth (if available), age (in years), sex, race, ethnicity, height (in cm), weight (in kg) and body mass index (BMI). The age will be directly entered into the study database and will not be re-calculated for the statistical analysis.

BMI in kg/m^2 is calculated based on the height (in m) and the weight (in kg) using the following formula:

$$\text{BMI } (kg/m^2) = \text{weight (kg)}/[\text{height (m)}]^2$$

BMI will be reported to 1 decimal place.

All Baseline demographic characteristics (with the exception of year of birth) will be summarized by dose arm and overall for the SS. Number and percentage of patients with a BMI equal or higher than 30 will also be summarized by dose arm.

The summary of age will include descriptive statistics and categorical summaries, the latter based on requirements for EudraCT and clinicaltrials.gov reporting.

For the EudraCT reporting, the categories will include:

- 18 to <65 years
- 65 to <85 years
- ≥85 years

For the clinicaltrials.gov reporting, the categories will include:

- ≤18 years
- 19 to <65 years
- ≥65 years

Childbearing potential will be listed for the SS.

6.2 Other Baseline characteristics

Baseline disease characteristics will be listed and summarized by dose arm for the SS including the following:

- Duration of disease
- Karnofsky Performance Scale Index
- ITP bleeding scale (skin, visible mucosae and organs, with gradation of severity [SMOG])
- ITP-specific autoantibodies [redacted] expressed in terms of optical density (OD) for MAIPA analysis and pre-chloroquine minus post chloroquine treated scores for PIFT

- Immunological variables (IgG [including total IgG and IgG subclasses measured by ACM Global Central Laboratory], IgM, IgA, IgE and lymphocytes [B and T])
- Serum (C3 and C4) and plasma complement levels (C3a and C5a)
- Platelet count (measured by ACM Global Central Laboratory)
- Number of prior ITP medications received
- Number of prior ITP medications received categorized
- Prior ITP medications received by preferred term
- Medical history of splenectomy (MedDRA v20.2, Preferred Term=”Splenectomy”)

The duration of disease will be calculated as follows, where the date of diagnosis will be obtained from the ITP history page of the case report form (CRF):

Duration (years) = (Date of Screening – Date of Diagnosis)

If the date of diagnosis is missing, the duration of disease will not be calculated. In the case of the start day being missing, the day will be imputed with the 1st of the month in the calculation of the disease duration. In the case of the start day and month being missing, the date will be imputed with 01 January in the calculation of the disease duration.

The disease duration will be presented in years to 1 decimal place in the listings.

The Karnofsky Performance Scale index is a semi-quantitative score ranging from 0 to 100% in intervals of 10, where 0% is death and 100% is normal (no complaints, no evidence of disease). Summary statistics for the Karnofsky Performance Scale will include n, median, minimum and maximum only.

The ITP bleeding scale will be summarized (n, median, minimum and maximum) by dose arm for each domain (SMOG).

6.3 Medical history and concomitant diseases

Medical history will be summarized for the SS by dose arm and for all subjects by MedDRA system organ class (SOC), high level term (HLT) and preferred term (PT). The listing will also include the reported condition and the start and end date (or ongoing, if applicable). Procedure history and history of thrombocytopenia will be listed separately by dose arm for the procedure reported term based on the SS.

Concomitant medical procedures performed during the study will be listed for the SS.

6.4 Past, prior, baseline and concomitant medications

Past, prior, baseline and concomitant medications will be summarized for the SS by dose arm and for all subjects by WHODD Anatomical Main Group [Level 1], Therapeutic Subgroup [Level 2] and PT.

All medications will be listed and will include coding information, reported term, dose per intake and unit, frequency, formulation, route of administration, indication, category (past/prior and concomitant/concomitant) and start and end date (or ongoing, if applicable).

6.4.1 Past medication definition

Past medications will include any medications that started and stopped prior to the first administration of UCB7665.

6.4.2 Prior medication definition

Prior medications will include any medications that started prior to the first administration of UCB7665. This includes medications that started and stopped prior to dosing (past medications) as well as those that started prior to dosing and continued after (classified as prior and concomitant medications).

6.4.3 Baseline medication definition

Baseline medications will include any medications that started prior to dosing and continued after (classified as prior and concomitant medications).

6.4.4 Concomitant medication definition

Concomitant medications will include any medication that has been taken at least once (after the first administration of UCB7665) during the Dosing Period and/or the Observation Period.

This includes medications that started prior to the dosing and continued after (classified as prior and concomitant medications) as well as any medication that started after the first administration of UCB7665 (classified as concomitant).

Any medications with missing dates and/or times will be handled as described in Section 4.2.7 in order to classify them as prior and/or concomitant.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

The study medication will be administered and monitored by the investigator or designee. The measured plasma concentrations will provide information regarding compliance. Any dosing deviations (eg, incomplete infusion volume administered, infusion discontinued) will be discussed at the DEM and any actions taken regarding the analyses will be documented accordingly and discussed in the CSR.

There will be no specific analysis of compliance. Exposure to UCB7665 will be presented as described in Section 10.1.

8 EFFICACY ANALYSES

All analyses of the efficacy variables will be performed on the FAS. Additional outputs may be repeated for the PPS where indicated. Treatment (dose arm) assignment for efficacy analysis will be according to the actual treatment regimen.

8.1 Platelets

All efficacy analyses are based on platelet count measured by ACM Global Central Laboratory. Measurements of platelet count obtained by the local laboratory will be listed and summarized as part of the safety laboratory data. These are not included in the analyses described in the sections below. All tabulations and mean figures will be presented for both the FAS and the PPS unless otherwise stated. Median figures and individual figures will be presented for the FAS only. In case rescue medications are taken, only the platelet data up to the start date of rescue medication will be utilized for the summary tables (refer to Section 8.1.4). In case prohibited medications

affecting platelets are taken, only the platelet data up to the start date of prohibited medication will be utilized for the summary tables for the PPS (refer to Section 3.4). Listings will contain all the data but a footnote will be included indicating the patients for which some data has been excluded from the summary tables. In case of partial dates, the imputation rules for partial dates described in Section 4.2.7 will be applied.

8.1.1 Definition of variables

The main efficacy variable is defined as the following:

- Maximum Increase from Baseline: the Maximum Increase from Baseline (Day 1, predose) is defined as the highest positive change from Baseline during the study. In the event that the platelet count was to decrease during the study the Maximum Increase from Baseline may be negative and would correspond to the smallest decrease from the Baseline value.

The following additional variables will be defined for the platelet count, the calculation rules for which are provided in the section immediately below:

- Response: a platelet count $\geq 30x10^9$/L and at least 2-fold increase from the Baseline value, by visit, and at any timepoint during the study
- Time to Response: the first time that a given response is achieved during the study. Thus, in the event that the platelet count was to increase above the threshold level, decrease below the threshold level, and subsequently increase again the time to response would be to the first time the definition of response was achieved. The time to response will be calculated in days and presented to 1 decimal place in the listings.

  Time to response (days) = Date/time of first response – Date/time of first dose of UCB7665
- 'No' or 'Loss of' Response: a platelet count $<30x10^9$/L OR $>=30x10^9$/L WITHOUT at least a 2-fold increase from the Baseline value, by visit
- Duration of Response (including Complete Response, Response and Platelet Count $\geq 50x10^9$/L): the duration of the first time the response was achieved to first loss of response. The duration of response will be calculated in days and presented to 1 decimal place in the listings.

  Duration of response (days) = Date/time of loss of first response – Date/time of first response, where "loss of first response" is defined as platelet count$<30x10^9$/L OR (platelet count $\geq 30x10^9$/L WITHOUT at least a 2-fold increase from the Baseline value)

  If the platelet value meets the criterion for a specific response for a second time (following a loss of initial response), the second response period will be added to the overall duration of response. This rule will be applied for any subsequent 'response periods'. For subject in whom the response is maintained until the end of the study the duration of response will be calculated using the date of the end of study visit as the 'end of response date'. Any such cases will be flagged in the data listings
- Complete Response: a platelet count $\geq 100x10^9$/L, by visit, and at any timepoint during the study
- 'No' or 'Loss of' Complete Response: a platelet count <100x109/L, by visit.

- Time to Complete Response: the time from starting treatment (Day 1) to achievement of Complete Response
- Platelet Count ≥50x10^9/L, by visit, and at any timepoint during the study
- 'No' or 'Loss of' Platelet Count ≥50x109/L: a platelet count <50x109/L, by visit.
- Time to Platelet Count ≥50x10^9/L: the time to Platelet Count ≥50x10^9/L is defined as the time from starting treatment (Day 1) to achievement of Platelet Count ≥50x10^9/L
- Maximum: the maximum value for platelet count over all visits in the study
- Value and change from Baseline in platelet count over time
- Baseline-corrected AUEC for platelet count calculated from Baseline to the end of study visit for each of the defined dose arms.

For all the above response variables the following rules will apply:

- Both scheduled and unscheduled measurements may be included in the calculation of a response, time to response or duration of response
- The Baseline-corrected AUEC will be calculated according to the following rules:
  - The AUEC will be calculated according to the linear trapezoidal rule using protocol scheduled visits
  - Unscheduled visits will not be included in the calculation
  - No imputation of any missing data will be performed
  - To account for differences in the timing of Baseline samples for each subject the Baseline measurement will be considered as time zero in the calculation
  - The units of the AUEC will be 10^9/L*day
  - The measurements at Baseline and at the last visit must be available
  - A minimum of 10 out of 14 measurements must be available for the calculation in Dose Arm 1; a minimum of 9 out of 12 measurements must be available for the calculation in Dose Arm 2; a minimum of 8 out of 11 must be available for the calculation in Dose Arm 3; a minimum of 7 out of 9 must be available for the calculation in Dose Arms 4 and 5. These include the Baseline and measurement at the last visit
  - The AUEC will not be calculated in the case of early withdrawal from the study

8.1.2 Presentation of results

The individual platelet measurements will be listed by dose arm and visit including changes from Baseline (Day 1, pre-dose). Descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by dose arm and scheduled visit for both absolute values and changes from Baseline based on the FAS only. Summary tabulations by dose arm will be repeated for the subgroups defined in Section 4.8 (based on the FAS only too).

In addition, a separate listing and summary will be presented (by visit, where applicable) including the following:

- *Response by visit and over all visits
- Time to Response
- Duration of Response
- *Complete Response by visit and over all visits
- Time to Complete Response
- Duration of Complete Response
- *Platelet Count $\geq 50x10^9$/L by visit and over all visits
- Time to Platelet Count $\geq 50x10^9$/L
- Duration of Platelet Count $\geq 50x10^9$/L
- Maximum value
- Maximum Increase from Baseline
- Baseline-corrected AUEC

*All the above variables will be included in the listing. The number and percentage of responders (for variables denoted with an asterisk) will be tabulated separately as described in Section 8.1.3.3.

Summary tabulations by dose arm will be repeated for the subgroups defined in Section 4.8 (based on the FAS only).

Mean and mean change from Baseline platelet values will be plotted versus scheduled visit by dose arm with all dose arms overlaid on the same plot. Similar plots will be provided for response rate over time (response, complete response and platelet count $\geq 50x10^9$/L). Mean median, mean change and median change from Baseline total IgG results will be plotted over time by dose arm with all dose arms overlaid on the same plot.

Individual platelet and total IgG (including IgG subclasses, measured by ACM Global Central Laboratory) concentrations will be displayed graphically over time (Day 1 to Day 85 for Dose Arm 1; Day 1 to Day 71 for Dose Arm 2; Day 1 to Day 64 for Dose Arm 3 and Day 1 to Day 57 for Dose Arms 4 and 5) for each subject (linear scale). The platelet and total IgG concentrations will be overlaid on the same plot (discrete y-axes) with separate plots for each subject (2 lines per plot). Additional plots will be presented with the platelet and IgG subclasses overlaid on the same figure (5 lines per plot). All plots will include a vertical reference line to indicate when the last dose was administered for each subject. The mean (and median in a separate plot) change from baseline in platelet and the mean (median) change from baseline in total IgG concentrations will be overlaid on the same plot (discrete y-axes) with separate plots for each dose arm (2 lines per plot).

In addition scatter plots will be presented showing the Maximum value for platelet count versus the corresponding total IgG i.e., the value of total IgG at the time of the Maximum platelet value. All subjects will be included on the same plot with distinct symbols to distinguish the dose arms. This plot will be repeated for the Maximum platelet value versus percentage change in total IgG i.e., the percentage change from Baseline in total IgG at the time of the Maximum platelet value.

8.1.3 Statistical analysis of platelets

8.1.3.1 Analysis of maximum increase from Baseline

In order to investigate if the average maximum increase from Baseline in platelet count is greater than zero, for dose arms with ≥10 subjects, a 1-sided one sample t-test will be performed at the 5% level. For each dose arm the following null and alternative hypotheses will be tested:

- H_0: Average maximum increase from Baseline within dose arm is less than or equal to zero
- H_1: Average maximum increase from Baseline within dose arm is greater than zero

An assessment of the distribution of the maximum increase from Baseline in platelet count will be performed prior to the statistical analysis in order to check the validity of the proposed parametric analysis method. This will be based on visual inspection of histograms and quantile-quantile plots for each dose arm which will be included as part of the statistical appendices. If the data show a departure from normality, a non-parametric Wilcoxon signed rank test (1-sided) will be applied in addition to the t-test.

If the data are deemed to be normally distributed a parametric analysis will be performed using a one sample t-test. The mean maximum increase from Baseline, the 90% CI and the p-value obtained from the statistical analysis will be tabulated. In order for the null hypothesis (H_0) to be rejected the p-value must be less than 5%.

Analyses will be performed for the FAS and repeated for the PPS.

8.1.3.2 Analysis of time to response

The time to first response will be analyzed with the log-rank test and displayed using Kaplan-Meier curves.

Kaplan-Meier curves will be presented for the variables Time to Response, Time to Complete Response, and Time to Platelet Count $\geq 50x10^9$/L. Descriptive statistics will include the p-value for the log-rank test for the equality over dose arms. The point estimate for the median number of days to response with 90% CIs will be given if estimable. Further a summary including the number and percent of censored subjects, the number of responders and total subjects by dose arm and in total will be given.

For the purpose of the analysis subjects with no response will be censored at the end of the study or at the date of withdrawal.

Analyses will be performed for the FAS and repeated for the PPS.

8.1.3.3 Analysis of responder rate

The number and percentage of subjects achieving a Response, Complete Response and Platelet Count $\geq 50x10^9$/L will be summarized by dose arm at each scheduled post-Baseline visit. The 90% CI for the percentage of responders will be included, calculated using a Wilson approximation. The tabulation will also include an overall summary (across all visits) of the number and percentage of subjects achieving a Response, Complete Response and Platelet Count $\geq 50x10^9$/L at any time during the study. For the purpose of the tabulation the lower and upper 90% CI for the percentage of subjects will be truncated at 0 and 100% respectively.

In addition the percentage of subjects achieving a Response, Complete Response and Platelet Count ≥50x10^9/L will be plotted at each post-Baseline visit. Separate plots will be presented for each response type with all dose arms overlaid on the same plot.

Analyses will be performed for the FAS and repeated for the PPS. Summary tabulations by dose arm will be repeated for the subgroups defined in Section 4.8 (based on the FAS only). Percentage of days without bleeding will also be described by dose arm for each type of response (response, complete response and platelet Count >=50x10/L). Percentage of days without bleeding is calculated using the following formula:

((N of visits with a SMOG score – N of these visits where bleeding occurred) / N of visits with a SMOG score) x 100

In case rescue medications are taken, only the data up to the start date of rescue medication will be utilized for the summary tables. Listings will contain all the data but a footnote will be included indicating the patients for which some data has been excluded from the summary tables. In case of partial dates, the imputation rules for partial dates described in Section 4.2.7 will be applied.

8.1.4 Rescue medication definition (after medical inspection)

In the rescue medication section of the protocol, rescue medication is defined as platelet substitution or treatment with a commercially available IVIg. In addition, the prohibited medications PLEX, dexamethasone and rituximab will also be considered as a rescue medication for analysis.

8.2 Other efficacy variables

8.2.1 ITP bleeding score

The ITP bleeding score is a consensus-based ITP-specific Bleeding Assessment Tool (ITP-BAT) based on a precise definition of bleeding manifestations and on the grading of their severity (Rodeghiero et al, 2013). The ITP bleeding score will be assessed using the ITP-BAT tool version 1.0 at the visits indicated in Section 2.2.2.

Bleeding manifestations will be grouped into 3 major domains, with gradation of severity (SMOG):

- Skin (S)
- Visible mucosae (M)
- Organs (O)

Each bleeding manifestation is assessed at the time of examination and each domain is subcategorized into different types of bleeding. Severity is graded from Grade 0 to 3 or 4, with Grade 5 for any fatal bleeding. Bleeding reported by the subject without medical documentation is graded as 1. The worst bleeding manifestation since the last visit (or in the 15 days preceding the first visit) is graded for each bleeding type (within each domain), and the highest grade within each domain is reported as part of the SMOG.

The overall SMOG index will be reported as S2M2O3 for example. Intracranial bleeding will always be reported, irrespective of its grade. For example, if a female subject had S2 (subcutaneous hematoma) M2 (epistaxis) O3 (menorrhagia) and an intracranial bleeding Grade 2

(post trauma, requiring hospitalization), the SMOG index is S2M2O3 (intracranial 2). If the same subject also had intracranial bleeding Grade 3, the SMOG index is S2M2O3 (intracranial 3).

Further details regarding the bleeding types and scoring algorithms are provided in Section 13.3.

The individual responses for the ITP bleeding score will be listed by dose arm and visit for those items related to the SMOG score. A separate listing will be presented for the bleeding history obtained at Screening including the date and results of any platelet counts (obtained outside the clinical study) together with any medications taken which may interfere with hemostasis; this information will not form part of the SMOG score. Details of bleeding after surgery, invasive procedures and hemostatic challenges, including platelet counts associated with such procedures will also be listed. This information will not form part of the SMOG score.

A separate listing of the grades for each bleeding type will be presented for each domain, and will include the overall score (highest grade) for the specific domain which will be used in the derivation of the SMOG.

The results for the ITP bleeding score will be summarized (n, median, minimum and maximum) by dose arm and visit (absolute values only) for each domain. In addition the number and percentage of subjects with severe or clinically relevant bleeding will be summarized at each visit. Clinically relevant bleeding is defined as follows:

- Skin (S) severity of Grade 3
- Mucosal (M) severity of Grade 2 or higher and/or
- Organ (O) severity of Grade 2 or higher

The number and percentage of subjects with absence of bleeding at each visit will also be included in the summary. Absence of bleeding will correspond to a Grade 0 for each domain.

Summaries will be presented for both the FAS and the PPS.

8.2.1.1 ITP bleeding score and platelet response

In addition to the platelet response variables defined in Section 8.1.1 the following variables will also be defined based on a combination of platelet response and information from the ITP bleeding score (these will be referred to as Clinical Response variables). In case rescue medications or prohibited medications potentially affecting platelet counts are taken, only the platelet data up to the start date of rescue medication will be utilized for the summary tables (refer to Section 8.1.4):

- Clinical Response: a Clinical Response is defined as a platelet count $\geq 30 \times 10^9$/L with at least 2-fold increase from the Baseline value AND absence of bleeding, by visit. This must be confirmed by a second measurement at least 5 days later (to allow for the ±2-day visit window), showing a platelet count $\geq 30 \times 10^9$/L and at least 2-fold increase from the Baseline.
- Time to Clinical Response is defined as the time from starting treatment (Day 1) to achievement of Clinical Response. The will be taken as the time to the first platelet assessment (obtained at the same time as the corresponding ITP bleeding score assessment). If the second assessment does not fulfill the required criteria for a clinical response, the subject will be considered as a nonresponder at the respective visits.

