STATISTICAL ANALYSIS PLAN

Protocol: TIGET-WAS

Protocol Version 12, 19 Sep 2023

A phase I/II clinical trial of hematopoietic stem cell gene therapy for the Wiskott-Aldrich Syndrome (TIGET-WAS)

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2 Abbreviations and Definitions

ACP	Abnormal Clone Proliferation
ADaM	Analysis Data Model
ATC	Anatomical Therapeutic Chemical
AE	Adverse Event
ANC	Absolute Neutrophil Count
ATG	Anti-thymocyte Globulin
AUC	Area Under the Curve
BM	Bone Marrow
BMI	Body Mass Index
CFU	Colony Forming Unit
CFU-C	Colony Forming Unit Cell
CI	Confidence Interval
CPM	Cells Per Minute
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
DM	Data Management
eCRF	Electronic Case Report Form
ELTFU	Extended Long-Term Follow-up
GT	Gene Therapy
HSCT	Hematopoietic stem cell transplantation
ICH E9	International Conference on Harmonization Statistical Principles for Clinical
ICH E3	International Conference on Harmonization Structure and Content of
ISA	Integration Site Analysis

ITT	Intention to Treat
IVIG	Intravenous Immunoglobulin
LV	Lentiviral
LVV	Lentiviral Vector
mAb	Monoclonal Antibodies
MPV	Mean Platelet Volume
NCI	National Cancer Institute
PIP	Paediatric Investigation Plan
PB	Peripheral Blood
MedDRA	Medical Dictionary for Regulatory Activities
SOC	System Organ Class
PT	Preferred Term
PBSC	Peripheral Blood Stem Cells
RCL	Replication Competent Lentivirus
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SD	Standard Deviation
SI	Stimulation Index
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
VCN	Vector Copy Number
VSV-G	Vesicular stomatitis virus
WAS	Wiskott-Aldrich Syndrome
WASP	Wiskott-Aldrich Syndrome Protein

WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

3 Introduction

As per ICH E9 "Statistical Principles for Clinical Trials", the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol. This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol TIGET-WAS. It describes the data to be summarised and analysed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 12, dated 19 Sep 2023.

4 Study Objectives, Endpoints

4.1 Primary Objective

1. To evaluate the safety of the administration of autologous $CD34^+$ cells transduced with a lentiviral vector containing the Wiskott-Aldrich Syndrome (WAS) protein gene in subjects with WAS, after a reduced intensity conditioning regimen;
2. To evaluate the long-term engraftment of WASP-expressing transduced cells;
3. To evaluate the efficacy of gene therapy assessed as:
    a. Improvement of the subject's immune function, specifically of T cell function and antigen-specific responses to vaccinations;
    b. Improvement of thrombocytopenia.

4.2 Secondary Objectives

To evaluate the efficacy of gene therapy (OTL-103) in improving the subject's clinical conditions assessed by a reduction in frequency of severe infections, and bleeding episodes and reduction of auto-immunity phenomena and eczema.

4.3 Safety Objectives

The safety objectives of the study are contained within the Primary Objectives outlined above in Section 4.1.