- Duration of Clinical Response: the duration of Clinical Response is defined as the time between achievement of a Clinical Response to the first time a loss of Clinical Response occurred (defined as platelet count <30x10^9/L or less than 2-fold increase from Baseline OR presence of bleeding). Refer to Section 8.1.1 in case a subject has several clinical responses or the clinical response is maintained until the end of the study".
- Complete Clinical Response: a Complete Clinical Response is defined as a platelet count ≥100x10^9/L AND absence of bleeding, by visit. This must be confirmed by a second measurement at least 5 days later (to allow for the ±2-day visit window), showing a platelet count ≥100x10^9/L.
- Time to Complete Clinical Response: the time to Complete Clinical Response is defined as the time from starting treatment (Day 1) to achievement of Complete Clinical Response
- Duration of Complete Clinical Response: the duration of Complete Clinical Response is defined as the time between achievement of a Complete Clinical Response to the first time a loss of Complete Clinical Response occurred (defined as platelet count <100x10^9/L OR presence of bleeding). Refer to Section 8.1.1 in case a subject has several clinical responses or the clinical response is maintained until the end of the study".
- No Clinical Response or a loss of clinical response: the platelet count must be defined as a platelet count <30x10^9/L OR >=30x10^9/L WITHOUT at least a 2-fold increase from the Baseline value OR presence of bleeding, by visit. This must be confirmed by a second measurement 1 to 9 days* later, showing a platelet count <30x10^9/L OR >=30x10^9/L WITHOUT at least a 2-fold increase from the Baseline value.

For all the above response criteria, the calculation rules included in Section 8.1.1 will apply. In addition the following will be applicable:

- The Clinical Response variables will be assessed only for visits for which both platelet counts and the ITP bleeding score are assessed. The last visit cannot be a clinical response as no confirmation after that is available.
- Absence of bleeding is indicated by Grade 0 for all domains of the SMOG, or a Skin Grade of 0 or 1
- Presence of bleeding is indicated by a Mucosae or Organs Grade of ≥1, or Skin Grade of ≥2

*This differs from the published definition (Rodeghiero et al, 2009) which requires 2 platelet measurements 1 day apart to define no response or loss of response. In the current protocol platelet count assessments are not as frequently planned (unless unscheduled measurements are performed), thus it was deemed appropriate to modify the definition above to take into account the schedule of assessments in this study.

As a result the following clinical response variables are not in complete accordance with the guideline:

- Duration of Clinical Response
- Duration of Complete Clinical Response
- No Clinical Response

All response variables described above will be listed by dose arm and subject and summarized by dose arm and visit where appropriate. The responder rates will be tabulated as described in Section 8.1.3.3. Moreover the change in category of bleeding from Baseline will also be presented in shift table at all post-Baseline visits by dose arm. Summary tabulations for Clinical Response by dose arm will be repeated according to past intravenous immunoglobulin medication (Yes/No) and the number of past ITP therapies (≤2/>2). All analyses described in this section will be performed for the FAS.

In case rescue medications are taken, only the data up to (not including) the start date of rescue medication will be utilized for the summary tables. Listings will contain all the data but a footnote will be included indicating the patients for which some data has been excluded from the summary tables. In case of partial dates, the imputation rules for partial dates described in Section 4.2.7 will be applied.

8.2.2 Patient reported outcomes

8.2.2.1 NFI-MS

The NFI-MS was developed in multiple sclerosis and consists of 23 items in four subscales:

- Physical (8 items)
- Cognitive (4 items)
- Relief by diurnal sleep or rest (6 items)
- Abnormal nocturnal sleep and sleepiness (5 items)

Each item is answered using a 4-point Likert scale according to the following:

- 0 = Strongly disagree
- 1 = Disagree
- 2 = Agree
- 3 = Strongly agree

Within each subscale a summary score is calculated by adding up the responses to each item, i.e., the summary score for the physical subscale ranges from 0 to 24. In addition, an overall summary score (ranging from 0 to 30) is calculated using specified items from the Physical and Cognitive subscales. The individual items and further detail regarding the scoring algorithm are presented in Section 13.2. A listing with the questionnaire glossary will be described.

The individual NFI-MS item results and calculated summary scores (for each subscale and for the Physical/Cognitive subscales) will be listed by dose arm and visit including changes from Baseline (Day 1, predose). Descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by dose arm and visit for both absolute values and changes from Baseline. Summaries will be presented for both the FAS and PPS.

Mean and change from Baseline values will be plotted over time by dose arm with all dose arms overlaid on the same plot, for both the FAS and PPS. Separate plots will be presented for each individual subscale and the Physical/Cognitive overall score.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Pharmacokinetics

Due to the blood sampling regimen there will be no calculation of PK parameters using standard methods eg, noncompartmental analysis. Population PK analysis may be conducted and will be described in a separate Data Analysis Plan and reported outside the CSR.

The actual blood sampling timepoints for UCB7665 concentration will be obtained relative to the start time of the first infusion. No time deviations will be calculated as the blood sampling is not scheduled at a specified timepoint at each visit.

Individual concentrations of UCB7665 will be listed by dose arm for the SS and will include the actual sampling time in days relative to the first dose. The planned dose in mg will be calculated based on the body weight at Screening and the dose arm, and included in the listing. The actual dose administered will be calculated based on the planned dose and the percent of planned dose administered as follows:

Actual dose (mg) = Planned dose (mg)*Percent of planned dose administered

The percent of planned dose administered is calculated as described in Section 10.1. The actual dose will also be included in the concentration listing.

Individual concentrations will be summarized by dose arm and scheduled sampling day for the PK-PPS using n, arithmetic mean, median, SD, minimum, maximum, geoMean and 95% CI, geoCV (assuming log-normally distributed data).

For each subject, individual concentration versus time (day) profiles will be presented graphically in linear and semi-logarithmic scale. Individual plasma concentration versus time (day) profiles will also be displayed for each dose arm with all subjects within each dose arm overlaid on the same plot (linear and semi-logarithmic scale).

Geometric mean profiles of UCB7665 with corresponding lower and upper limit of the 95% CI (linear scale plot only) will also be presented with all dose arms overlaid on the same plot.

All figures will include the LLOQ on the semi-logarithmic plots.

The following rules will apply for PK data listings and summaries:

- Values below the LLOQ will be reported as BLQ in the listings
- Descriptive statistics of concentrations will be calculated if at most 1/3rd of the individual data points are missing or are not quantifiable (<LLOQ). Values that are BLQ will be replaced by the numerical value of the LLOQ/2 in this instance. However if n≤3, then only n, minimum and maximum will be presented. The other descriptive statistics will be left blank.
- If no subjects have data, only n=0 will be presented. The other descriptive statistics will be left blank.

  The 95% CI for the geoMean will be calculated by obtaining the lower and upper 95% CI for the arithmetic mean on the log-transformed data and back-transforming to obtain the respective values for the geoMean
- The 95% CI lower and 95% CI upper should be left blank if the SD (or equivalently, the geoCV) is 0

- The geoCV will be calculated using the following formula where SD is the standard deviation from the log-transformed data

  geoCV (%) = sqrt[(exp (SD^2) – 1)] x 100

The above summaries will be repeated separately for the subjects in the PK/PD substudy sample, in the event of very few subjects (<5 subjects) only listings will be provided.

Further analyses and summaries relating to the population PK analyses and PK/PD analyses will be described in a separate SAP and reported separately.

9.2 Pharmacodynamics

The analysis of the PD data will be performed on the FAS with the exception of the total IgG and IgG subclasses, which will be analyzed on the PD-PPS. All listings will be presented for the SS.

The above summaries will be repeated separately for the subjects in the PK/PD substudy sample, in the event of very few subjects (<5 subjects) only listings will be provided.

9.2.1 ITP-specific autoantibodies

The following ITP-specific autoantibodies will be measured using the indirect MAIPA method and pre-chloroquine minus post chloroquine treated scores for PIFT

- [redacted]
- [redacted]
- [redacted]

The results will be expressed in the form of the OD value and for indirect PIFT method using the following categories: 0 = negative; 0.5 = week positive; 1 = positive; 2 = positive; 3 = strong positive; 4 = strong positive.

ITP-specific autoantibodies (OD value and PIFT categories) will be listed by dose arm and timepoint. OD values that are ALD will be displayed as such in the listings.

Descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by dose arm and visit for absolute values only. Any values that are ALD will be handled as described in Section 4.2.3 for the calculation of the descriptive statistics.

Mean values will be plotted over time by dose arm with all dose arms overlaid on the same plot and separate plots for each variable. In addition, combined individual (spaghetti) plots will be plotted over time by dose arm for each variable (absolute values only). All subjects within each dose arm will be overlaid on the same plot.

In order to evaluate the relationship between changes in platelet count and total IgG, IgG subclasses and ITP-specific autoantibodies the following figures will be presented:

- Spaghetti plot of individual ITP-specific autoantibodies and platelet counts (measured by ACM Global Central Laboratory) will be displayed graphically over time (Day 1 to Day 85 for Dose Arm 1; Day 1 to Day 71 for Dose Arm 2; Day 1 to Day 64 for Dose Arm 3 and Day 1 to Day 57 for Dose Arms 4 and 5) for each subject (linear scale). The ITP-specific autoantibodies [redacted] and platelet counts will be overlaid on the same plot (discrete y-axes) with separate plots for each subject (4 lines per plot)

- A scatter plot of platelet counts (measured by ACM Global Central Laboratory) versus ITP-specific autoantibodies measured at the same visit will be presented in linear scale, with separate plots for each dose arm and for each variable [redacted] All subjects and visits will be included on the same plot for each dose arm
- Individual ITP-specific autoantibodies and total IgG (from ACM Global Central Laboratory) will be displayed graphically over time (Day 1 to Day 85 for Dose Arm 1; Day 1 to Day 71 for Dose Arm 2; Day 1 to Day 64 for Dose Arm 3 and Day 1 to Day 57 for Dose Arms 4 and 5) for each subject (linear scale). The ITP-specific autoantibodies [redacted] and total IgG will be overlaid on the same plot (discrete y-axes) with separate plots for each subject (4 lines per plot). These plots will be repeated for each of the IgG subclasses.

The plots versus time will include 2 y-axes with the ITP-specific autoantibodies on the left hand y-axis and the platelet counts (or total IgG and IgG subclasses) on the right hand y-axis. Only patients with positive ITP-specific autoantibodies will be described.

All analyses described in this section will be performed on the FAS.

9.2.2 Total IgG and IgG subclasses

Total IgG concentrations (measured by ACM Global Central Laboratory) and IgG subclasses will be listed by dose arm and visit including changes from Baseline and percentage changes from Baseline. Descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by dose arm and visit for absolute values, changes from Baseline and percentage changes from Baseline. The maximum decrease from Baseline in total IgG (absolute and percentage decrease) will be reported in the listing and summarized for each dose arm based on the results obtained from ACM Global Central Laboratory. Summary tabulations (for total IgG only) by dose arm will be repeated for the subgroups defined in Section 4.8.

In the event that a decrease from Baseline in total IgG is not observed in a given subject, the maximum decrease will be reported as the smallest increase from Baseline.

Mean, median, median change from Baseline and mean and median percentage change from Baseline values in total IgG (measured by ACM Global Central Laboratory) will be plotted over time by dose arm with all dose arms overlaid on the same plot. Additional figures will be presented in conjunction with the ADA results as described in Section 9.3.4 as well as figures in conjunction with the platelet results as described in Section 8.1.1.

Finally, a separate figure will be presented by subject showing the individual total IgG results from ACM Global Central Laboratory.

Any values that are BLQ or ALQ will be handled as described in Section 4.2.3.

All analyses described in this section will be performed on the PD-PPS. In case rescue medications are taken, only the IgG data up to the start date of rescue medication will be utilized for the summary tables. Listings will contain all the data but a footnote will be included indicating the patients for which some data has been excluded from the summary tables. In case of partial dates, the imputation rules for partial dates described in Section 4.2.7 will be applied.

9.3 Other immunological variables

The analysis of the immunological data will be performed on the FAS. All listings will be presented for the SS.

9.3.1 Serum immunoglobulins and lymphocytes

Serum immunoglobulins (IgA, IgE and IgM) will be listed by dose arm and visit including changes from Baseline. Descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by dose arm and visit for both absolute values and changes from Baseline. The listing and summary tabulation will be repeated for B- and T-lymphocytes.

Mean and mean change from Baseline values will be plotted over time by dose arm with all dose arms overlaid on the same plot and separate plots for each variable (IgA, IgE, IgM, B- and T-lymphocytes).

Similar plots will be presented by dose arm for the mean and mean change from Baseline values in IgA, IgE, IgM and total IgG only. Separate plots will be presented for each dose arm with all variables overlaid on the same plot.

In addition, individual immunoglobulin (IgA, IgE, IgM and total IgG) values will be graphically displayed over time with all variables overlaid on the same plot and separate plots for each subject.

For all overlaid plots for the immunoglobulin variables, discrete y-axes may be used for applicable variables to accommodate changes in the scale of measurement.

Any values are that BLQ or ALQ will be handled as described in Section 4.2.4.

All analyses described in this section will be performed on the FAS.

9.3.2 Serum and plasma complement levels

Serum (C3 and C4) and plasma (C3a and C5a) complement variables will be listed by dose arm and visit including changes from Baseline. Descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by dose arm and visit for both absolute values and changes from Baseline.

Mean and mean change from Baseline values will be plotted over time by dose arm with all dose arms overlaid on the same plot and separate plots for each variable.

Any values are that BLQ or ALQ will be handled as described in Section 4.2.4.

All analyses described in this section will be performed on the FAS.

9.3.3 Serum biomarkers

Serum safety biomarkers [redacted] and BAFF will be listed by dose arm and timepoint including changes from Baseline. Descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by dose arm and timepoint for both absolute values and changes from Baseline.

Mean and mean change from Baseline values will be plotted over time by dose arm with all dose arms overlaid on the same plot and separate plots for each variable.

Any values are that BLQ or ALQ will be handled as described in Section 4.2.4.

All analyses described in this section will be performed on the FAS.

9.3.4 Anti-drug antibodies

Immunological variables will be analyzed for all subjects in the SS. Anti-UCB7665 antibody data will be summarized at each scheduled visit, and the rate of ADA positive subjects will be calculated.

A calibrator screening assay measures ADA as relative mass units (RMU) in units/mL. A cut point will be determined by the bioanalytical laboratory that will be used to determine the status of ADA as above the cut point (ACP) or below the cut point (BCP). The RMU result from the calibrator screening assay will be used to report ADA levels.

For any ADA levels that are ACP, a further confirmatory assay will be performed, the results of which will be determined as either 'confirmed positive' (CP) or 'not confirmed positive' (NCP).

The results for the ADA measurements will be listed by treatment group and time point based on the SS, including the screening assay, confirmatory assay and level in units/mL.

The following definitions will be applied:

- An ADA status of positive will be concluded for any subject with an ADA level that is ACP and CP at any time point
- An ADA status of negative will be concluded for any subject with an ADA level that is either BCP or ACP and NCP at any time point
- A subject will be classified as having ADA positivity at Baseline if the Day 1, predose result is ACP and CP
- A subject will be classified as having treatment-emergent ADA positivity when meeting one of the following criteria:
  - The Baseline result is either BCP or ACP and NCP, and at least one post-Baseline time point is ACP and CP
  - The Baseline result is positive (ACP and CP) and at least one post-Baseline measurement shows a pre-defined fold increase in units/mL from the Baseline value (the fold increase from Baseline required to meet this criterion will be defined with the development of the assay and will be included in the TFLs)
- A subject will be classified as overall positive if at least one post-Baseline measurement is ACP and CP (this includes subject who have negative results at Baseline)
- A subject will be classified as overall negative if at all post-Baseline visits the ADA status is negative (this includes subjects who have positive [ACP and CP] results at Baseline)
- Inconclusive: pre-ADA negative or pre-ADA positive subjects with negative ADA samples post baseline for which time matched drug levels are above the demonstrated drug tolerance characteristics of the ADA screening assay at one or more sampling time points

- Missing: relevant samples are missing

The ADA status (positive/negative) will be summarized as a categorical endpoint (number and percentage of subjects) for all time points and overall, based on the SS.

In addition, the first occurrence of treatment-emergent ADA positivity (based on the definitions above) will be summarized (number and percentage of subjects) at each post-Baseline visit, based on the SS. This tabulation will count the number of subjects at each post-Baseline visit who fulfill at least one of the above defined criteria for treatment-emergent positivity; subjects will be counted in the numerator based on the earliest visit at which one of these criteria is fulfilled. At other visits, subjects will be counted in the denominator (assuming a measurement is available). For all tabulations, percentages will be based on the number of observations at each visit.

A separate listing will be presented (based on the SS) showing the UCB7665 concentrations and ADA measurements in the same output in adjacent columns. The listing will include the UCB7665 concentration, ADA status (ACP or BCP) and confirmatory assay results if applicable (NCP or CP), together with the units/mL for results that are CP. In addition the time since the previous administration of IMP will be reported (in days).

Finally, individual subject plots (based on the SS) will be presented displaying the ADA units/mL and UCB7665 concentrations overlaid on the same figure. The figure will also show the timing and dose of each administration of UCB7665 received during the study.

The rules for handling values that are BLQ in the UCB7665 concentration data are described in Section 4.2.5 For the ADA data, any negative results for which there are no units/mL available at a specific visit will be substituted with 0.001 for the purpose of the figure.

9.3.5 Cytokines

Cytokines will be obtained at Baseline in all subjects and at subsequent visits only in subjects experiencing severe infusion reactions (or due to DMC's or sponsor's request). Only for subjects for whom additional measurements were obtained the results of the cytokine assessments will be listed by dose arm and timepoint including changes from Baseline.

If appropriate (i.e., sufficient data are available), summaries will be presented by dose arm and timepoint for both absolute values and changes from baseline. Depending on the availability of data, it may be also decided to summarize the data overall without stratification by dose arm.

A minimum of 5 subjects per dose arm with any post-dose cytokine measurements will be required in order to produce summaries by dose arm. Similarly, a minimum of 5 subjects across all dose arms with any post-dose cytokine measurements will be required to produce the summaries without stratification by dose arm.

The cytokines to be measured are presented in Section 13.4.

All analyses described in this section will be performed on the FAS.

10 SAFETY ANALYSES

All safety analyses will be presented using the SS. Listing will be presented by dose arm and subject; tabulations will be presented by dose arm and overall (AE data only), with the lowest dose per kg presented first and continuing in ascending order.

10.1 Extent of exposure

All drug administration details (including date, start and stop time of infusion, location of infusion site, interruptions, discontinuations [including reasons] and volume delivered) will be listed. The duration of the infusion, in minutes, will also be calculated.

The percent of planned dose administered will be calculated based on the actual volume delivered as follows:

Percent of Planned Dose Administered (%) = [100*(Actual volume/Planned volume)]

For all subjects the planned volume is 10mL.

The overall exposure to UCB7665 will be calculated in days as follows and listed for each subject:

Total exposure (days) = (Date of last dose – Date of first dose) +1

The planned dose regimens are as follows:

- Subjects in Dose Arm 1 will receive 5 sc doses of UCB7665 4mg/kg at 1-week intervals
- Subjects in Dose Arm 2 will receive 3 sc doses of UCB7665 7mg/kg at 1-week intervals
- Subjects in Dose Arm 3 will receive 2 sc doses of UCB7665 10mg/kg at 1-week intervals
- Subjects in Dose Arm 4 will receive 1 sc dose of UCB7665 15mg/kg
- Subjects in Dose Arm 5 will receive 1 sc doses of UCB7665 20mg/kg

The DMC may decide to modify the dosing regimen following review of emerging safety data. In this case the modified dose regimen will be considered as a new dose arm for the study.

10.2 Adverse events

Adverse events will be recorded from the time of informed consent until study completion. All AEs will be coded (Section 3.8) and will be categorized by relationship to UCB7665.

In addition, AEs will be classified according to the CTCAE Version 4.03 for severity. For any AEs where it is not possible to provide a CTCAE grading, the events will be assessed using a standard intensity classification (mild, moderate and severe). For the purpose of the tabulations all CTCAE severity classifications will be mapped to a mild/moderate/severe grade as described in the below sections. Bleeding events classified as Grade 1 or Grade 2 (based on CTCAE) will not be reported as AEs as these will be assessed and reported as part of the ITP-BAT assessments. Bleeding events classified as Grade 3 or higher, based on CTCAE, will be reported as AEs.

A TEAE is defined as any event that was not present prior the first administration of UCB7665 or any unresolved event already present before the first administration of UCB7665 that worsens in intensity following exposure to treatment. Adverse events starting before the first administration of UCB7665 or after 8 weeks following the final dose of UCB7665 will not be considered as TEAEs. Such events will be listed only.

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent. Handling of missing dates/times for classification of AEs as TEAEs is described in Section 4.2.7.

The following rules will be used to assign a TEAE to a study period:

- A TEAE will be assigned to the Dosing Period for the tabulations if the start date/time of the event is at the time of or after the first administration of UCB7665 until 7 days after the final dose; for the purpose of the analysis this will be calculated as the start date/time of the final infusion plus 168 hours;
- A TEAE will be assigned to the Observation Period for the tabulations if the start date/time of the event is greater than 7 days after the final dose until 8 weeks following the final dose; events starting later than 8 weeks following the final dose of UCB7665 are not considered as TEAEs.

Adverse events with missing start date/times will be handled as described in Section 4.2.7 for this classification.

The number and percentage of subjects who experience TEAEs will be summarized for each dose arm and overall. The following summaries will be presented:

- Incidence of TEAEs (overview including number and percentage of subjects with any TEAEs, serious TEAEs, discontinuations due to TEAEs, TEAEs leading to permanent withdrawal of UCB7665, related TEAEs, TEAEs with CTCAE Grade 3 and above [or rated as 'severe' for events with no CTCAE classification], and deaths; event counts will also be included)
- Incidence of TEAEs (overview as described above) during the Dosing Period
- Incidence of TEAEs by SOC, HLT and PT
- Incidence of TEAEs during the Dosing Period by SOC, HLT and PT
- Incidence of serious TEAEs by SOC, HLT and PT
- Incidence of non-serious TEAEs by SOC, HLT and PT
- Incidence of AEs of special interest by SOC, HLT and PT
- Incidence of AEs of interest by SOC, HLT and PT
- Incidence of TEAEs by relationship, SOC, HLT and PT
- Incidence of serious TEAEs by relationship, SOC, HLT and PT
- Incidence of non-serious TEAEs by relationship, SOC, HLT and PT
- Incidence of fatal TEAEs by relationship, SOC, HLT and PT
- Incidence of TEAEs by maximum relationship, SOC, HLT and PT
- Incidence of TEAEs by maximum intensity (mild, moderate and severe), SOC, HLT and PT
- Incidence of non-serious TEAEs above threshold of 5% of subjects by SOC and PT
- Incidence of non-serious TEAEs above threshold of 5% of subjects by relationship, SOC and PT
- Discontinuation due to AEs

Summary tables will contain counts of subjects, percentages of subjects in parentheses and the number of events where applicable. A subject who has multiple events in the same SOC, HLT and PT will be counted only once in the subject counts but all events will be included.

In summaries including relationship to UCB7665, the following relationship categories will be included:

- Related
- Not related

Subjects who experience the same event multiple times will be included in the most related category for tabulations by maximum relationship. Events with missing relationship will be considered as 'Related' to the UCB7665 for summary purposes but shown as missing in the data listings.

In summaries including intensity, the CTCAE categories will be summarized according to the following categories:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Severe
- Grade 5: Severe

These will be tabulated together with the AEs that were not classified according to CTCAE criteria i.e., all Grade 1 AEs as per CTCAE criteria will be included in the 'mild' category together with those AEs classified as mild as per the 'standard' intensity classification.

Subjects who experience the same event multiple times will be included in the most severe category for tabulations by maximum intensity. Events with missing intensity will be considered as 'Severe' for summary purposes. All data will be presented as recorded in the database for the listings.

Adverse event summaries will be ordered by alphabetical SOC, alphabetical HLT within SOC and decreasing frequency of PT in the overall column for tables including event counts. For tables including only number and percentage of subjects, summaries will be ordered by alphabetical SOC, alphabetical HLT within SOC and decreasing incidence of PT within SOC in the overall column.

A listing of all AEs will be presented by subject and dose arm. The listing will include the onset date/time and outcome date/time of the event (including relative days), the AE duration, days since first dose of UCB7665, days since most recent dose of UCB7665, pattern of event, severity/intensity, relationship, action taken and outcome. In addition the listing will flag AEs that led to discontinuation, TEAEs, AEs of interest, AEs of special interest, infusion reactions, SAEs, Sampson criteria and CTCAE grade.

10.3 Clinical laboratory evaluations

Laboratory data (chemistry [excluding follicle stimulating hormone, FSH], hematology, coagulation and urinalysis) and changes from Baseline (if applicable) for numeric variables will

be listed by dose arm and visit. Any laboratory measurements that are BLQ or ALQ will be handled as described in Section 4.2.2. Values outside the reference range for the numeric variables will be flagged in the listings and in addition, results considered as markedly abnormal laboratory results (CTCAE Grade 3 and above) will be listed separately. The reference ranges will also be reported in the listings.

Chemistry [excluding FSH], hematology and coagulation variables will be summarized by dose arm at each visit, for both absolute values and changes from Baseline.

Laboratory variables will be grouped according to the laboratory function panel (Table 10-1) and categorized as normal, high or low, if applicable, based on the reference range supplied by the analytical laboratory. For selected variables that are identified in Table 10-1, the change in category from Baseline will be presented in shift tables at all post-Baseline visits.

Table 10–1: Clinical laboratory measurements

Category	Panel	Variable
Serology	Serology	HIV, HBsAg, anti-HBs, anti-HBc, anti-HCV
Hematology	Red blood cell	RBC count[a], hemoglobin[a], hematocrit
	Platelet	Platelet[ab]
	White blood cell	WBC count[a]
	White blood cell differential	Absolute counts: ANC[a], basophils[a], eosinophils[a], ALC[a], monocytes[a] Percentages: neutrophils/leukocytes[a], basophils/leukocytes[a], eosinophils/leukocytes[a], lymphocytes/leukocytes[a], monocytes/leukocytes[a].
Coagulation	Coagulation	INR[a], prothrombin time[a], aPTT[a], fibrinogen[a]
Chemistry	Electrolytes	Sodium[a], chloride[a], potassium[a]
	Minerals	Calcium[a], phosphate[a], magnesium[a]
	Kidney function	BUN[a], creatinine[a]
	Proteins	Total protein[a], albumin[a], α1-globulin[a], α2-globulin[a], β-globulin[a], gamma globulin[a]. For all parameters except total protein, both absolute and percentage values will be reported as part of the serum protein electrophoresis.
	Liver function	AST[a], ALT[a], GGT[a], ALP[a], LDH[a], total bilirubin[a], direct bilirubin (if indicated)
	Lipids	Total cholesterol[a], triglycerides[a]
	Hormones	FSH
	Other	hsCRP[a], amylase[a]
Urinalysis	Dipstick	pH[a], protein, glucose, ketones, urobilinogen, bilirubin, blood, nitrite, leucocytes

Category	Panel	Variable
	Quantitative	Albumin, creatinine
	Urine sediment[c]	RBC, WBC. epithelial cells, casts, crystals, yeast, bacteria, amorphous urates, amorphous phosphates
Pregnancy test		Urine HCG[d], serum HCG[e]
Other		HbA1c

ALC=absolute lymphocyte count; ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANC=absolute neutrophil count; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; anti-HCV=hepatitis C virus antibody; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle stimulating hormone; GGT=gamma-glutamyltransferase; HbA1c=glycosylated hemoglobin; HBsAg=hepatitis B surface antigen; HCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; hsCRP=high sensitivity C-reactive protein; INR=International Normalized Ratio; LDH=lactate dehydrogenase; RBC=red blood cell; TB=tuberculosis; WBC=white blood cell.

[a] Shift tables will be presented for these variables.

[b] Only platelet results measured at the local laboratory will be included in the safety outputs. Measurements obtained at the central laboratory will be reported as part of the efficacy analyses.

[c] If indicated, based on results of urine dipstick.

[d] Urine pregnancy test will be performed predose on dosing days and at the End-of-Study Visit

[e] Serum pregnancy test is done at Visit 1 (Screening) and to confirm results of positive urine test if applicable.

The number and percentage of subjects with markedly abnormal laboratory results (CTCAE Grade 3 and above) will be tabulated by dose arm and laboratory variable at each visit. The criteria for identifying abnormal laboratory results are detailed in Section 13.5.

Figures of mean and mean change from Baseline will be plotted over time by dose arm for all quantitative laboratory variables (with the exception of any variables measured only at Screening and/or Baseline, eg serology, HbA1c and FSH), with all dose arms overlaid on the same plot. The reference range for each variable (male and female, if applicable) will be included on the plot for absolute values. For the differential WBC counts, figures will be presented based on percentage values only.

Any additional laboratory variables not included in the outputs described previously (including pregnancy testing, FSH and serology) will be listed separately.

Finally, in order to provide a comparison between the platelet counts measured locally and centrally, a separate listing will be presented including only the observed platelet counts from each laboratory at each visit where both measurements are obtained. Difference between laboratories will also be presented.

10.3.1 Potential drug-induced liver injury

Subjects who meet any of the following criteria at a given timepoint will be listed:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase ≥5xupper limit of normal (ULN)
- ALT or AST increase ≥3xULN and total bilirubin ≥2xULN
- ALT or AST increase ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity.

- ALT or AST increase ≥3xULN (and ≥2xBaseline) and <5xULN, with total bilirubin <2xULN
- ALT or AST increase ≥5xULN (and ≥2xBaseline), with total bilirubin <2xULN and no eosinophilia (i.e., ≤5%), with no fever, rash, or symptoms of hepatitis
- Alkaline phosphatase (ALP) ≥2xULN

A summary of subjects who met the criteria for potential drug-induced liver injury (PDILI) will be presented together with any additional relevant data collected, if applicable.

10.4 Vital signs, physical findings, and other observations related to safety

10.4.1 Vital signs

The following vital signs measurements will be obtained:

- Pulse rate
- Systolic and diastolic blood pressure
- Temperature
- Respiratory rate

A by-subject listing of all vital sign measurements and change from Baseline will be presented by dose arm and timepoint. The listing will include a flag for measurements identified as treatment-emergent markedly abnormal (TEMA)/potentially clinically significant (PCS) as calculated by the criteria outlined in Table 10–2.

Descriptive statistics will be reported for all vital sign measurements. Measured values and changes from Baseline will be summarized by vital signs variable and timepoint for each dose arm.

Figures of mean change from Baseline will be presented for each variable by dose arm. All dose arms will be overlaid on the same plot.

The number and percentage of subjects with TEMA/PCS vital sign values will be summarized by dose arm at each timepoint.

Table 10–2: TEMA/PCS criteria for vital signs

Variable	Unit	Low	High
Systolic blood pressure	mmHg	Value <90 and ≥20 decrease from Baseline	Value >180 and ≥15 increase from baseline
Diastolic blood pressure	mmHg	Value <50 and ≥15 decrease from Baseline	Value >105 and ≥15 increase from Baseline

Note: The change in measurement (increase or decrease) will be calculated relative to the value obtained at Baseline.
[a]Both conditions must be satisfied for a measurement to be considered PCS.

Repeated and unscheduled measurements will be handled as described in Section 4.3.

10.4.2 Electrocardiograms

All standard 12-lead ECG recordings will be taken in triplicate with the subject resting in the supine position for at least 15 minutes and before obtaining any blood samples. The following variables will be reported:

- Heart rate
- RR interval
- PQ/PR interval
- QRS duration
- QT interval
- QT corrected for heart rate using Fridericia's formula ($QTcF = QT/RR^{0.33}$)

The individual measurements and the mean of the triplicate measurements will be reported in the by-subject listings. The listing will also include the change from Baseline and percentage change from Baseline (based on the mean of the triplicate measurements at each timepoint). TEMA/PCS ECG values will be flagged in the listing.

Measured values, changes, and percentage changes from Baseline will be summarized by dose arm at each timepoint and by ECG variable (based on the mean of the triplicate values at each visit). Mean change from Baseline and percentage change from Baseline in QTcF will be displayed graphically over time by dose arm, with all dose arms overlaid on the same plot.

The following cut-points in QTcF (raw data and change from Baseline) based on the mean of the triplicate data will be summarized categorically (number and percentage of subjects) by dose arm at each visit.

For raw data:

- <450msec
- ≥450 to <480msec
- ≥480 to <500msec
- ≥500msec

Change from Baseline in QTcF:

- <30msec
- ≥30 to <60msec
- ≥60 msec

ECG findings for the individual triplicate measurements will be listed separately.

Repeated and unscheduled measurements will be handled as described in Section 4.3.

The number and percentage of subjects with TEMA/PCS ECG values will be summarized by dose arm at each visit.

Table 10–3: TEMA/PCS criteria for ECG

Variable	Criteria
QT corrected for heart rate using Fridericia's formula (QTcF)	≥501ms OR ≥60ms compared to baseline
PR prolongation	≥210ms and ≥10ms change from baseline

10.4.3 Other safety variables

Body weight will be listed by subject and visit. Subjects with abnormalities in the physical examination will be listed including details of the abnormality.

11 OTHER ANALYSES

Subjects who experience severe headaches will complete a headache questionnaire followed by a neurological assessment (including fundoscopy). This will be performed daily until resolution. Additionally, a computed tomography (CT) or magnetic resonance imaging (MRI) scan, and lumbar puncture (LP) for CSF collection may be performed if indicated at the discretion of the Investigator.

The neurological assessment will include general appearance and, if indicated, assessments of cranial nerves, motor system examination, reflexes, coordination and fundoscopy. Each parameter within each body system (with the exception of fundoscopy) will be assessed as normal, abnormal not clinically significant or abnormal clinically significant. For the fundoscopy assessment, the result will be assessed as normal or abnormal, and the specific abnormalities will be documented in the CRF.

The results of the CT scan (or MRI) will be reported including the date and time of the assessment and the evaluation (normal, abnormal not clinically significant, or abnormal clinically significant).

The assessments to be performed from the CSF collection will include the following biomarkers:

- Assessment of CSF/serum albumin quotients
- Assessment of CSF/serum IgG quotients
- Labile mediators such as the prostanoids
- Soluble intercellular adhesion molecule-1 (ICAM-1) and histamine
- [redacted]
- Transforming growth factor-beta (TGFβ)
- IL-10/CSF/serum IL-10 quotients

Symptoms and frequency of severe headache questionnaire glossary will be listed. The results of the headache questionnaire, neurological examination and any additional tests performed

(CT/MRI scan, fundoscopy and LP for CSF collection) will be listed for each subject. No summary tabulations will be provided for these assessments.

There will be an exit interview performed for all subjects at the end of the study. The results of the exit interview will be reported to UCB and not included in the TFLs as part of the CSR.

12 REFERENCES

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Rodeghiero F, Michel M, Gernsheimer T, Ruggeri M, Blanchette V, Bussel JB, et al. Standardization of bleeding assessment in immune thrombocytopenia: report from the International Working Group. Blood. 2013;121(14):2596-606.

Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009; 113(11):2386-93.

14 AMENDMENTS TO THE STATISTICAL ANALYSIS PLAN

14.1 Amendment 1

14.1.1 Rationale for the amendment

This SAP was amended following global protocol amendment 3 dated 15 February 2017 and local protocol amendments 3.5 (Georgia and Bulgaria) dated 23 August 2017 and 3.6 (Moldova) dated 7 September 2017. The main changes were to include three additional cohorts and a non-mandatory genomic substudy. Other changes were made in line with the protocol amendment and all changes are detailed in the sections below.

The list of abbreviations was updated as required and a few other minor formatting updates were made.

All of the changes that were made in previous version of the SAP amendment 1 that are still applicable to the current version will be included in this section.

14.1.2 List of changes

Specific changes

Change #1

Introduction (Section 1)

This SAP is based upon, and assumes familiarity, with the following documents:

- Final Protocol: 09 November 2015
- Protocol Amendment 0.1 (Moldova): 18 November 2015
- Protocol Amendment 0.2 (Germany): 12 January 2016
- Protocol Amendment 0.3 (Poland): 23 May 2016
- Protocol Amendment 0.4 (Romania): 11 August 2016
- Protocol Amendment 1 (Global): 19 May 2016
- Protocol Amendment 1.1 (Moldova): 23 May 2016
- Protocol Amendment 1.3 (Poland): 09 June 2016

Has been changed to:

This SAP is based upon, and assumes familiarity, with the following documents:

- Final Protocol: 09 November 2015
- Protocol Amendment 0.1 (Moldova): 18 November 2015
- Protocol Amendment 0.2 (Germany): 12 January 2016
- Protocol Amendment 0.3 (Poland): 23 May 2016
- Protocol Amendment 0.4 (Romania): 11 August 2016
- Protocol Amendment 1 (Global): 19 May 2016

- Protocol Amendment 1.1 (Moldova): 23 May 2016
- Protocol Amendment 1.3 (Poland): 09 June 2016
- Protocol Amendment 2.0 (Global; not implemented): 21 October 2016
- Protocol Amendment 3.0 (Global): 15 February 20117
- Protocol Amendment 3.1 (Moldova): 08 March 2017
- Protocol Amendment 3.3 (Poland): 07 March 2017
- Ptoeocol Amendment 3.4 (Romania): 10 March 2017
- Protocol Amendment 3.5 (Georgia and Bulgaria): 23 August 2017
- Protocol Amendment 3.6 (Moldova): 07 September 2017

Change #2

Introduction (Section 1)

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP will be amended accordingly. In addition, if analysis definitions have to be modified or updated prior to database lock, a SAP amendment will be required. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, these changes will be described in the CSR together with the associated rationale. The content of this SAP is compatible with the International Council for Harmonisation (ICH)/Food and Drug Administration (FDA) E9 Guidance documents.

Has been changed to:

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP amendment will be updated accordingly. In addition, if analysis definitions have to be modified or updated prior to database lock, a further SAP amendment will be required. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, these changes will be described in the CSR together with the associated rationale. The content of this SAP is compatible with the International Council for Harmonisation (ICH)/Food and Drug Administration (FDA) E9 Guidance documents.