5 Study Methods

5.1 General Study Design and Plan

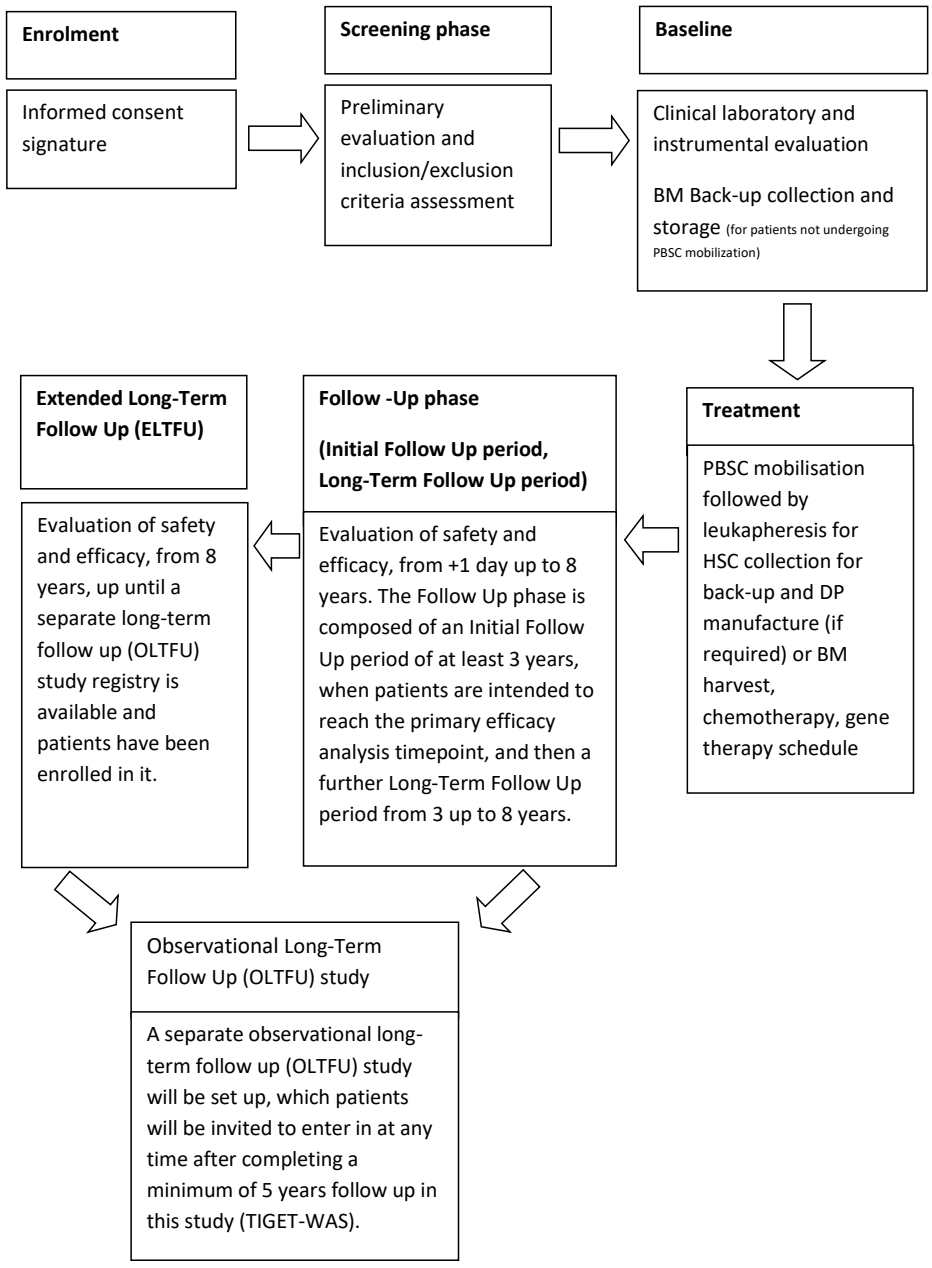
This is a non-randomized, open label, single centre, phase I/II, prospective study involving a single infusion of autologous CD34+ cells transduced with a 3rd generation VSV-G pseudo typed lentiviral vector in 8 subjects diagnosed with WAS without a suitable matched donor for allogeneic transplant or ineligible for hematopoietic stem cell transplantation (HSCT).

Five protocol phases are foreseen, after signature of the informed consent:

1. Screening phase, during which the conditions required by the clinical protocol for subjects' enrolment will be assessed and fulfilment of the inclusion/exclusion criteria of the study will be evaluated;
2. Baseline phase, carried from the end of the screening phase to the day before the harvest of peripheral blood stem cells, if performed, or the day before rituximab administration (day -22);
3. Treatment phase, from the end of the Baseline phase to day 1 (day of OTL-103 infusion);
4. Follow Up phase: the Follow Up phase is composed of an Initial Follow Up period of at least 3 years, when patients are intended to reach the primary efficacy timepoint, and then a further Long -Term Follow Up period from 3 up to 8 years. ;
5. Extended Long-Term Follow-Up (ELTFU) phase: patients who complete the Follow-up phase will then be contacted annually, in order to collect long-term safety and selected efficacy data, until a separate observational long-term follow-up (OLTFU) study is initiated and patients have enrolled in it.
   Once the OLTFU study is set up, patients will be invited to enter the OLTFU study at any time after they have completed a minimum of 5 years follow up in this study (WAS Pivotal, 201228). As part of the OLTFU study, patients will continue to be followed up for a total of 15 years from the date of treatment with gene therapy.

Screening and baseline phases will be summarised as pre-treatment in the analysis outputs.

Figure 1 Trial Flow Chart



The schedule of events can be found in Appendix 3 and is as per Section 7 of the protocol. After gene therapy treatment there are 12 visits over the first 36 months and then one visit annually from year 4 to year 8 (5 visits), unless a subject is transferred to the OLTFU after year 5 but prior to year 8.

5.2 Randomisation and Blinding

As this is a non-randomised open label study, no randomisation or blinding is required.

5.3 Derived variables

5.3.1 Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of infusion of transduced CD34+ cells (Day 1).

- If the date of the event is on or after the reference start date then:
  Study Day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference start date then:
  Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day and any corresponding durations will be presented based on the imputations specified in Section 7.3.1.

5.3.2 Baseline

For all endpoints the baseline value will be the last assessment prior to treatment phase, unless otherwise stated.

5.3.3 Retests, Unscheduled Visits and Early Termination Data

All visits (scheduled and unscheduled) will be windowed per Table 1 (Section 5.3.5).

Early termination data will be mapped to the next available visit number (as per visit schedule for each specific assessment) for by-visit summaries.