Change #3

Exploratory objectives (Section 2.1.3)

The following objectives have been added:

- To evaluate the genomic components of ITP to understand the molecular etiology, progression, and treatment of the disease, applicable only for subjects consenting to participate in the optional genomic analyses substudy
- [redacted]

Change #4

Other safety variables (Section 2.2.1.2)

The other safety variables are:

- Vital sign values and change from Baseline (systolic and diastolic blood pressure, temperature, pulse rate, respiratory rate and body weight) to each visit in the Dosing Period and in the Observation Period up to Day 85 in the 4mg/kg dose arm and up to Day 71 in the 7mg/kg dose arm. Body weight is measured only at Screening and Day 85 or Day 71 in the 4mg/kg and 7 mg/kg dose arm respectively
- 12-lead electrocardiogram (ECG) parameters and change from Baseline to each dosing visit in the Dosing Period and to Day 36 and Day 85 in the Observation Period in the 4mg/kg dose arm, and at Day 22 and Day 71 in the Observation Period in the 7mg/kg dose arm
- Laboratory values and change from Baseline (hematology including coagulation parameters, clinical chemistry, and urinalysis) to each visit in the Dosing Period and in the Observation Period up to Day 85 in the 4mg/kg dose arm and up to Day 71 in the 7mg/kg dose arm
- TEAEs leading to withdrawal of investigational medicinal product (IMP)

Has been changed to:

The other safety variables are:

- Vital sign values and change from Baseline (systolic and diastolic blood pressure, temperature, pulse rate and respiratory rate) to each visit in the Dosing Period and in the Observation Period up to Day 85 in Dose Arm 1 (4mg/kg once weekly [QWK]), up to Day 71 in Dose Arm 2 (7mg/kg QWK), up to Day 64 in Dose Arm 3 (10mg/kg QWK) and up to Day 57 in Dose Arms 4 (15mg/kg) and 5 (20mg/kg). Body weight is measured only at Screening and at the corresponding EOS visit as outlined in the protocol
- 12-lead electrocardiogram (ECG) parameters and change from Baseline to each dosing visit in the Dosing Period and to Day 36 and Day 85 in the Observation Period in Dose Arm 1, to Day 22 and Day 71 in the Observation Period in Dose Arms 2, to Day 15 and Day 64 in Dose Arm 3 and to Day 8 and Day 57 in Dose Arms 4 and 5
- Laboratory values and change from Baseline (hematology including coagulation parameters, clinical chemistry, and urinalysis) to each visit in the Dosing Period and in the Observation Period up to the corresponding EOS visit as outlined in the protocol
- Values and change from Baseline in concentrations of total protein, albumin, α-globulin, and β-globulin to each visit in the Dosing Period and in the Observation Period up to Day 85 in Dose Arm 1, up to Day 71 in Dose Arm 2, up to Day 64 in Dose Arm 3 and up to Day 57 in Dose Arm 4 and 5
- TEAEs leading to withdrawal of UCB7665
- Change from Baseline in serum biomarkers [redacted] to each visit in the Dosing Period and up to Day 71 in the

Observation Period in Dose Arm 1, up to Day 57 in the Observation Period in Dose Arm 2, up to the last visit prior to the corresponding EOS visit as outlined in the protocol

Change #5

Efficacy variables (Section 2.2.2)

- Baseline-corrected area under the effect curve (AUEC) for platelet count calculated from Baseline to the end of study visit (Day 85 in the Observation Period in the 4mg/kg dose arm and Day 71 in the Observation Period in the 7mg/kg dose arm)
- Assessment of ITP bleeding score over time at Baseline and at each dosing visit in the Dosing Period and to Day 36, Day 50, Day 64 and Day 85 in the Observation Period in the 4mg/kg dose arm, and to Day 22, Day 36, Day 50 and Day 71 in the Observation Period in the 7mg/kg dose arm
- Value and change from Baseline in Neurological Fatigue Index for Multiple Sclerosis (NFI-MS) summary score to Day 36, Day 50, Day 64 and Day 85 in the Observation Period in the 4mg/kg dose arm and to Day 22, Day 36, Day 50 and Day 71 in the Observation Period in the 7mg/kg dose arm

Has been changed to:

- Baseline-corrected area under the effect curve (AUEC) for platelet count calculated from Baseline to the end of study visit (Day 85 in the Observation Period in Dose Arm 1, Day 71 in the Observation Period in Dose Arm 2, Day 64 in the Observation Period in Dose Arm 3 and Day 57 in Observation Period in Dose Arms 4 and 5)
- Assessment of ITP bleeding score over time at Baseline and at each dosing visit in the Dosing Period and to Day 36, Day 50, Day 64 and Day 85 in the Observation Period in Dose Arm 1, to Day 22, Day 36, Day 50 and Day 71 in the Observation Period in Dose Arm 2, to Day 15, Day 29, Day 43 and Day 64 in the Observation Period in Dose Arm 3 and to Day 8, Day 22, Day 36 and Day 57 in the Observation Period in Dose Arms 4 and 5
- Value and change from Baseline in Neurological Fatigue Index for Multiple Sclerosis (NFI-MS) summary score to Day 36, Day 50, Day 64 and Day 85 in the Observation Period in Dose Arm 1, to Day 22, Day 36, Day 50 and Day 71 in the Observation Period in Dose Arm 2, to Day 15, Day 29, Day 43 and Day 64 in the Observation Period in Dose Arm 3 and to Day 8, Day 22, Day 36 and Day 57 in the Observation Period in Dose Arms 4 and 5

Change #6

Efficacy variables (Section 2.2.2)

Some variables have been re-ordered to align with the order in the protocol.

Change #7

Pharmacokinetic variable (Section 2.2.3.1)

- Plasma concentration of UCB7665 over time, at each visit during the Dosing Period and 3 and 7 days following the last dose of UCB7665

Has been changed to:

- Plasma concentration of UCB7665 over time, at each visit during the Dosing Period and 3 and 7 days following the last dose of UCB7665 in each dose arm

Change #8

Pharmacokinetic variable (Section 2.2.3.1)

The following bullet point has been added at the end of this section:

- Additional blood samples for the optional PK/PD substudy (early blood sampling) will be drawn at Visit 2 (predose and 4 hours after end of infusion on Day 1), Visit 2a (24 and 36 [optional] hours after the start of Day 1 UCB7665 infusion) and Visit 2b (48 hours after the start of Day 1 UCB7665 infusion).

Change #9

Pharmacodynamic variables (Section 2.2.3.2)

- Value and change from Baseline (absolute and percentage) in total IgG concentrations (measured by ACM Global Central Laboratory) to each visit in the Dosing Period and in the Observation Period up to Day 85 in the 4mg/kg dose arm and up to Day 71 in the 7mg/kg dose arm
- Value and change from Baseline in total and endogenous IgG (measured via IgG depletion assay by LGC) to each visit in the Dosing Period and to Day 32, Day 36, Day 43, Day 57, Day 71 and Day 85 in the Observation Period in the 4mg/kg dose arm, and to Day 18, Day 22, Day 29, Day 43, Day 57 and Day 71 in the Observation Period in the 7mg/kg dose arm
- ITP-specific autoantibodies in serum [redacted] over time, measured at Day 1, Day 36 and Day 85 in the 4mg/kg dose arm and at Day 1, Day 22 and Day 71 in the 7mg/kg dose arm
- Change from Baseline in IgG subclass concentrations (measured by ACM Global Central Laboratory) to each visit in the Dosing Period and in the Observation Period up to Day 85 in the 4mg/kg dose arm and up to Day 71 in the 7mg/kg dose arm

Has been changed to:

- Value and change from Baseline (absolute and percentage) in total IgG concentrations (measured by ACM Global Central Laboratory) to each visit in the Dosing Period and in the Observation Period up to Day 85 in Dose Arm 1, up to Day 71 in Dose Arm 2, up to Day 64 in Dose Arm 3 and up to Day 57 in Dose Arms 4 and 5
- Value and change from Baseline in total IgG (measured via IgG depletion assay by LGC) to each visit in the Dosing Period and to Day 32, Day 36, Day 43, Day 57, Day 71 and Day 85 in the Observation Period in Dose Arm 1, to Day 18, Day 22, Day 29, Day 43, Day 57 and

Day 71 in the Observation Period in Dose Arm 2, to Day 11, Day 15, Day 22, Day 36, Day 50 and Day 64 in Dose Arm 3 and to Day 4, Day 8, Day 15, Day 29, Day 43 and Day 57 in Dose Arms 4 and 5

- ITP-specific autoantibodies in serum [redacted] over time, measured at Day 1, Day 36 and Day 85 in Dose Arm 1, at Day 1, Day 22 and Day 71 in Dose Arm 2, at Day 1, Day 15, and Day 64 in Dose Arm 3 and at Day 1, Day 8 and Day 57 in Dose Arms 4 and 5
- Change from Baseline in IgG subclass concentrations (measured by ACM Global Central Laboratory) to each visit in the Dosing Period and in the Observation Period up to Day 85 in Dose Arm 1 and up to Day 71 in Dose Arm 2, up to Day 64 in Dose Arm 3 and up to Day 57 in Dose Arms 4 and 5

Change #10

Other immunological variables (Section 2.2.4)

- Change from Baseline in serum immunoglobulin concentrations (total IgA, IgE, and IgM) to the last visit in the Dosing Period and to Day 36 and Day 71 in the Observation Period in the 4mg/kg dose arm, and to Day 22 and Day 57 in the Observation Period in the 7mg/kg dose arm
- Change from Baseline in B- and T-lymphocyte concentrations to each visit in the Dosing Period and in the Observation Period up to Day 85 in the 4mg/kg dose arm and up to Day 71 in the 7mg/kg dose arm
- Change from Baseline in serum (C3 and C4) and plasma (C3a and C5a) complement levels to Day 15 (Dosing Period) and to Day 32 and Day 57 in the Observation Period in the 4mg/kg dose arm, and to Day 15 (Dosing Period) and to Day 18 and Day 43 in the Observation Period in the 7mg/kg dose arm
- Change from Baseline in serum biomarkers [redacted] to each visit in the Dosing Period and to Day 32, Day 36, Day 43, Day 50, Day 57, Day 64 and Day 71 in the Observation Period in the 4mg/kg dose arm, and to Day 18, Day 22, Day 29, Day 36, Day 43, Day 50 and Day 57 in the Observation Period in the 7mg/kg dose arm
- Change from Baseline in serum biomarkers [redacted] to each visit in the Dosing Period in both the 4mg/kg dose arm and the 7mg/kg dose arm
- Value and change from Baseline in ADA relative mass units (RMU) to each visit in the Dosing Period and to Day 32, Day 36, Day 43, Day 57, Day 71 and Day 85 in the Observation Period in the 4mg/kg dose arm, and to Day 18, Day 22, Day 29, Day 43, Day 57 and Day 71 in the Observation Period in the 7mg/kg dose arm
- Anti-drug antibody screening status (positive/negative) at each of the visits described above. For ADA screening positive results the confirmatory ADA result will be reported as either confirmed positive (CP) or not confirmed positive (NCP)

- Change from Baseline in cytokines over time. Cytokines will be measured at all visits in both dose arms for subjects who experience infusion reactions only
- Change from Baseline in serum B cell activating factor (BAFF) levels to each dosing visit in the Dosing Period and to Day 43 and Day 71 in the Observation Period in the 4mg/kg dose arm, and to Day 29 and Day 57 in the Observation Period in the 7mg/kg dose arm

Has been changed to:

- Change from Baseline in serum immunoglobulin concentrations (total IgA, IgE, and IgM) to the last visit in the Dosing Period and to Day 36 and Day 71 in the Observation Period in Dose Arm 1, to Day 22 and Day 57 in the Observation Period in Dose Arm 2, to Day 15 and Day 50 in the Observation Period in Dose Arm 3 and to Day 8 and Day 43 in the Observation Period in Dose Arms 4 and 5
- Change from Baseline in serum (C3 and C4) and plasma (C3a and C5a) complement levels to Day 15 (Dosing Period) and to Day 32 and Day 57 in the Observation Period in Dose Arm 1, to Day 15 (Dosing Period) and to Day 18 and Day 43 in the Observation Period in Dose Arm 2, to Day 11 and Day 36 in Observation Period in Dose Arm 3 and to Day 4 and Day 29 in Observation Period in Dose Arms 4 and 5
- Change from Baseline in exploratory biomarkers relating to mechanism of action, disease activity, treatment response, and clinical outcome
- Value and change from Baseline in ADA relative mass units (RMU) to each visit in the Dosing Period and to Day 32, Day 36, Day 43, Day 57, Day 71 and Day 85 in the Observation Period in Dose Arm 1, and to Day 18, Day 22, Day 29, Day 43, Day 57 and Day 71 in the Observation Period in Dose Arm 2, to Day 11, Day 15, Day 22, Day 36, Day 50 and Day 64 in Dose Arm 3 and to Day 4, Day 8, Day 15, Day 29, Day 43 and Day 57 in Dose Arms 4 and 5
- Anti-drug antibody screening status (positive/negative) at each of the visits described above. For ADA screening positive results the confirmatory ADA result will be reported as either confirmed positive (CP) or not confirmed positive (NCP)
- Change from Baseline in cytokines over time. Cytokines will be measured at all visits in all dose arms for subjects who experience infusion reactions only. Further description of the cytokines variables can be found in Appendix 13.4. Additional exploratory biomarkers may be investigated if needed using the samples already available.
- Change from Baseline in serum B cell activating factor (BAFF) levels to each dosing visit in the Dosing Period and to Day 43 and Day 71 in the Observation Period in Dose Arm 1, to Day 29 and Day 57 in the Observation Period in Dose Arm 2, to Day 22 and Day 50 in the Observation Period in Dose Arm 3 and to Day 15 and Day 43 in the Observation Period in Dose Arms 4 and 5
- Change from Baseline in B- and T-lymphocyte concentrations to each visit in the Dosing Period and in the Observation Period up to Day 85 in Dose Arm 1, up to Day 71 in Dose Arm 2, up to Day 64 in Dose Arm 3 and up to Day 57 in Dose Arms 4 and 5

Change #11

Other immunological variables (Section 2.2.4)

One item has been re-ordered to align with the order in the protocol.

Change #12

Other immunological variables (Section 2.2.4)

The following paragraph has been removed since it is already mentioned within the section:

Cytokine samples will be taken at Baseline for all subjects and at subsequent visits only if the subject experiences infusion reactions.

Change #13

Study design and conduct (Section 2.3)

This is a Phase 2, multicenter, open-label, multiple-dose 2-dose-arm study to evaluate the safety, tolerability, and efficacy of UCB7665 in subjects with primary persistent or chronic ITP. The 2 dose arms will be as follows:

- Dose Arm 1: UCB7665 4mg/kg sc (5 doses at an interval of 1 week)
- Dose Arm 2: UCB7665 7mg/kg sc (3 doses at an interval of 1 week)

The maximum duration of the study per subject is approximately 16 weeks, consisting of a Screening Period (1 to 28 days), a Dosing Period of 2 or 4 weeks, and an Observation Period of 8 weeks.

A data monitoring committee (DMC) will monitor emergent safety data during the study. The first 6 subjects in the study will receive UCB7665 4mg/kg. These subjects in Dose Arm 1 will not be randomized. While recruitment is still ongoing safety data for the first 3 subjects up to 7 days after the final dose of the third subject will be reviewed by the DMC.

During a second DMC meeting, all available safety data up to the cut off date defined as 7 days after the final dose of the sixth subject will be reviewed. During these reviews recruitment in the dose arm will not be stopped. Following this review, the DMC will make a decision on whether to open Dose Arm 2 for enrollment. Once the DMC has approved the opening of Dose Arm 2 for enrollment, subjects will subsequently be randomized to 1 of the 2 dose arms using interactive voice/web response system (IXRS). If the new dose arm will be initiated and if the UCB7665 4mg/kg will be continued, new subjects will be randomized to 1 of the 2 dose arms in an allocation ratio of 1:1 (once 15 subjects are in the 4mg/kg group, the remaining subjects will not be randomized; these subjects will be allocated to the 7mg/kg group).

At least 4 interim analyses will be performed. Based on the interim analysis the DMC will assess the safety of UCB7665, determine whether to initiate the UCB7665 7mg/kg dose arm and may decide to adapt the dose regimen.

The analyses and TFLs required for the interim analyses are described in a separate interim SAP.

Has been changed to:

This is a Phase 2, multicenter, open-label, multiple-dose, multiple-arm study to evaluate the safety, tolerability, and efficacy of UCB7665 in subjects with primary persistent or chronic ITP. The 5 dose arms will be as follows:

- Dose Arm 1 (15 subjects): UCB7665 4mg/kg sc (5 doses at an interval of 1 week)
- Dose Arm 2 (15 subjects): UCB7665 7mg/kg sc (3 doses at an interval of 1 week)
- Dose Arm 3 (6 to 12 subjects): UCB7665 10mg/kg sc (2 doses at intervals of 1 week)
- Dose Arm 4 (6 to 12 subjects): UCB7665 15mg/kg sc (1 dose)
- Dose Arm 5 (6 to 12 subjects): UCB7665 20mg/kg sc (1 dose)

The maximum duration of the study per subject is approximately 16 weeks, consisting of a Screening Period (1 to 28 days), a Dosing Period of 1 to 4 weeks, and an Observation Period of 8 weeks.

A data monitoring committee (DMC) will monitor emergent safety data during the study. The first 6 subjects in the study will receive UCB7665 4mg/kg. These subjects in Dose Arm 1 will not be randomized. While recruitment is still ongoing safety data for the first 3 subjects up to 7 days after the final dose of the third subject in Dose Arm 1 will be reviewed by the DMC.

During a second DMC meeting, all available safety data up to the cut off date defined as 7 days after the final dose of the sixth subject in Dose Arm 1 will be reviewed. During these reviews recruitment in the dose arm will not be stopped. Following this review, the DMC will make a decision on whether to open Dose Arm 2 for enrollment. Once the DMC has advocated the initiation of Dose Arm 2, the subsequent subjects will be randomly assigned in 1:1 ratio to either Dose Arm 1 or Dose Arm 2 using an interactive voice/web response system (IXRS). Once 15 subjects are enrolled in Dose Arm 1, the remaining subjects will enrolled in Dose Arm 2.

After the safety data review of at least 6 subjects in Dose Arm 2 is done, the DMC will make a recommendation on whether to open Dose Arm 3 for enrollment. Once the DMC has advocated the initiation of Dose Arm 3 and the enrollment of 15 subjects in Dose Arm 2 has been completed, the subsequent subjects will be assigned to Dose Arm 3 only. After every third subject has been enrolled, the DMC will review all available safety data up to cut off date defined as 7 days after the dosing. Depending on the emerging safety data of 6 subjects in Dose Arm 3, the DMC will recommend whether to open Dose Arm 4 for enrollment or to include additional subjects in Dose Arm 3. A maximum of 12 subjects may be enrolled in Dose Arm 3.

Once the DMC has advocated the initiation of Dose Arm 4, the enrollment of Dose Arm 3 will be closed and all subsequent subjects will be assigned to Dose Arm 4. After every third subject is enrolled, the DMC will review all available safety data up to the cutoff date defined as 7 days after the dosing. Depending on the emerging safety data of 6 subjects in Dose Arm 4, the DMC will recommend to include additional subjects in Dose Arm 4 or not. A maximum of 12 subjects may be enrolled in Dose Arm 4. The DMC will recommend to open Dose Arm 5 for enrollment in a subsequent meeting, if applicable.

Once the DMC has advocated the initiation of Dose Arm 5, the enrollment of Dose Arm 4 will be closed and all subsequent subjects will be assigned to Dose Arm 5. After every third subject is

enrolled, the DMC will review all available safety data up to the cutoff date defined as 7 days after the dosing. Depending on the emerging safety data of 6 subjects in Dose Arm 5, the DMC will recommend to include additional subjects in Dose Arm 5. A maximum of 12 subjects may be enrolled in Dose Arm 5.

At least 11 interim analyses will be performed. Based on the interim analyses the DMC will assess the safety of UCB7665, determine whether to initiate subsequent dose arms and may decide to adapt the dose regimen. The analyses and TFLs required for the interim analyses are described in a separate interim SAP.

During this study, subjects will also have the option of providing additional informed consent for exploratory DNA and RNA analyses. Participation in this additional portion of the study is optional and does not preclude subject's eligibility for participation in the main study. The additional genomic samples must not be collected if the subject has not consented to participate in this exploratory genomic substudy. Any results from this analysis will be reported separately and will not form a part of the main CSR. Thus, these analyses are not described further in this SAP.

During this study, subjects from Bulgaria, Georgia and Moldova who are enrolled in Dose Arm 3, 4 or 5, will also have the option of providing additional informed consent for a PK/PD substudy (early blood sampling) at selected study sites. Participation in this additional portion of the study is optional and does not preclude subject's eligibility for participation in the main study. The additional PK/PD blood samples must not be collected if the subject has not consented to participate in this exploratory substudy.

Change #14

Determination of sample size (Section 2.4, first paragraph)

The sample size of 15 subjects, in each dose arm, is mainly based on the efficacy objective of the study. In addition, the inclusion of 15 subjects in each dose arm will ensure that sufficient data are available to form conclusions about the safety of administering UCB7665.

Has been changed to:

The sample size of 15 subjects in Dose Arms 1 and 2, is mainly based on the efficacy objective of the study. In addition, the inclusion of 15 subjects in Dose Arms 1 and 2 will ensure that sufficient data are available to form conclusions about the safety of administering UCB7665. Based on the safety data from Dose Arms 1 and 2, the sample size of 6 to 12 subjects in Dose Arms 3, 4 and 5 were judged to be sufficient in order to explore subjects' safety and IgG reductions under different dose regimens and is not based on a formal sample size calculation.

Change #15

General presentation of summaries and analyses (Section 3.1, last paragraph)

In the event that the number of infusions in the planned dose arms (3x7mg/kg and 5x4mg/kg) are modified following review by the DMC, the data will be summarized based on the actual dose arms completing the study. For example, if the 5x4mg/kg dose arm is modified such that some subjects receive only 4 infusions, then the data will be summarized separately for this new dose regimen.

In the TFLs the dose arms will be displayed as follows where applicable:

- UCB7665 5x4mg/kg
- UCB7665 3x7mg/kg

If additional dose arms are initiated during the study these will be displayed similarly. For example, if the 5x4 mg/kg dose arm is modified such that some subjects receive only 4 infusions this dose arm will be displayed as UCB7665 4x4mg/kg in the TFLs.

Has been changed to:

In the event that the number of planned infusions in the dose arms are modified following review by the DMC, the data will be summarized based on the actual dose arms completing the study. For example, if the 5x4mg/kg QWK dose arm is modified such that some subjects receive only 4 infusions, then the data will be summarized separately for this new dose regimen.

In the TFLs the dose arms will be displayed as follows where applicable:

- UCB7665 5x4mg/kg QWK
- UCB7665 3x7mg/kg QWK
- UCB7665 2x10mg/kg QWK
- UCB7665 1x15mg/kg
- UCB7665 1x20mg/kg

If additional dose arms are initiated during the study these will be displayed similarly. For example, if the 5x4mg/kg QWK dose arm is modified such that some subjects receive only 4 infusions this dose arm will be displayed as UCB7665 4x4mg/kg QWK in the TFLs.

Data listings containing all documented data and all derived data will be generated.

Change #16

Study periods (Section 3.2.1.2)

- Dosing Period: Up to 4 weeks; during the Dosing Period subjects will receive weekly doses of IMP (5 doses of 4mg/kg in Dose Arm 1 and 3 doses of 7mg/kg in Dose Arm 2). The dose regimen may be adapted following review by the DMC;
- Observation Period: 8 weeks; a visit will be scheduled 3 days after the final dose and weekly thereafter to collect safety and efficacy data.

Has been changed to:

- Dosing Period: 1 to 4 weeks; during the Dosing Period subjects will receive weekly doses of UCB7665 (5 doses of 4mg/kg [QWK] in Dose Arm 1, 3 doses of 7mg/kg [QWK] in Dose Arm 2, 2 doses of 10mg/kg [QWK] in Dose Arm 3, 1 dose of 15mg/kg in Dose Arm 4 and 1 dose of 20mg/kg in Dose Arm 5). The dose regimen may be adapted following review by the DMC
- Observation Period: 8 weeks; a visit will be scheduled 3 days after the final dose (or only dose administration for Dose Arms 4 and 5) and weekly thereafter to collect safety and efficacy data

Change #17

Definition of Baseline values (section 3.3)

Table 14–1: Definition of Baseline

Measurement	Definition of Baseline
Safety data: • Clinical chemistry (including proteins) • Hematology (including platelets measured locally) • Coagulation • Urinalysis • Vital signs • 12-lead ECG	• Predose Day 1 or if missing the Screening value[a]
Efficacy variables: • Platelets (measured by ACM Global Central Laboratory) • ITP bleeding scale • NFI-MS	• Platelets: Predose Day 1 or if missing the Screening value • ITP bleeding scale: Predose Day 1 or if missing the Screening assessment • NFI-MS: Predose Day 1
Pharmacodynamic variables: • Total IgG • IgG subclasses	• Total IgG: Predose Day 1 or if missing the Screening value • IgG subclasses: Predose Day 1 or if missing the Screening value • ITP-specific autoantibodies: Predose Day 1
Immunological variables: • Immunoglobulins (IgA, IgE and IgM) • B- and T-lymphocytes • Serum (C3 and C4) and plasma complement (C3a and C5a) • ADA • Serum biomarkers [redacted] • Serum BAFF • Cytokines	• Predose Day 1 (except B- and T-lymphocytes) • B- and T-lymphocytes: Predose Day 1 or if missing the Screening value

ADA=anti-drug antibody; BAFF= B cell activating factor; ECG=electrocardiogram; Ig=immunoglobulin; ITP=primary immune thrombocytopenia; NFI-MS= Neurological Fatigue Index for Multiple Sclerosis; [redacted]

Has been changed to:

Table 14–1: Definition of Baseline

Measurement	Definition of Baseline
Safety data: • Clinical chemistry (including proteins) • Hematology (including platelets measured locally) • Coagulation • Urinalysis • Vital signs • 12-lead ECG • Serum safety biomarkers [redacted]	• Predose Day 1 or if missing the Screening value[a]
Efficacy variables: • Platelets (measured by ACM Global Central Laboratory) • ITP bleeding scale • NFI-MS	• Platelets: Predose Day 1 or if missing the Screening value • ITP bleeding scale: Predose Day 1 or if missing the Screening assessment • NFI-MS: Predose Day 1
Pharmacodynamic variables: • Total IgG • IgG subclasses • • ITP-specific autoantibodies in serum [redacted]	• Total IgG: Predose Day 1 or if missing the Screening value • IgG subclasses: Predose Day 1 or if missing the Screening value • • ITP-specific autoantibodies: Predose Day 1
Immunological variables: • Immunoglobulins (IgA, IgE and IgM) • B- and T-lymphocytes • Serum (C3 and C4) and plasma complement (C3a and C5a) • ADA • Serum BAFF • Cytokines, if applicable (as outlined in the protocol)	• Predose Day 1 (except B- and T-lymphocytes) • B- and T-lymphocytes: Predose Day 1 or if missing the Screening value

ADA=anti-drug antibody; BAFF= B cell activating factor; ECG=electrocardiogram; Ig=immunoglobulin; ITP=primary immune thrombocytopenia; NFI-MS= Neurological Fatigue Index for Multiple Sclerosis; [redacted]

Change #18

Full Analysis Set (Section 3.5.3)

The analysis of the PD (excluding total IgG, IgG subclasses and IgG depletion assay), efficacy and immunologic variables will be performed on the FAS. Efficacy analyses will be repeated for the PPS where stated in the SAP.

Has been changed to:

The analysis of the PD (excluding total IgG, IgG subclasses and IgG depletion assay), efficacy and immunologic variables will be performed on the FAS. Efficacy analyses will be repeated for the pharmacodynamics per protocol set (PD-PPS) where stated in the SAP.

Change #19

Pharmacodynamic Per Protocol Set (section 3.5.6)

The Pharmacodynamic Per Protocol Set (PD-PPS) is a subset of the FAS, consisting of those subjects who had no important protocol deviations potentially affecting the serum concentration of total IgG, as confirmed during a pre-analysis review of the data prior to database lock.

The PD-PPS will be used for the analysis of the total IgG, IgG subclasses and IgG depletion assay.

Has been changed to:

The Pharmacodynamic Per Protocol Set (PD-PPS) is a subset of the FAS, consisting of those subjects who had no important protocol deviations potentially affecting the serum concentration of total IgG, as confirmed during a pre-analysis review of the data prior to database lock. Protocol deviations may not necessarily lead to total exclusion of a subject from the PD-PPS but may lead to exclusion of specific data.

The PD-PPS will be used for the analysis of the total IgG, IgG subclasses and IgG depletion assay.

Change #20

Treatment assignment and treatment groups (Section 3.6)

Treatment (dose arm) assignment for the SS, FAS, PK-PPS, PD-PPS and the PPS will be according to the actual treatment regimen received.

In the event that the number of infusions in the planned dose arms (3x7mg/kg and 5x4mg/kg) are modified following review by the DMC, the data will be summarized based on the actual dose arms completing the study. For example, if the 5x4mg/kg dose arm is modified such that some subjects receive only 4 infusions, then the data will be summarized separately for this new dose regimen.

Has been changed to:

Treatment (dose arm) assignment for the SS, FAS, PK-PPS, PD-PPS and the PPS will be according to the actual planned treatment regimen (reflecting the potential DMC decisions).

In the event that the number of planned infusions in the dose arms are modified following review by the DMC, the data will be summarized based on the actual dose arms completing the study.

For example, if the weekly 5x4mg/kg QWK dose arm is modified such that some subjects receive only 4 infusions, then the data will be summarized separately for this new dose regimen.

Change #21

Changes to protocol-defined analyses (Section 3.9)

All text was deleted with the exception of the final paragraph.

Change #22

Pharmacodynamic data (section 4.2.3)

Measurements BLQ are not anticipated in the PD data (total IgG [measured by ACM Global Central Laboratory, IgG subclasses and total IgG [via IgG depletion assay from LGC]). In the event that any BLQ measurements are received, these will be discussed at the DEM.

Has been changed to:

Measurements BLQ are not anticipated in the PD data (total IgG [measured by ACM Global Central Laboratory] and IgG subclasses). In the event that any BLQ measurements are received, these will be discussed at the DEM.

Change #23

Dates and times (Section 4.2.7)

Partial dates may be imputed for the following reasons:

- Classification of AEs as treatment-emergent
- Classification of medications as prior or concomitant

Has been changed to:

Partial dates may be imputed for the following reasons:

- Classification of AEs as treatment-emergent
- Classification of medications as past, prior or concomitant

Change #24

Handling of repeat and unscheduled measurements

All repeated and unscheduled measurements will be presented in the listings, where applicable. The following general rules will apply to all repeated and unscheduled measurements:

- For repeated measurements obtained prior to the first dose of UCB7665 the latest value (which may be scheduled or unscheduled) will be used in the calculation of descriptive statistics;
- For repeated measurements obtained at the designated Baseline visit, the latest value (which may be scheduled or unscheduled) will be defined as the Baseline provided that this occurred prior to the first dose of UCB7665;
- For repeated measurements obtained at any timepoint after the first dose of UCB7665, the first value of any repeated measurements will be used in the calculation of changes from

Baseline and for the descriptive statistics. Unscheduled and repeated measurements will not be included in the descriptive statistics at timepoints after the first dose of UCB7665.

The above rules are not applicable for the determination of the response variables for the platelet measurements; both scheduled and unscheduled measurements may be used in the calculation of response, time to response and duration of response (Section 8.1.1).

Has been changed to:

All repeated and unscheduled measurements will be presented in the listings, where applicable. The following general rules will apply to all repeated and unscheduled measurements:

- For repeated and unscheduled measurements obtained prior to the first dose of UCB7665 the latest value (which may be scheduled or unscheduled) will be used in the calculation of descriptive statistics;
- For repeated and unscheduled measurements obtained at the designated Baseline visit, the latest value (which may be scheduled or unscheduled) will be defined as the Baseline provided that this occurred prior to the first dose of UCB7665;
- For repeated measurements obtained at any timepoint after the first dose of UCB7665, the first value of any repeated measurements will be used in the calculation of changes from Baseline and for the descriptive statistics. Unscheduled and repeated measurements will not be included in the descriptive statistics at timepoints after the first dose of UCB7665, however they may be included in any summaries for abnormal measurements.

The above rules are not applicable for the determination of the response variables for the platelet measurements; both scheduled and unscheduled measurements may be used in the calculation of response, time to response and duration of response (Section 8.1.1).

Change #25

Interim analyses and data monitoring (Section 4.4)

For the sequential adaptive design in this study, at least 4 interim analyses will be performed. Safety data from the interim analyses will be reviewed by the DMC to monitor the safety, to adapt the dose regimen, and to decide when and if the UCB7665 7mg/kg dose arm should be opened.

Has been changed to:

For the sequential adaptive design in this study, at least 11 interim analyses will be performed. Safety data from the interim analyses will be reviewed by the DMC to monitor the safety, to adapt the dose regimen, and to decide when and if the UCB7665 7mg/kg weekly group (Dose Arm 2), UCB7665 10mg/kg weekly group (Dose Arm 3), UCB7665 15mg/kg group (Dose Arm 4) and UCB7665 20mg/kg group (Dose Arm 5) should be opened. .

Change #26

Examination of subgroups (Section 4.8)

The following subgroups will be defined within each dose arm:

- Use of corticosteroid medication: Present

- Use of corticosteroid medication: Absent

Only medication classified as either 'prior and concomitant' or 'concomitant' will be considered. Past use of corticosteroids (not ongoing after dosing) will not be considered for this classification. The list of applicable Anatomical Therapeutic Chemical (ATC) codes in order to identify the presence/absence of corticosteroids is provided in Section 13.1.

The descriptive summaries for platelets and total IgG will be presented for the subgroups above. Subgroup analyses will only be presented if the number of subjects in each subgroup is greater than or equal to 5 (n≥5) in each stratum.

Has been changed to:

The following subgroups will be defined within each dose arm:

- Use of corticosteroid medication: Present
- Use of corticosteroid medication: Absent
- Responder at the end of previous ITP treatment: No
- Responder at the end of previous ITP treatment: Yes

Only medication classified as either 'prior and concomitant' or 'concomitant' will be considered. Past use of corticosteroids (not ongoing after dosing) will not be considered for this classification. The list of applicable Anatomical Therapeutic Chemical (ATC) codes in order to identify the presence/absence of corticosteroids is provided in Section 13.1.

The descriptive summaries for platelets and total IgG will be presented for the subgroups above.

Change #27

Subject disposition (Section 5.1, second paragraph)

The listing of subject disposition will include the date of informed consent, date of randomization (if applicable), date and time of first and last dose of UCB7665, date of premature termination and primary reason (if applicable) and date of final contact.

The listing of study discontinuation will include the reason for discontinuation and the number of days on UCB7665.

The number of days on IMP will be calculated as follows:

Number of days on IMP= [(Date of Last Dose Received) – (Date of First Dose Received)] + 1

Has been changed to:

The listing of subject disposition will include the date of informed consent, date of genomic consent (if applicable), date of randomization (if applicable), date and time of first and last dose of UCB7665 (if applicable), date of premature termination and primary reason (if applicable) and date of final contact.

The listing of study discontinuation will include the reason for discontinuation and the number of days on UCB7665.

The number of days on UCB7665 will be calculated as follows:

Number of days on UCB7665= [(Date of Last Dose Received) – (Date of First Dose Received)] + 1

Change #28

Other Baseline characteristics (Section 6.2, 4th bullet point)

- ITP-specific autoantibodies [redacted] expressed in terms of optical density (OD)

Has been changed to:

- ITP-specific autoantibodies [redacted] expressed in terms of optical density (OD) for MAIPA analysis and pre-chloroquine minus post chloroquine treated scores for PIFT

Change #29

Efficacy analyses (Section 8)

The following sentence has been added at the end of this section:

Treatment (dose arm) assignment for efficacy analysis will be according to the actual treatment regimen.

Change #30

Platelets (Section 8.1)

The following sentence has been added at the end of this section:

In case rescue medications were taken, only the platelet data up to the time point where the rescue medication was taken will be utilized.

Change #31

Definition of variables (Section 8.1.1, 13th bullet)

- Baseline-corrected AUEC for platelet count calculated from Baseline to the end of study visit (Day 85 in the Observation Period in the 4mg/kg dose arm and Day 71 in the Observation Period in the 7mg/kg dose arm)

Has been changed to:

- Baseline-corrected AUEC for platelet count calculated from Baseline to the end of study visit for each of the defined dose arms.

Change #32

Definition of variables (Section 8.1.1, last bullet)

- The Baseline-corrected AUEC will be calculated according to the following rules:
  - The AUEC will be calculated according to the linear trapezoidal rule using protocol scheduled visits
  - Unscheduled visits will not be included in the calculation

- No imputation of any missing data will be performed
- To account for differences in the timing of Baseline samples for each subject the Baseline measurement will be considered as time zero in the calculation
- The units of the AUEC will be 10^9/L*day
- The measurements at Baseline and at the last visit must be available
- A minimum of 10 out of 14 measurements must be available for the calculation in the 5x4mg/kg dose arm; a minimum of 8 out of 12 measurements must be available for the calculation in the 3x7mg/kg dose arm. These include the Baseline and measurement at the last visit
- The AUEC will not be calculated in the case of early withdrawal from the study

Has been changed to:

- The Baseline-corrected AUEC will be calculated according to the following rules:
  - The AUEC will be calculated according to the linear trapezoidal rule using protocol scheduled visits
  - Unscheduled visits will not be included in the calculation
  - No imputation of any missing data will be performed
  - To account for differences in the timing of Baseline samples for each subject the Baseline measurement will be considered as time zero in the calculation
  - The units of the AUEC will be 10^9/L*day
  - The measurements at Baseline and at the last visit must be available
  - A minimum of 10 out of 14 measurements must be available for the calculation in Dose Arm 1; a minimum of 8 out of 12 measurements must be available for the calculation in Dose Arm 2; a minimum of 7 out of 11 must be available for the calculation in Dose Arm 3; a minimum of 5 out of 9 must be available for the calculation in Dose Arms 4 and 5. These include the Baseline and measurement at the last visit
  - The AUEC will not be calculated in the case of early withdrawal from the study

Change #33

Presentation of results (Section 8.1.2)

Individual platelet and total IgG (including IgG subclasses, measured by ACM Global Central Laboratory) concentrations will be displayed graphically over time (Day 1 to Day 85 for the 4mg/kg dose arm and Day 1 to Day 71 for the 7mg/kg dose arm) for each subject (linear scale). The platelet and total IgG concentrations will be overlaid on the same plot (discrete y-axes) with separate plots for each subject (2 lines per plot). Additional plots will be presented with the platelet and IgG subclasses overlaid on the same figure (5 lines per plot). All plots will include a vertical reference line to indicate when the last dose was administered for each subject.

Has been changed to:

Individual platelet and total IgG (including IgG subclasses, measured by ACM Global Central Laboratory) concentrations will be displayed graphically over time (Day 1 to Day 85 for Dose Arm 1; Day 1 to Day 71 for Dose Arm 2; Day 1 to Day 64 for Dose Arm 3 and Day 1 to Day 57 for Dose Arms 4 and 5) for each subject (linear scale). The platelet and total IgG concentrations will be overlaid on the same plot (discrete y-axes) with separate plots for each subject (2 lines per plot). Additional plots will be presented with the platelet and IgG subclasses overlaid on the same figure (5 lines per plot). All plots will include a vertical reference line to indicate when the last dose was administered for each subject.

Change #34

Analysis of time to responder (Section 8.1.3.2)

The point estimate for the median number of days to response with 95% CIs will be given if estimable. Further a summary including the number and percent of censored subjects, the number of responders and total subjects by dose arm and in total will be given.

Has been changed to:

The point estimate for the median number of days to response with 90% CIs will be given if estimable. Further a summary including the number and percent of censored subjects, the number of responders and total subjects by dose arm and in total will be given.

Change #35

Pharmacokinetics (Section 9.1)

The following paragraphs have been added at the end of this section:

The above summaries will be repeated separately for the subjects in the PK/PD substudy sample, in the event of very few subjects (<10 subjects) only listings will be provided.

Further analyses and summaries relating to the population PK analyses and PK/PD analyses will described in a separate SAP and reported separately.

Change #36

Pharmacodynamics (Section 9.2)

The following paragraph has been added at the end of this section:

The above summaries will be repeated separately for the subjects in the PK/PD substudy sample, in the event of very few subjects (<5 subjects) only listings will be provided.

Change #37

ITP-specific autoantibodies (Section 9.2.1)

In order to evaluate the relationship between changes in platelet count and total IgG, IgG subclasses and ITP-specific autoantibodies the following figures will be presented:

- Individual ITP-specific autoantibodies and platelet counts (measured by ACM Global Central Laboratory) will be displayed graphically over time (Day 1 to Day 85 for the 4mg/kg dose

arm and Day 1 to Day 71 for the 7mg/kg dose arm) for each subject (linear scale). The ITP-specific autoantibodies [redacted] and platelet counts will be overlaid on the same plot (discrete y-axes) with separate plots for each subject (4 lines per plot)

- A scatter plot of platelet counts (measured by ACM Global Central Laboratory) versus ITP-specific autoantibodies measured at the same timepoint will be presented in linear scale, with separate plots for each dose arm and for each variable [redacted] All subjects and timepoints will be included on the same plot for each dose arm
- Individual ITP-specific autoantibodies and total IgG (from ACM Global Central Laboratory) will be displayed graphically over time (Day 1 to Day 85 for the 4mg/kg dose arm and Day 1 to Day 71 for the 7mg/kg dose arm) for each subject (linear scale). The ITP-specific autoantibodies [redacted] and total IgG will be overlaid on the same plot (discrete y-axes) with separate plots for each subject (4 lines per plot). These plots will be repeated for each of the IgG subclasses.

Has been changed to:

In order to evaluate the relationship between changes in platelet count and total IgG, IgG subclasses and ITP-specific autoantibodies the following figures will be presented:

- Individual ITP-specific autoantibodies and platelet counts (measured by ACM Global Central Laboratory) will be displayed graphically over time (Day 1 to Day 85 for Dose Arm 1; Day 1 to Day 71 for Dose Arm 2; Day 1 to Day 64 for Dose Arm 3 and Day 1 to Day 57 for Dose Arms 4 and 5) for each subject (linear scale). The ITP-specific autoantibodies [redacted] and platelet counts will be overlaid on the same plot (discrete y-axes) with separate plots for each subject (4 lines per plot)
- A scatter plot of platelet counts (measured by ACM Global Central Laboratory) versus ITP-specific autoantibodies measured at the same timepoint will be presented in linear scale, with separate plots for each dose arm and for each variable [redacted]. All subjects and timepoints will be included on the same plot for each dose arm
- Individual ITP-specific autoantibodies and total IgG (from ACM Global Central Laboratory) will be displayed graphically over time (Day 1 to Day 85 for Dose Arm 1; Day 1 to Day 71 for Dose Arm 2; Day 1 to Day 64 for Dose Arm 3 and Day 1 to Day 57 for Dose Arms 4 and 5) for each subject (linear scale). The ITP-specific autoantibodies [redacted] and total IgG will be overlaid on the same plot (discrete y-axes) with separate plots for each subject (4 lines per plot). These plots will be repeated for each of the IgG subclasses.

Change #38

Serum biomarkers ([redacted] BAFF) will be listed by dose arm and timepoint including changes from Baseline. Descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by dose arm and timepoint for both absolute values and changes from Baseline.

Has been changed to:

Serum safety biomarkers [redacted] and BAFF will be listed by dose arm and timepoint including changes

from Baseline. Descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by dose arm and timepoint for both absolute values and changes from Baseline.

Change #39Anti-drug antibodies (Section 9.3.4)

Full section has been updated with the following text:

Immunological variables will be analyzed for all subjects in the SS. Anti-UCB7665 antibody data will be summarized at each scheduled visit, and the rate of ADA positive subjects will be calculated.

A calibrator screening assay measures ADA as relative mass units (RMU) in units/mL. A cut point will be determined by the bioanalytical laboratory that will be used to determine the status of ADA as above the cut point (ACP) or below the cut point (BCP). The RMU result from the calibrator screening assay will be used to report ADA levels.

For any ADA levels that are ACP, a further confirmatory assay will be performed, the results of which will be determined as either 'confirmed positive' (CP) or 'not confirmed positive' (NCP).

The results for the ADA measurements will be listed by treatment group and time point based on the SS, including the screening assay, confirmatory assay and level in units/mL.

The following definitions will be applied:

- An ADA status of positive will be concluded for any subject with an ADA level that is ACP and CP at any time point
- An ADA status of negative will be concluded for any subject with an ADA level that is either BCP or ACP and NCP at any time point
- A subject will be classified as having ADA positivity at Baseline if the Day 1, predose result is ACP and CP
- A subject will be classified as having treatment-emergent ADA positivity when meeting one of the following criteria:
  - The Baseline result is either BCP or ACP and NCP, and at least one post-Baseline time point is ACP and CP
  - The Baseline result is positive (ACP and CP) and at least one post-Baseline measurement shows a pre-defined fold increase in units/mL from the Baseline value (the fold increase from Baseline required to meet this criteria will be defined with the development of the assay and will be included in the TFLs)
- A subject will be classified as overall positive if at least one post-Baseline measurement is ACP and CP (this includes subject who have negative results at Baseline)
- A subject will be classified as overall negative if at all post-Baseline visits the ADA status is negative (this includes subjects who have positive [ACP and CP] results at Baseline)
- Inconclusive: pre-ADA negative or pre-ADA positive subjects with negative ADA samples post baseline for which time matched drug levels are above the demonstrated drug tolerance characteristics of the ADA screening assay at one or more sampling time points

- Missing: relevant samples are missing

The ADA status (positive/negative) will be summarized as a categorical endpoint (number and percentage of subjects) for all time points and overall, based on the SS.

In addition, the first occurrence of treatment-emergent ADA positivity (based on the definitions above) will be summarized (number and percentage of subjects) at each post-Baseline visit, based on the SS. This tabulation will count the number of subjects at each post-Baseline visit who fulfill at least one of the above defined criteria for treatment-emergent positivity; subjects will be counted in the numerator based on the earliest visit at which one of these criteria is fulfilled. At other visits, subjects will be counted in the denominator (assuming a measurement is available). For all tabulations, percentages will be based on the number of observations at each visit.

A separate listing will be presented (based on the SS) showing the UCB7665 concentrations and ADA measurements in the same output in adjacent columns. The listing will include the UCB7665 concentration, ADA status (ACP or BCP) and confirmatory assay results if applicable (NCP or CP), together with the units/mL for results that are CP. In addition the time since the previous administration of IMP will be reported (in days).

Finally, individual subject plots (based on the SS) will be presented displaying the ADA units/mL and UCB7665 concentrations overlaid on the same figure. The figure will also show the timing and dose of each administration of UCB7665 received during the study.

The rules for handling values that are BLQ in the UCB7665 concentration data are described in Section 4.2.5 For the ADA data, any negative results for which there are no units/mL available at a specific visit will be substituted with 0.001 for the purpose of the figure.

Change #40

Extent of exposure (Section 10.1)

The planned dose regimens are as follows:

- Subjects in Dose Arm 1 will receive 5 sc doses of UCB7665 4mg/kg at 1-week intervals
- Subjects in Dose Arm 2 will receive 3 sc doses of UCB7665 7mg/kg at 1-week intervals

Has been changed to:

The planned dose regimens are as follows:

- Subjects in Dose Arm 1 will receive 5 sc doses of UCB7665 4mg/kg at 1-week intervals
- Subjects in Dose Arm 2 will receive 3 sc doses of UCB7665 7mg/kg at 1-week intervals
- Subjects in Dose Arm 3 will receive 2 sc doses of UCB7665 10mg/kg at 1-week intervals
- Subjects in Dose Arm 4 will receive 1 sc dose of UCB7665 15mg/kg
- Subjects in Dose Arm 5 will receive 1 sc doses of UCB7665 20mg/kg

Change #35

Adverse events (Section 10.2)

In addition, AEs will be classified according to the CTCAE Version 4.03 for severity. For any AEs where it is not possible to provide a CTCAE grading, the events will be assessed using a standard intensity classification (mild, moderate and severe). For the purpose of the tabulations all CTCAE severity classifications will be mapped to a mild/moderate/severe grade as described in the below sections.

Has been changed to:

In addition, AEs will be classified according to the CTCAE Version 4.03 for severity. For any AEs where it is not possible to provide a CTCAE grading, the events will be assessed using a standard intensity classification (mild, moderate and severe). For the purpose of the tabulations all CTCAE severity classifications will be mapped to a mild/moderate/severe grade as described in the below sections. Bleeding events classified as Grade 1 or Grade 2 (based on CTCAE) will not be reported as AEs as these will be assessed and reported as part of the ITP-BAT assessments. Bleeding events classified as Grade 3 or higher, based on CTCAE, will be reported as AEs.

Change #36

Potential drug-induced liver injury (Section 10.3.1)

Subjects who meet any of the following criteria at a given timepoint will be listed:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase ≥5 x upper limit of normal (ULN)
- Alanine aminotransferase or AST increase ≥3 x ULN and total bilirubin ≥2 x ULN
- Alanine aminotransferase or AST increase ≥3 x ULN (and ≥2 x Baseline) and <5 x ULN, with total bilirubin <2 x ULN
- Alanine aminotransferase or AST increase ≥5 x ULN (and ≥2 x Baseline), with total bilirubin <2 x ULN
- Alanine aminotransferase or AST increase ≥8 x ULN
- Alkaline phosphatase (ALP) ≥2 x ULN

Has been changed to:

Subjects who meet any of the following criteria at a given timepoint will be listed:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase ≥5 x upper limit of normal (ULN)
- ALT or AST increase ≥3 x ULN and total bilirubin ≥2 x ULN
- ALT or AST increase ≥3 x ULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity.
- ALT or AST increase ≥3 x ULN (and ≥2 x Baseline) and <5 x ULN, with total bilirubin <2 x ULN

- ALT or AST increase ≥5 x ULN (and ≥2 x Baseline), with total bilirubin <2 x ULN and no eosinophilia (i.e., ≤5%), with no fever, rash, or symptoms of hepatitis
- Alkaline phosphatase (ALP) ≥2 x ULN
- **Change #37**

Treatment group assignment for the TFLs (Section 13.6)

	Treatment Label		
TFL group	**UCB7665 5x4mg/kg**	**UCB7665 3x7mg/kg**	**All Subjects**
Subject disposition	X	X	X
Protocol deviations	X	X	X
Demographics	X	X	X
Baseline characteristics	X	X	
Medical history	X	X	X
Prior and concomitant medications	X	X	X
Adverse events	X	X	X
Safety measurements (including safety laboratory tests, vital signs and ECG)	X	X	
Efficacy (platelets, ITP bleeding score, NFI-MS)	X	X	
PK	X	X	
PD (ITP-specific autoantibodies, total IgG,IgG subclasses and IgG depletion assay)	X	X	
Immunological (serum immunoglobulins, B- and T-lymphocytes, serum and plasma complement, serum biomarkers, ADA and cytokines)	X	X	

Has been changed to:

	Treatment Label[a]					
TFL group	**UCB7665 5x4mg/kg weekly (Dose Arm 1)**	**UCB7665 3x7mg/kg weekly (Dose Arm 2)**	**UCB7665 2x10mg/kg weekly (Dose Arm 3)**	**UCB7665 1x15mg/kg (Dose Arm 4)**	**UCB7665 1x20mg/kg (Dose Arm 5)**	**All Subjects**
Subject disposition	X	X	X	X	X	X
Protocol deviations	X	X	X	X	X	X
Demographics	X	X	X	X	X	X
Baseline characteristics	X	X	X	X	X	
Medical history	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Safety measurements (including safety laboratory tests, vital signs and ECG)	X	X	X	X	X	
Efficacy (platelets, ITP bleeding score, NFI-MS)	X	X	X	X	X	
PK	X	X	X	X	X	
PD (ITP-specific autoantibodies, total IgG,IgG subclasses and IgG depletion assay)	X	X	X	X	X	
Immunological (serum immunoglobulins, B- and T-lymphocytes, serum and plasma complement, serum biomarkers, ADA and cytokines)	X	X	X	X	X	

14.2 Amendment 2

14.2.1 Rationale for the amendment

The second SAP amended has been developed to include some requirements observed during the study Dry Run as well as to include the ad-hoc outputs which were not part of the initial SAP. Updates made in the CRF are also described here. Few other minor formatting updates were made.

14.2.2 List of changes

Specific changes

Change #1

General along the document

In some places, “timepoint” has been changed to “visit” to make the text more appropriate to how the data is collected; hence “timpoint” is now only referring to a “moment of time” within a visit or to a general moment during the study conduction.

Change #2

Definition of Baseline values (Section 3.3)

Baseline will be the last available predose value prior to the first infusion of UCB7665, or if missing, the Screening values.

Measurement-specific Baseline timepoints (based on the planned measurements) are presented in Table 3–1.

Table 14–1: Definition of Baseline

Measurement	Definition of Baseline
Safety data: • Clinical chemistry (including proteins) • Hematology (including platelets measured locally) • Coagulation • Urinalysis • Vital signs • 12-lead ECG • Serum safety biomarkers [redacted]	• Predose Day 1 or if missing the Screening value[a]
Efficacy variables: • Platelets (measured by ACM Global Central Laboratory) • ITP bleeding scale • NFI-MS	• Platelets: Predose Day 1 or if missing the Screening value • ITP bleeding scale: Predose Day 1 or if missing the Screening assessment • NFI-MS: Predose Day 1
Pharmacodynamic variables: • Total IgG • IgG subclasses • • ITP-specific autoantibodies in serum [redacted]	• Total IgG: Predose Day 1 or if missing the Screening value • IgG subclasses: Predose Day 1 or if missing the Screening value • ITP-specific autoantibodies: Predose Day 1
Immunological variables: • Immunoglobulins (IgA, IgE and IgM) • B- and T-lymphocytes • Serum (C3 and C4) and plasma complement (C3a and C5a) • ADA • Serum BAFF • Cytokines, if applicable (as outlined in the protocol)	• Predose Day 1 (except B- and T-lymphocytes) • B- and T-lymphocytes: Predose Day 1 or if missing the Screening value

If the Screening value is to be used as Baseline (i.e., predose Day 1 is missing), the highest value for the platelet count obtained from the 2 measurements at Screening will be used as the Baseline.

Has been changed to:

Baseline will be the last available predose value prior to the first infusion of UCB7665, or if missing, the latest no missing value prior to Baseline (screening value or unscheduled visit value).

Measurement-specific Baseline timepoints (based on the scheduled or unscheduled measurements) are presented in Table 3–1.

Table 14–1: Definition of Baseline

Measurement	Definition of Baseline
Safety data: • Clinical chemistry (including proteins) • Hematology (including platelets measured locally) • Coagulation • Urinalysis • Vital signs • 12-lead ECG • Serum safety biomarkers [redacted]	• Predose Day 1 or if missing the latest no missing value prior to Day 1
Efficacy variables: • Platelets (measured by ACM Global Central Laboratory) • ITP bleeding scale • NFI-MS	• Platelets: Predose Day 1 or if missing the latest no missing value prior to Day 1 • ITP bleeding scale: Predose Day 1 or if missing the latest no missing value prior to Day 1 • NFI-MS: Predose Day 1
Pharmacodynamic variables: • Total IgG • IgG subclasses • • ITP-specific autoantibodies in serum [redacted]	• Total IgG: Predose Day 1 or if missing the latest no missing value prior to Day 1 • IgG subclasses: Predose Day 1 or if missing the latest no missing value prior to Day 1 • ITP-specific autoantibodies: Predose Day 1
Immunological variables: • Immunoglobulins (IgA, IgE and IgM) • B- and T-lymphocytes • Serum (C3 and C4) and plasma complement (C3a and C5a) • ADA • Serum BAFF • Cytokines, if applicable (as outlined in the protocol)	• Predose Day 1 (except B- and T-lymphocytes) • B- and T-lymphocytes: Predose Day 1 or if missing the latest no missing value prior to Day 1

If the latest non missing value prior to Baseline is to be used as Baseline (i.e., predose Day 1 is missing), the highest value for the platelet count obtained from the last 2 non missing measurements prior to Baseline will be used as the Baseline.

Change #3

Electrocardiograma data (Section 4.2.6)

For the ECG data, all calculations of changes from Baseline and descriptive statistics will be based on the mean of the triplicate assessments at each timepoint. In the event that there are not 3 available measurements at a given timepoint, the mean will be calculated based on the number of measurements for which data is provided.

Has been changed to:

For the ECG data, all calculations of changes from Baseline and descriptive statistics will be based on the mean of the triplicate assessments at each visit. In the event that there are not 3 available measurements at a given visit, the mean will be calculated based on the number of measurements for which data is provided (variables analyzed will be those described in Section 10.4.2).

Change #4

Examination of subgroups (Section 4.8)

The following subgroups will be defined within each dose arm:

- Use of corticosteroid medication: Present
- Use of corticosteroid medication: Absent
- Responder at the end of previous ITP treatment: No
- Responder at the end of previous ITP treatment: Yes

Only medication classified as either 'prior and concomitant' or 'concomitant' and medical procedure will be considered for ITP treatment. Responder categories will be defined taking into account the last valid value reported (either Yes or No) for each patient. Past use of corticosteroids (not ongoing after dosing) will not be considered for this classification. The list of applicable Anatomical Therapeutic Chemical (ATC) codes in order to identify the presence/absence of corticosteroids is provided in Section 13.1.

Has been changed to:

The following subgroups will be defined within each dose arm:

- Use of corticosteroid medication: Present/Absent
- Responder at the end of previous ITP treatment: No/Yes/Unknown
- Previous intravenous immunoglobulin (IVIg) therapy: Yes/No
- Number of previous ITP therapies: ≤2/>2

Only medication classified as either 'prior and concomitant' or 'concomitant' and medical procedure will be considered for ITP treatment. Responder categories will be defined taking into account the last reported ITP treatment value (either Yes or No) for each patient. If this value is

unknown, the second-last reported ITP treatment value will be used, then the third-last, and so on, until a known response is provided. The Unknown responder category will only be considered in cases where the investigator has never reported a category (Yes or No) for any of the previous ITP treatments. Past use of corticosteroids (not ongoing after dosing) will not be considered for this classification. The list of applicable Anatomical Therapeutic Chemical (ATC) codes in order to identify the presence/absence of corticosteroids is provided in Section 13.1.

Change #5

Demographics (Section 6.1)

All Baseline demographic characteristics (with the exception of year of birth) will be summarized by dose arm and overall for the SS.

Has been changed to:

All Baseline demographic characteristics (with the exception of year of birth) will be summarized by dose arm and overall for the SS. Number and percentage of patients with a BMI equal or higher than 30 will also be summarized by dose arm.

Change #6

Other Baseline characteristics (Section 6.2)

Baseline disease characteristics will be listed and summarized by dose arm for the SS including the following:

- Duration of disease
- Karnofsky Performance Scale Index
- ITP bleeding scale (skin, visible mucosae and organs, with gradation of severity [SMOG])
- ITP-specific autoantibodies [redacted] expressed in terms of optical density (OD) for MAIPA analysis and pre-chloroquine minus post chloroquine treated scores for PIFT
- Immunological variables (IgG [including total IgG and IgG subclasses measured by ACM Global Central Laboratory], IgM, IgA, IgE and lymphocytes [B and T])
- Serum (C3 and C4) and plasma complement levels (C3a and C5a)
- Platelet count (measured by ACM Global Central Laboratory)

Has been changed to:

Baseline disease characteristics will be listed and summarized by dose arm for the SS including the following:

- Duration of disease
- Karnofsky Performance Scale Index
- ITP bleeding scale (skin, visible mucosae and organs, with gradation of severity [SMOG])

- ITP-specific autoantibodies [redacted] expressed in terms of optical density (OD) for MAIPA analysis and pre-chloroquine minus post chloroquine treated scores for PIFT
- Immunological variables (IgG [including total IgG and IgG subclasses measured by ACM Global Central Laboratory], IgM, IgA, IgE and lymphocytes [B and T])
- Serum (C3 and C4) and plasma complement levels (C3a and C5a)
- Platelet count (measured by ACM Global Central Laboratory)
- Number of prior ITP medications received
- Number of prior ITP medications received categorized
- Prior ITP medications received by preferred term
- Medical history of splenectomy (MedDRA v20.2, Preferred Term=”Splenectomy”)

Change #7

Measurements of treatment compliance (Section 7)

The study medication will be administered and monitored by the investigator or designee. The measured plasma concentrations will provide information regarding compliance. Any dosing deviations (eg, incomplete infusion volume administered, infusion temporarily interrupted, infusion discontinued) will be discussed at the DEM and any actions taken regarding the analyses will be documented accordingly and discussed in the CSR.

Has been changed to:

The study medication will be administered and monitored by the investigator or designee. The measured plasma concentrations will provide information regarding compliance. Any dosing deviations (eg, incomplete infusion volume administered, infusion discontinued) will be discussed at the DEM and any actions taken regarding the analyses will be documented accordingly and discussed in the CSR.

Change #8

Platelets (Section 8.1)

All efficacy analyses are based on platelet count measured by ACM Global Central Laboratory. Measurements of platelet count obtained by the local laboratory will be listed and summarized as part of the safety laboratory data. These are not included in the analyses described in the sections below. All tabulations and mean figures will be presented for both the FAS and the PPS unless otherwise stated. Individual figures will be presented for the FAS only. In case rescue medications are taken, only the platelet data up to the time point where the rescue medication is taken will be utilized.

Has been changed to:

All efficacy analyses are based on platelet count measured by ACM Global Central Laboratory. Measurements of platelet count obtained by the local laboratory will be listed and summarized as part of the safety laboratory data. These are not included in the analyses described in the sections below. All tabulations and mean figures will be presented for both the FAS and the PPS unless

otherwise stated. Median figures and individual figures will be presented for the FAS only. In case rescue medications are taken, only the platelet data up to the time point where the rescue medication is taken will be utilized for the summary tables. Listings will contain all the data but a footnote will be included indicating the patients for which some data has been excluded from the summary tables.

Change #9

Presentation of results (Section 8.1.2)

The individual platelet measurements will be listed by dose arm and timepoint including changes from Baseline (Day 1, predose). Descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by dose arm and scheduled timepoint for both absolute values and changes from Baseline. Summary tabulations by dose arm will be repeated for the subgroups defined in Section 4.8 (based on the FAS only).

Has been changed to:

The individual platelet measurements will be listed by dose arm and visit including changes from Baseline (Day 1, pre-dose). Descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by dose arm and scheduled visit for both absolute values and changes from Baseline based on the FAS only. Summary tabulations by dose arm will be repeated for the subgroups defined in Section 4.8 (based on the FAS only too).

Change #10

Presentation of results (Section 8.1.2)

Mean and mean change from Baseline platelet values will be plotted versus scheduled visit by dose arm with all dose arms overlaid on the same plot. Similar plots will be provided for response rate over time (response, complete response and platelet count $\geq 50x10^9/L$).

Individual platelet and total IgG (including IgG subclasses, measured by ACM Global Central Laboratory) concentrations will be displayed graphically over time (Day 1 to Day 85 for Dose Arm 1; Day 1 to Day 71 for Dose Arm 2; Day 1 to Day 64 for Dose Arm 3 and Day 1 to Day 57 for Dose Arms 4 and 5) for each subject (linear scale). The platelet and total IgG concentrations will be overlaid on the same plot (discrete y-axes) with separate plots for each subject (2 lines per plot). Additional plots will be presented with the platelet and IgG subclasses overlaid on the same figure (5 lines per plot). All plots will include a vertical reference line to indicate when the last dose was administered for each subject.

Has been changed to:

Mean and mean change from Baseline platelet values will be plotted versus scheduled visit by dose arm with all dose arms overlaid on the same plot. Similar plots will be provided for response rate over time (response, complete response and platelet count ≥50x109/L). Mean median, mean change and median change from Baseline total IgG results will be plotted over time by dose arm with all dose arms overlaid on the same plot.

Individual platelet and total IgG (including IgG subclasses, measured by ACM Global Central Laboratory) concentrations will be displayed graphically over time (Day 1 to Day 85 for Dose Arm 1; Day 1 to Day 71 for Dose Arm 2; Day 1 to Day 64 for Dose Arm 3 and Day 1 to Day 57 for Dose Arms 4 and 5) for each subject (linear scale). The platelet and total IgG concentrations

will be overlaid on the same plot (discrete y-axes) with separate plots for each subject (2 lines per plot). Additional plots will be presented with the platelet and IgG subclasses overlaid on the same figure (5 lines per plot). All plots will include a vertical reference line to indicate when the last dose was administered for each subject. The mean (and median in a separate plot) change from baseline in platelet and the mean (median) change from baseline in total IgG concentrations will be overlaid on the same plot (discrete y-axes) with separate plots for each dose arm (2 lines per plot).

Change #11

Analysis of responder rate (Section 8.1.3.3)

The following paragraphs have been added at the end of this subsection:

Moreover, for responder rate, summary tabulations by dose arm will be repeated according to previous intravenous immunoglobulin therapy (Yes/No) and the number of previous medications (≤2/>2). Percentage of days without bleeding will also be described by dose arm for each type of response (response, complete response and platelet Count >=50x10/L). Percentage of days without bleeding is calculated using the following formula:

((N of visits with a SMOG score – N of these visits where bleeding occurred) / N of visits with a SMOG score) x 100

In case rescue medications are taken, only the data up to the start date of rescue medication will be utilized for the summary tables. Listings will contain all the data but a footnote will be included indicating the patients for which some data has been excluded from the summary tables. In case of partial dates, the imputation rules for partial dates described in Section 4.2.7 will be applied.

Change #12

IPT bleeding score and platelet response (Section 8.2.1.1)

All response variables described above will be listed by dose arm and subject and summarized by dose arm and visit where appropriate. The responder rates will be tabulated as described in Section 8.1.3.3. All analyses described in this section will be performed for the FAS.

Has been changed to:

All response variables described above will be listed by dose arm and subject and summarized by dose arm and visit where appropriate. The responder rates will be tabulated as described in Section 8.1.3.3. Moreover the change in category of bleeding from Baseline will also be presented in shift table at all post-Baseline timepoints by dose arm. Summary tabulations for Clinical Response by dose arm will be repeated according to previous intravenous immunoglobulin therapy (Yes/No) and the number of previous medications (≤2/>2). All analyses described in this section will be performed for the FAS.

In case rescue medications are taken, only the data up to the start date of rescue medication will be utilized for the summary tables. Listings will contain all the data but a footnote will be included indicating the patients for which some data has been excluded from the summary tables. In case of partial dates, the imputation rules for partial dates described in Section 4.2.7 will be applied.

Change #13

Pharmacokinetics (Section 9.1)

The following sentence has been removed from this section:

If applicable, a separate listing of UCB7665 concentrations in the cerebrospinal fluid (CSF) will be presented by dose arm. These data will not be summarized.

Change #14

ITP-specific autoantibodies (Section 9.2.1)

The results will be expressed in the form of the OD value.

ITP-specific autoantibodies (OD value) will be listed by dose arm and timepoint. Values that are ALD will be displayed as such in the listings.

Has been changed to:

The results will be expressed in the form of the OD value and for indirect PIFT method using the following categories: 0 = negative; 0.5 = week positive; 1 = positive; 2 = positive; 3 = strong positive; 4 = strong positive.

ITP-specific autoantibodies (OD value and PIFT categories) will be listed by dose arm and timepoint. OD values that are ALD will be displayed as such in the listings.

Change #15

ITP-specific autoantibodies (Section 9.2.1)

The following sentence has been added at the end of this section:

Only patients with positive ITP-specific autoantibodies will be described.

Change #16

Total IgG and IgG subclasses (Section 9.2.2)

Mean and mean percentage change from Baseline values in total IgG (measured by ACM Global Central Laboratory) will be plotted over time by dose arm with all dose arms overlaid on the same plot. Additional figures will be presented in conjunction with the ADA results as described in Section 9.3.4 as well as figures in conjunction with the platelet results as described in Section 8.1.1.

Finally, a separate figure will be presented by subject showing the individual total IgG results from ACM Global Central Laboratory.

Any values that are BLQ or ALQ will be handled as described in Section 4.2.32.

All analyses described in this section will be performed on the PD-PPS. In case rescue medications are taken, only the IgG data up to the timepoint where the rescue medication is taken will be utilized for the summary tables. Listings will contain all the data but a footnote will be included indicating the patients for which some data has been excluded from the summary tables.

Has been changed to:

Mean, median, median change from Baseline and mean and median percentage change from Baseline values in total IgG (measured by ACM Global Central Laboratory) will be plotted over time by dose arm with all dose arms overlaid on the same plot. Additional figures will be presented in conjunction with the ADA results as described in Section 9.3.4 as well as figures in conjunction with the platelet results as described in Section 8.1.1.

Finally, a separate figure will be presented by subject showing the individual total IgG results from ACM Global Central Laboratory.

Any values that are BLQ or ALQ will be handled as described in Section 4.2.3.

All analyses described in this section will be performed on the PD-PPS. In case rescue medications are taken, only the IgG data up to the start date of rescue medication will be utilized for the summary tables. Listings will contain all the data but a footnote will be included indicating the patients for which some data has been excluded from the summary tables. In case of partial dates, the imputation rules for partial dates described in Section 4.2.7 will be applied.

Change #17

Adverse events (Section 10.2)

In addition the listing will flag AEs that led to discontinuation, TEAEs, AEs of interest, AEs of special interest, infusion reactions and SAEs.

Has been changed to:

In addition the listing will flag AEs that led to discontinuation, TEAEs, AEs of interest, AEs of special interest, infusion reactions, SAEs, Sampson criteria and CTCAE grade.

Change #18

Clinical laboratory evaluations (Section 10.3)

Values outside the reference range for the numeric variables will be flagged in the listings and in addition, will be listed separately. The reference ranges will also be reported in the listings.

Has been changed to:

Values outside the reference range for the numeric variables will be flagged in the listings and in addition, results considered as markedly abnormal laboratory results (CTCAE Grade 3 and above) will be listed separately. The reference ranges will also be reported in the listings.

Change #19

Vital signs (Section 10.4.1)

Table 10-2 has been updated as follows:

Variable	Unit	Low	High
Systolic blood pressure	mmHg	Value <90 and ≥20 decrease from Baseline	Value >180 and ≥15 increase from baseline
Diastolic blood pressure	mmHg	Value <50 and ≥15 decrease from Baseline	Value >105 and ≥15 increase from Baseline

Change #20

Electrocardiograms (Section 10.4.2)

The following sentence has been added at the end of this subsection:

The number and percentage of subjects with TEMA/PCS ECG values will be summarized by dose arm at each timepoint.

Change #21

Electrocardiograms (Section 10.4.2)

- QT corrected for heart rate using Fridericia's formula (QTcF)

The individual measurements and the mean of the triplicate measurements will be reported in the by-subject listings. The listing will also include the change from Baseline and percentage change from Baseline (based on the mean of the triplicate measurements at each timepoint) and will be presented by dose arm and timepoint.

Has been changed to:

- QT corrected for heart rate using Fridericia's formula ($QTcF = QT/RR^{0.33}$)

The individual measurements and the mean of the triplicate measurements will be reported in the by-subject listings. The listing will also include the change from Baseline and percentage change from Baseline (based on the mean of the triplicate measurements at each timepoint). TEMA/PCS ECG values will be flagged in the listing.

Change #22

Electrocardiograms (Section 10.4.2)

The following table has been added:

Variable	Criteria
QT corrected for heart rate using Fridericia's formula (QTcF)	≥501ms OR ≥60ms compared to baseline
PR prolongation	≥210ms and ≥10ms change from baseline

Change #23

Classification of markedly abnormal laboratory values based in CTCAE grades (Section 13.5)

Table 13-2 has been updated as follows:

Category	Panel	Variable	Criteria (CTCAE [a]Grade 3 and above)
Hematology	Red blood cell	Hemoglobin (Decrease)	<8g/dL (<80g/L)

Category	Panel	Variable	Criteria (CTCAE [a]Grade 3 and above)
		Hemoglobin (Increase)	>4g/dL (>40g/L) above ULN OR >4g/dL (>40g/L) above baseline if baseline is > ULN
	White blood cell	WBC count (Decrease)	<2000/mm^3 (<2.0x10^9/L)
		WBC count (Increase)	>20,000/mm^3
	White blood cell differential	ALC (Decrease)	<500/mm^3 (<0.5x10^9/L)
		ALC (Increase)	>20,000/mm^3 (>20x10^9/L)
		ANC	<1000/mm^3 (<1.0x10^9/L)
Chemistry	Liver Function	ALT	>5.0xULN
		ALP	>5.0xULN
		AST	>5.0xULN
		Total bilirubin	>3.0xULN
		GGT	>5.0xULN
	Kidney Function	Creatinine	>3.0xbaseline value OR >3.0xULN
		Creatinine (Acute kidney injury)	>3xbaseline value OR >4xULN
		Creatinine phosphokinase	>5xULN
		eGFR or CrCI	≤29ml/min/1.73m^2
	Minerals	Calcium (Decrease)	corrected <7mg/dL (<1.75mmol/L); ionized <0.9 mmol/L
		Calcium (Increase)	corrected >13.5mg/dL (>3.1mmol/L); ionized >1.8mmol/L
		Magnesium (Decrease)	<0.4mmol/L (<0.9mg/dL)
		Magnesium (Increase)	>1.23mmol/L (>3mg/dL)
		Phosphate	<0.6mmol/L (<2mg/dL)
	Metabolic	Glucose (Decrease)	<2.2mmol/L (<40mg/dl)

Category	Panel	Variable	Criteria (CTCAE [a]Grade 3 and above)
		Glucose (Increase)	>250mmol/L (>13.9mg/dl)
	Electrolytes	Potassium (Decrease)	<3.0mmol/L
		Potassium (Increase)	>6.0mmol/L
		Sodium (Decrease)	<130mmol/L
		Sodium (Increase)	>155mmol/L
	Lipids	Total cholesterol	>10.34mmol/L (>400mg/dL)
		Triglycerides	>5.7mmol/L (>500mg/dL)
	Proteins	Albumin	<20g/L (<2g/dL)
	Other	Amylase	>2.0xULN

14.3 Amendment 3

14.3.1 Rationale for the amendment

Various updates were suggested prior to and during the Data Evaluation Meeting in December 2018.

14.3.2 List of changes

Change #1

Front page

SAP amendment 3 has been added:

Final SAP	07 Oct 2016
SAP Amendment 1	14 Nov 2017
SAP Amendment 2	14 May 2018
SAP Amendment 3	24 Jan 2019

Change #2

List of Abbreviations

The following abbreviations have been added:-

IVIg	intravenous immunoglobulin
TPO-R	thrombopoietin-receptor

Change #3

Introduction (4th paragraph)

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP amendment will be updated accordingly. In addition, if analysis definitions have to be modified or updated prior to database lock, a further SAP amendment will be

required. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, these changes will be described in the CSR together with the associated rationale. The content of this SAP is compatible with the International Council for Harmonisation (ICH)/Food and Drug Administration (FDA) E9 Guidance documents.

Has been changed to:

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP amendment will be updated accordingly. In addition, if analysis definitions have to be modified or updated prior to database lock, a further SAP amendment will be required.

This SAP amendment 3 is due to various updates and clarifications of the analysis definitions suggested prior to and during the Data Evaluation Meeting 3 part 1 in December 2018.

If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, these changes will be described in the CSR together with the associated rationale. The content of this SAP is compatible with the International Council for Harmonisation (ICH)/Food and Drug Administration (FDA) E9 Guidance documents.

Change #4

Table 3-1 (Definition of Baseline)

The following footnote has been removed:

Error! Reference source not found. Platelets measured locally are not measured at Screening.

Change #5

Full Analysis Set (Section 3.5.3)

The following paragraph has been added:

Platelet data for subjects who have taken rescue medications (based on medical review and defined in Section 8.1.4) will only be utilized in the summary tables up to the start of these rescue medications.

Change #6

Per Protocol Set (Section 3.5.4)

The Per Protocol Set (PPS) is a subset of the FAS, consisting of those subjects who had received all foreseen sc infusions, had a platelet count measurement (measured by ACM Global Central Laboratory) during the Observation Period, and no important protocol deviations that may potentially affect the platelet count as confirmed during a pre-analysis review of the data prior to database lock. Protocol deviations may not necessarily lead to total exclusion of a subject from the PPS but may lead to exclusion of specific data and/or timepoints from the analysis.

Has been changed to:

The Per Protocol Set (PPS) is a subset of the FAS, consisting of those subjects who had received all foreseen sc infusions, had a platelet count measurement (measured by ACM Global Central Laboratory) during the Observation Period, and no important protocol deviations that may potentially affect the platelet count as confirmed during a pre-analysis review of the data prior to

database lock. Protocol deviations may not necessarily lead to total exclusion of a subject from the PPS but may lead to exclusion of specific data and/or timepoints from the analysis.

Platelet data for subjects who have taken prohibited medications potentially affecting platelet counts such as PLEX, dexamethasone or rituximab (based on medical review) will only be utilised in the summary tables up to the start of these medications.

Change #7

Dates and times (Section 4.2.7, final bullet on partial stop dates)

- If the stop date is completely unknown, do not impute the stop date

Has been changed to:

- If the stop date is completely unknown, do not impute the stop date, except for ITP medications where end date is missing and ongoing is ticked as 'no', which will be imputed as "Past" medications.

Change #8

Examination of Subgroups (Section 4.8)

The following subgroups will be defined within each dose arm:

- Use of corticosteroid medication: Present/Absent
- Responder at the end of previous ITP treatment: No/Yes/Unknown
- Previous tintravenous immunoglobulin (IVIG) therapy: Yes/No
- Number of previous ITP therapies: ≤2/>2

Only medication classified as either 'prior and concomitant' or 'concomitant' and medical procedure will be considered for ITP treatment. Responder categories will be defined taking into account the last reported ITP treatment value (either Yes or No) for each patient. If this value is unknown, the second-last reported ITP treatment value will be used, then the third-last, and so on, until a known response is provided. The Unknown responder category will only be considered in cases where the investigator has never reported a category (Yes or No) for any of the previous ITP treatments. Past use of corticosteroids (not ongoing after dosing) will not be considered for this classification. The list of applicable Anatomical Therapeutic Chemical (ATC) codes in order to identify the presence/absence of corticosteroids is provided in Section 13.1.

The descriptive summaries for platelets and total IgG will be presented for the subgroups above.

Has been changed to:

The following subgroups will be defined within each dose arm:

- Concomitant corticosteroid medication: Yes/No

  Concomitant medication is defined in Section 6.4.4. The list of applicable Anatomical Therapeutic Chemical (ATC) codes to be utilized as corticosteroids is provided in Section 13.1.

- Responder at the end of past ITP therapy: No/Yes/Unknown

Responder categories will be defined utilizing the value (either Yes or No) for the last reported ITP therapy for each patient. If this value is unknown, the second-last reported ITP therapy value will be used, then the third-last, and so on, until a known response is provided. The Unknown responder category will only be considered in cases where the investigator has never reported a category (Yes or No) for any of the past ITP therapies. For the 'Response' definition, the CRF entries will be utilized.

The past ITP therapy is defined as procedure history related to ITP or past medication related to ITP, where past medication is defined in Section 6.4.1. For 'related to ITP' CRF entries will be utilized.

The corticosteroid medication given more than 3 months prior to screening was routinely not recorded and cannot be considered. Thus, some patients with an unknown response might have had a known response.

- Past intravenous immunoglobulin (IVIg) medication: Yes/No

  Past medication is defined in Section 6.4.1. The ATC Therapeutic Subgroup code (Level 2) 'IMMUNE SERA AND IMMUNOGLOBULINS' will be utilized.

- Number of past ITP therapies: ≤2/>2

  The past ITP therapy is defined as procedure history related to ITP or past medication related to ITP, where past medication is defined in Section 6.4.1. For 'related to ITP' CRF entries will be utilized.

  The corticosteroid medication given more than 3 months prior to screening was routinely not recorded and cannot be considered. Thus, some patients might have had 1 more past ITP therapy than utilized for subgroup determination.

The descriptive summaries for platelets and total IgG will be presented for the subgroups above.

Change #9

Past, prior and concomitant medications (Section 6.4)

Past, prior and concomitant medications will be summarized for the SS by dose arm and for all subjects by WHODD Anatomical Main Group [Level 1], Therapeutic Subgroup [Level 2] and PT.

Separate tabulations will be presented for the following:

- Past medications
- Prior and concomitant medications
- Concomitant medications

All medications will be listed and will include coding information, reported term, dose per intake and unit, frequency, formulation, route of administration, indication, category (past/prior and concomitant/concomitant) and start and end date (or ongoing, if applicable).

Has been changed to:

Past, prior, baseline and concomitant medications

Past, prior, baseline and concomitant medications will be summarized for the SS by dose arm and for all subjects by WHODD Anatomical Main Group [Level 1], Therapeutic Subgroup [Level 2] and PT.

All medications will be listed and will include coding information, reported term, dose per intake and unit, frequency, formulation, route of administration, indication, category (past/prior and concomitant/concomitant) and start and end date (or ongoing, if applicable).

Change #10

This section has been added:-

Baseline Medication (Section 6.4.3)

Baseline medications will include any medications that started prior to dosing and continued after (classified as prior and concomitant medications).

Change #11

Concomitant medication definition (Section 6.4.4)

Concomitant medications will include any medication that has been taken at least once (after the first administration of UCB7665) during the Dosing Period and/or the Observation Period.

Any medication that started prior to the first administration of UCB7665 and continued after dosing will be classified as prior and concomitant. Any medication that started after the first administration of UCB7665 will be classified as concomitant only.

Any medications with missing dates and/or times will be handled as described in Section 4.2.7 in order to classify them as prior and/or concomitant.

Has been changed to:

Concomitant medications will include any medication that has been taken at least once (after the first administration of UCB7665) during the Dosing Period and/or the Observation Period.

This includes medications that started prior to the dosing and continued after (classified as prior and concomitant medications) as well as any medication that started after the first administration of UCB7665 (classified as concomitant).

Any medications with missing dates and/or times will be handled as described in Section 4.2.7 in order to classify them as prior and/or concomitant.

Change #12

Platelets (Section 8.1)

All efficacy analyses are based on platelet count measured by ACM Global Central Laboratory. Measurements of platelet count obtained by the local laboratory will be listed and summarized as part of the safety laboratory data. These are not included in the analyses described in the sections below. All tabulations and mean figures will be presented for both the FAS and the PPS unless otherwise stated. Median figures and individual figures will be presented for the FAS only. In case rescue medications are taken, only the platelet data up to the start date of rescue medication will be utilized for the summary tables. Listings will contain all the data but a footnote will be included indicating the patients for which some data has been excluded from the summary tables.

In case of partial dates, the imputation rules for partial dates described in Section 4.2.7 will be applied.

Has been changed to:

All efficacy analyses are based on platelet count measured by ACM Global Central Laboratory. Measurements of platelet count obtained by the local laboratory will be listed and summarized as part of the safety laboratory data. These are not included in the analyses described in the sections below. All tabulations and mean figures will be presented for both the FAS and the PPS unless otherwise stated. Median figures and individual figures will be presented for the FAS only. In case rescue medications are taken, only the platelet data up to the start date of rescue medication will be utilized for the summary tables (refer to Section 8.1.4). In case prohibited medications affecting platelets are taken, only the platelet data up to the start date of prohibited medication will be utilized for the summary tables for the PPS (refer to Section 3.4). Listings will contain all the data but a footnote will be included indicating the patients for which some data has been excluded from the summary tables. In case of partial dates, the imputation rules for partial dates described in Section 4.2.7 will be applied.

Change #13

Definition of Variables (Section 8.1.1)

The main efficacy variable is defined as the following:

- Maximum Increase from Baseline: the Maximum Increase from Baseline (Day 1, predose) is defined as the highest positive change from Baseline during the study. In the event that the platelet count was to decrease during the study the Maximum Increase from Baseline may be negative and would correspond to the smallest decrease from the Baseline value

The following additional variables will be defined for the platelet count, the calculation rules for which are provided in the section immediately below:

- Response: a Response is defined as a platelet count $\geq 30 \times 10^9$/L and at least 2-fold increase from the Baseline value, by visit, and at any timepoint during the study
- Time to Response: the time to Response is defined as the time from starting treatment (Day 1) to achievement of Response
- Duration of Response: the duration of Response is defined as the time between achievement of a Response to the first time a loss of Response occurred (defined as platelet count $<30 \times 10^9$/L or less than 2-fold increase from Baseline)
- Complete Response: a Complete Response is defined as a platelet count $\geq 100 \times 10^9$/L, by visit, and at any timepoint during the study
- Time to Complete Response: the time to Complete Response is defined as the time from starting treatment (Day 1) to achievement of Complete Response
- Duration of Complete Response: the duration of Complete Response is defined as the time between achievement of a Complete Response to the first time a loss of Complete Response occurred (defined as platelet count $<100 \times 10^9$/L)
- Platelet Count $\geq 50 \times 10^9$/L, by visit, and at any timepoint during the study

- Time to Platelet Count ≥50x10^9/L: the time to Platelet Count ≥50x10^9/L is defined as the time from starting treatment (Day 1) to achievement of Platelet Count ≥50x10^9/L
- Duration of Platelet Count ≥50x10^9/L: the duration of a Platelet Count ≥50x10^9/L is defined as the time between achievement of a Platelet Count ≥50x10^9/L to the first time the platelet count is <50x10^9/L
- Maximum: the maximum value for platelet count over all visits in the study
- Value and change from Baseline in platelet count over time
- Baseline-corrected AUEC for platelet count calculated from Baseline to the end of study visit for each of the defined dose arms.

For all the above response variables the following rules will apply:

- The time to response (including Complete Response, Response and Platelet Count ≥50x10^9/L) is defined as the first time that a given response is achieved during the study. Thus, in the event that the platelet count was to increase above the threshold level, decrease below the threshold level, and subsequently increase again the time to response would be to the first time the definition of response was achieved. The time to response will be calculated in days and presented to 1 decimal place in the listings.

  Time to response (days) = Date/time of first response – Date/time of first dose of UCB7665
- The duration of response (including Complete Response, Response and Platelet Count ≥50x10^9/L) will be defined as the duration of the first time the response was achieved to loss of first response. The duration of response will be calculated in days and presented to 1 decimal place in the listings.

  Duration of response (days) = Date/time of loss of first response – Date/time of first response

  If the platelet value meets the criterion for a specific response for a second time (following a loss of initial response), the second response period will be added to the overall duration of response. This rule will be applied for any subsequent 'response periods'. For subject in whom the response is maintained until the end of the study the duration of response will be calculated using the date of the end of study visit as the 'end of response date'. Any such cases will be flagged in the data listings
- Both scheduled and unscheduled measurements may be included in the calculation of a response, time to response or duration of response
- The Baseline-corrected AUEC will be calculated according to the following rules:
  - The AUEC will be calculated according to the linear trapezoidal rule using protocol scheduled visits
  - Unscheduled visits will not be included in the calculation
  - No imputation of any missing data will be performed
  - To account for differences in the timing of Baseline samples for each subject the Baseline measurement will be considered as time zero in the calculation
  - The units of the AUEC will be 10^9/L*day

- The measurements at Baseline and at the last visit must be available
- A minimum of 10 out of 14 measurements must be available for the calculation in Dose Arm 1; a minimum of 9 out of 12 measurements must be available for the calculation in Dose Arm 2; a minimum of 8 out of 11 must be available for the calculation in Dose Arm 3; a minimum of 7 out of 9 must be available for the calculation in Dose Arms 4 and 5. These include the Baseline and measurement at the last visit
- The AUEC will not be calculated in the case of early withdrawal from the study

Has been changed to:

The main efficacy variable is defined as the following:

- Maximum Increase from Baseline: the Maximum Increase from Baseline (Day 1, predose) is defined as the highest positive change from Baseline during the study. In the event that the platelet count was to decrease during the study the Maximum Increase from Baseline may be negative and would correspond to the smallest decrease from the Baseline value

The following additional variables will be defined for the platelet count, the calculation rules for which are provided in the section immediately below:

- Response: a platelet count $\geq 30x10^9$/L and at least 2-fold increase from the Baseline value, by visit, and at any timepoint during the study
- Time to Response: the first time that a given response is achieved during the study. Thus, in the event that the platelet count was to increase above the threshold level, decrease below the threshold level, and subsequently increase again the time to response would be to the first time the definition of response was achieved. The time to response will be calculated in days and presented to 1 decimal place in the listings.

  Time to response (days) = Date/time of first response – Date/time of first dose of UCB7665
- 'No' or 'Loss of' Response: a platelet count $<30x10^9$/L OR $>=30x10^9$/L WITHOUT at least a 2-fold increase from the Baseline value, by visit
- Duration of Response (including Complete Response, Response and Platelet Count $\geq 50x10^9$/L): the duration of the first time the response was achieved to first loss of response. The duration of response will be calculated in days and presented to 1 decimal place in the listings.

  Duration of response (days) = Date/time of loss of first response – Date/time of first response, where "loss of first response" is defined as platelet count$<30x10^9$/L OR (platelet count $\geq 30x10^9$/L WITHOUT at least a 2-fold increase from the Baseline value)

  If the platelet value meets the criterion for a specific response for a second time (following a loss of initial response), the second response period will be added to the overall duration of response. This rule will be applied for any subsequent 'response periods'. For subject in whom the response is maintained until the end of the study the duration of response will be calculated using the date of the end of study visit as the 'end of response date'. Any such cases will be flagged in the data listings

- Complete Response: a platelet count ≥100x10^9/L, by visit, and at any timepoint during the study
- 'No' or 'Loss of' Complete Response: a platelet count <100x109/L, by visit.
- Time to Complete Response: the time from starting treatment (Day 1) to achievement of Complete Response
- Platelet Count ≥50x10^9/L, by visit, and at any timepoint during the study
- 'No' or 'Loss of' Platelet Count ≥50x109/L: a platelet count <50x109/L, by visit.
- Time to Platelet Count ≥50x10^9/L: the time to Platelet Count ≥50x10^9/L is defined as the time from starting treatment (Day 1) to achievement of Platelet Count ≥50x10^9/L
- Maximum: the maximum value for platelet count over all visits in the study
- Value and change from Baseline in platelet count over time
- Baseline-corrected AUEC for platelet count calculated from Baseline to the end of study visit for each of the defined dose arms.

For all the above response variables the following rules will apply:

- Both scheduled and unscheduled measurements may be included in the calculation of a response, time to response or duration of response
- The Baseline-corrected AUEC will be calculated according to the following rules:
  - The AUEC will be calculated according to the linear trapezoidal rule using protocol scheduled visits
  - Unscheduled visits will not be included in the calculation
  - No imputation of any missing data will be performed
  - To account for differences in the timing of Baseline samples for each subject the Baseline measurement will be considered as time zero in the calculation
  - The units of the AUEC will be 10^9/L*day
  - The measurements at Baseline and at the last visit must be available
  - A minimum of 10 out of 14 measurements must be available for the calculation in Dose Arm 1; a minimum of 9 out of 12 measurements must be available for the calculation in Dose Arm 2; a minimum of 8 out of 11 must be available for the calculation in Dose Arm 3; a minimum of 7 out of 9 must be available for the calculation in Dose Arms 4 and 5. These include the Baseline and measurement at the last visit
  - The AUEC will not be calculated in the case of early withdrawal from the study

Change #14

Analysis of Time to Response (Section 8.1.3.2)

The time to first response will be analyzed with the log-rank test and displayed using Kaplan-Meier curves. Each response parameter will be considered in a separate analysis. The following parameters will be included in the analysis:

- Time to Response: the time to Response is defined as the time from starting treatment (Day 1) to achievement of Response (platelet count $\geq 30x10^9$/L and at least 2-fold increase from the Baseline value)
- Time to Complete Response: the time to Complete Response is defined as the time from starting treatment (Day 1) to achievement of Complete Response (platelet count $\geq 100x10^9$/L)
- Time to Platelet Count $\geq 50x10^9$/L

Kaplan-Meier curves will be presented for all three response parameters. Descriptive statistics will include the p-value for the log-rank test for the equality over dose arms. The point estimate for the median number of days to response with 90% CIs will be given if estimable. Further a summary including the number and percent of censored subjects, the number of responders and total subjects by dose arm and in total will be given.

For the purpose of the analysis subjects with no response will be censored at the end of the study or at the date of withdrawal.

Analyses will be performed for the FAS and repeated for the PPS.

Has been changed to:

The time to first response will be analyzed with the log-rank test and displayed using Kaplan-Meier curves.

Kaplan-Meier curves will be presented for the variables Time to Response, Time to Complete Response, and Time to Platelet Count $\geq 50x10^9$/L. Descriptive statistics will include the p-value for the log-rank test for the equality over dose arms. The point estimate for the median number of days to response with 90% CIs will be given if estimable. Further a summary including the number and percent of censored subjects, the number of responders and total subjects by dose arm and in total will be given.

For the purpose of the analysis subjects with no response will be censored at the end of the study or at the date of withdrawal.

Analyses will be performed for the FAS and repeated for the PPS.

Change #15

Analysis of responder rate (Section 8.1.3.3, 3rd paragraph)

Analyses will be performed for the FAS and repeated for the PPS. Summary tabulations by dose arm will be repeated for the subgroups defined in Section 4.8 (based on the FAS only). Moreover, for responder rate, summary tabulations by dose arm will be repeated according to previous intravenous immunoglobulin therapy (Yes/No) and the number of previous medications (≤2/>2). Percentage of days without bleeding will also be described by dose arm for each type of response (response, complete response and platelet Count >=50x10/L). Percentage of days without bleeding is calculated using the following formula:

((N of visits with a SMOG score – N of these visits where bleeding occurred) / N of visits with a SMOG score) x 100

Has been changed to:

Analyses will be performed for the FAS and repeated for the PPS. Summary tabulations by dose arm will be repeated for the subgroups defined in Section 4.8 (based on the FAS only). Percentage of days without bleeding will also be described by dose arm for each type of response (response, complete response and platelet Count >=50x10/L). Percentage of days without bleeding is calculated using the following formula:

((N of visits with a SMOG score – N of these visits where bleeding occurred) / N of visits with a SMOG score) x 100

Change #16

The following section has been added:

Rescue medication definition (after medical inspection) (Section 8.1.4)

In the rescue medication section of the protocol, rescue medication is defined as platelet substitution or treatment with a commercially available IVIg. In addition, the prohibited medications PLEX, dexamethasone and rituximab will also be considered as a rescue medication for analysis.

Change #17

ITP bleeding score and platelet response (Section 8.2.1.1)

In addition to the platelet response variables defined in Section 8.1.1 the following variables will also be defined based on a combination of platelet response and information from the ITP bleeding score (these will be referred to as Clinical Response variables). In case rescue medications or prohibited medications potentially affecting platelet counts are taken, only the platelet data up to the start date of rescue medication will be utilized for the summary tables (refer to Section 8.1.4):

- Clinical Response: a Clinical Response is defined as a platelet count ≥$30x10^9$/L and <$100x10^9$/L with at least 2-fold increase from the Baseline value AND absence of bleeding, by visit, and at any timepoint during the study
- Time to Clinical Response: the time to Clinical Response is defined as the time from starting treatment (Day 1) to achievement of Clinical Response
- Duration of Clinical Response: the duration of Clinical Response is defined as the time between achievement of a Clinical Response to the first time a loss of Clinical Response occurred (defined as platelet count <$30x10^9$/L or less than 2-fold increase from Baseline OR presence of bleeding)
- Complete Clinical Response: a Complete Clinical Response is defined as a platelet count ≥$100x10^9$/L AND absence of bleeding, by visit, and at any timepoint during the study
- Time to Complete Clinical Response: the time to Complete Clinical Response is defined as the time from starting treatment (Day 1) to achievement of Complete Clinical Response

- Duration of Complete Clinical Response: the duration of Complete Clinical Response is defined as the time between achievement of a Complete Clinical Response to the first time a loss of Complete Clinical Response occurred (defined as platelet count <100x10^9/L OR presence of bleeding)
- No Clinical Response: a platelet count <30x10^9/L and less than 2-fold increase from Baseline OR presence of bleeding, by visit, and at any timepoint during the study

For all the above response criteria, the calculation rules included in Section 8.1.1 will apply. In addition the following will be applicable:

- The clinical response variables will be assessed only for visits for which both platelet counts and the ITP bleeding score are assessed (with the exception of the confirmatory platelet assessments which may be obtained at any visit [scheduled or unscheduled] provided that they meet the criteria below)
- In order to define a clinical response, the platelet count must be confirmed on 2 separate occasions at least 7 days apart (i.e., the second assessment should be ≥168 hours after the first assessment). The time to response will be taken as the time to the first platelet assessment (obtained at the same time as the corresponding ITP bleeding score assessment). If the second assessment does not fulfill the required criteria for a clinical response, the subject will be considered as a nonresponder at the respective visits
- In order to define no response or a loss of response, the platelet count must be confirmed on 2 separate occasions within 1 to 7 days* (i.e., the second assessment should be ≥24 hours and ≤168 hours after the first assessment). The loss of response will be taken as the point at which the first platelet assessment was obtained (obtained at the same time as the corresponding ITP bleeding score assessment). If the second assessment does not fulfill the required criterion for no response or loss of response, the subject will be considered as a responder at the respective visits
- Absence of bleeding is indicated by Grade 0 for all domains of the SMOG
- Presence of bleeding is indicated by a Grade of 1 or above, for at least one domain of the SMOG

*This differs from the published definition (Rodeghiero et al, 2009) which requires 2 platelet measurements 1 day apart to define no response or loss of response. In the current protocol platelet count assessments are not as frequently planned (unless unscheduled measurements are performed), thus it was deemed appropriate to modify the definition above to take into account the schedule of assessments in this study.

As a result the following clinical response variables are not in complete accordance with the guideline:

- Duration of Clinical Response
- Duration of Complete Clinical Response
- No Clinical Response

All response variables described above will be listed by dose arm and subject and summarized by dose arm and visit where appropriate. The responder rates will be tabulated as described in

Section 8.1.3.3. Moreover the change in category of bleeding from Baseline will also be presented in shift table at all post-Baseline visits by dose arm. Summary tabulations for Clinical Response by dose arm will be repeated according to past intravenous immunoglobulin medication (Yes/No) and the number of past ITP therapies (≤2/>2). All analyses described in this section will be performed for the FAS.

In case rescue medications are taken, only the data up to the start date of rescue medication will be utilized for the summary tables. Listings will contain all the data but a footnote will be included indicating the patients for which some data has been excluded from the summary tables. In case of partial dates, the imputation rules for partial dates described in Section 4.2.7 will be applied.

Has been changed to:

In addition to the platelet response variables defined in Section 8.1.1 the following variables will also be defined based on a combination of platelet response and information from the ITP bleeding score (these will be referred to as Clinical Response variables). In case rescue medications are taken, only the platelet data up to the start date of rescue medication will be utilized for the summary tables (refer to Section 8.1.4):

- Clinical Response: a Clinical Response is defined as a platelet count ≥$30x10^9$/L with at least 2-fold increase from the Baseline value AND absence of bleeding, by visit. This must be confirmed by a second measurement at least 5 days later (to allow for the ±2-day visit window), showing a platelet count ≥$30x10^9$/L and at least 2-fold increase from the Baseline.
- Time to Clinical Response is defined as the time from starting treatment (Day 1) to achievement of Clinical Response. The will be taken as the time to the first platelet assessment (obtained at the same time as the corresponding ITP bleeding score assessment). If the second assessment does not fulfill the required criteria for a clinical response, the subject will be considered as a nonresponder at the respective visits.
- Duration of Clinical Response: the duration of Clinical Response is defined as the time between achievement of a Clinical Response to the first time a loss of Clinical Response occurred (defined as platelet count <$30x10^9$/L or less than 2-fold increase from Baseline OR presence of bleeding). Refer to Section 8.1.1 in case a subject has several clinical responses or the clinical response is maintained until the end of the study".
- Complete Clinical Response: a Complete Clinical Response is defined as a platelet count ≥$100x10^9$/L AND absence of bleeding, by visit. This must be confirmed by a second measurement at least 5 days later (to allow for the ±2-day visit window), showing a platelet count ≥$100x10^9$/L.
- Time to Complete Clinical Response: the time to Complete Clinical Response is defined as the time from starting treatment (Day 1) to achievement of Complete Clinical Response
- Duration of Complete Clinical Response: the duration of Complete Clinical Response is defined as the time between achievement of a Complete Clinical Response to the first time a loss of Complete Clinical Response occurred (defined as platelet count <$100x10^9$/L OR presence of bleeding). Refer to Section 8.1.1 in case a subject has several clinical responses or the clinical response is maintained until the end of the study".

- No Clinical Response or a loss of clinical response: the platelet count must be defined as a platelet count <30x10^9/L OR >=30x10^9/L WITHOUT at least a 2-fold increase from the Baseline value OR presence of bleeding, by visit. This must be confirmed by a second measurement 1 to 9 days* later, showing a platelet count <30x10^9/L OR >=30x10^9/L WITHOUT at least a 2-fold increase from the Baseline value.

For all the above response criteria, the calculation rules included in Section 8.1.1 will apply. In addition the following will be applicable:

- The Clinical Response variables will be assessed only for visits for which both platelet counts and the ITP bleeding score are assessed. The last visit cannot be a clinical response as no confirmation after that is available.
- Absence of bleeding is indicated by Grade 0 for all domains of the SMOG, or a Skin Grade of 0 or 1
- Presence of bleeding is indicated by a Mucosae or Organs Grade of ≥1, or Skin Grade of ≥2

*This differs from the published definition (Rodeghiero et al, 2009) which requires 2 platelet measurements 1 day apart to define no response or loss of response. In the current protocol platelet count assessments are not as frequently planned (unless unscheduled measurements are performed), thus it was deemed appropriate to modify the definition above to take into account the schedule of assessments in this study.

As a result the following clinical response variables are not in complete accordance with the guideline:

- Duration of Clinical Response
- Duration of Complete Clinical Response
- No Clinical Response

All response variables described above will be listed by dose arm and subject and summarized by dose arm and visit where appropriate. The responder rates will be tabulated as described in Section 8.1.3.3. Moreover the change in category of bleeding from Baseline will also be presented in shift table at all post-Baseline visits by dose arm. Summary tabulations for Clinical Response by dose arm will be repeated according to past intravenous immunoglobulin medication (Yes/No) and the number of past medications (≤2/>2). All analyses described in this section will be performed for the FAS.

In case rescue medications are taken, only the data up to (not including) the start date of rescue medication will be utilized for the summary tables. Listings will contain all the data but a footnote will be included indicating the patients for which some data has been excluded from the summary tables. In case of partial dates, the imputation rules for partial dates described in Section 4.2.7 will be applied.

Change #18

Table 10-1 (Clinical laboratory measurements)

HbA1c has been moved from the Hematology category to the “Other” category.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the SAP or amended SAP is released for execution.

Approval Signatures

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