In the case of a retest (same visit number assigned), the earliest available measurement for that visit will be used for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

5.3.4 Common Calculations

Change from baseline is defined as:

Post-Treatment Visit Value – Baseline

Person years observation (PYO) is calculated as the total observation period across all subjects within the given study period. The calculation will be made as below:

$$Person\ years\ observation = \sum_{i=1}^{n} \frac{(period\ end\ date)_i - (period\ start\ date)_i + 1}{365.25}$$

Where i is the individual subject and n is the total number of subjects with observation in the period.

The calculation of duration of follow-up is defined as:

Date of Study Completion Visit - Gene Therapy Treatment date+1

Where subjects are ongoing at interim analyses the study completion date is substituted with the data cut point.

Calculation of time to discontinuation of Intravenous Immunoglobulins (IVIG), platelet infusions and antimicrobial treatment is defined:

Date of Last Respective Treatment – Gene Therapy Treatment Date + 1

For patients where treatment has yet to stop this will be summarised as ongoing.

Unless otherwise stated, if the baseline value is missing, then the change from baseline will also be set to missing.

Baseline of platelet count is defined as the median of the (at least three) determinations performed before beginning of treatment.

5.3.5 Windowing Convention

All visits (scheduled and unscheduled) will be windowed as per the tables below.

Early termination data will be mapped to the next available visit number (as per visit schedule for each specific assessment) for by-visit summaries.

In the case of a retest (same visit number assigned), the earliest available measurement for that visit will be used for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

The following tables describe the windowing conventions used for various purposes of the TFLs.

Table 1 Windowing for Treatment Phases

Assigned Study Day (Inclusive)		**Visit Assigned**
From	**To**	
Informed Consent	Screening Date	Screening
Screening Date +1	PBSC Mobilization Date -1, if performed	Baseline*
	Day before Rituximab administration	
PBSC Mobilization, if performed	Date of GT (if administered) or date of EoS for subjects that did not receive GT	Treatment
Day of Rituximab administration		
2	11	Day 7
12	18	Day 14
19	26	Day 21
27	46	Day 30
47	76	Day 60
77	136	Day 90
137	273	Day 180
274	457	Year 1
458	639	Year 1.5
640	822	Year 2
823	1004	Year 2.5
1005	1278	Year 3
1279	1644	Year 4
1645	2009	Year 5
2010	2374	Year 6
2375	2739	Year 7
2740	3104	Year 8
3105	-	Final Assessment

* Efficacy measurements taken on the same day as PBSC mobilisation will be considered for baseline efficacy measures.
Screening and baseline periods will be grouped as pre-treatment in some outputs

Pre-treatment and on-treatment windowing will be defined separately for groups of data. For adverse events and concomitant medication data these will be defined below.

Table 2 Windowing for treatment phases; AEs and Concomitant Medications

Assigned Study Day (Inclusive)		Visit Assigned
From	To	
Screening date	Treatment phase start date -1	Pre-treatment
Treatment phase start date (see Table 2)	Date of GT (if administered) or date of EoS for subjects that did not receive GT	On-treatment
2	183	0-6 Months Follow-up
184	366	6-12 Months Follow-up
367	731	1-2 Years Follow-up
732	1097	2-3 Years Follow-up
1098	2923	3-8 Years Follow-up
2924	End of study	>8 Years Follow-up
2	End of Study	Post-Treatment

Severe infections and bleeding events will be classified according to the time of occurrence relative to treatment as in the Table 3 below. This classification will be used in displays containing severe infections and bleeding events data only. For AE displays including severe infections and bleeding events, the treatment phases for AE data defined in Table 2 will be followed.

Table 3 Windowing for treatment phases; Severe Infections, Bleeding Events and hospitalisations

Assigned Study Day (Inclusive)		Visit Assigned
From	To	
-365	-1	Pre-treatment
2	183	0-6 months follow-up
184	366	6-12 months follow-up
367	731	1-2 Years Follow-up
732	1097	2-3 Years Follow-up
1098	2923	3-8 Years Follow-up
2924	End of study	>8 Years Follow-up
184	End of study	> 6 months Follow-up

Windowing will be applied to the data prior to any missing data calculations.

6 Sample Size

Given the low frequency of disease and the degree of novelty of the proposed experimental approach, we plan to treat overall 8 patients, in an estimated 5-year period.

7 General Considerations

All study patients will be included for evaluation until the earliest time point of the following: completion of a minimum of 5 years follow up in this study (TIGET-WAS) and transition to a separate OLTFU study, death, withdrawal or loss to follow up. Patients who, at 1 year after gene therapy, show absence of transduced cell engraftment in peripheral blood and bone marrow will be subsequently evaluated for safety aspects only.

At the end of the study, when all subjects have completed a minimum of 5 years follow up and transitioned to a separate OLTFU study, a final statistical analysis will be performed with all data available up to the transition to the OLTFU study, and a final clinical study report will be compiled.

The final analyses will be performed after all required database cleaning activities have been completed and final database freeze and database release has been declared by Data Management (DM).

The default significance level will be 5%; confidence intervals will be 95% and all tests will be two-sided. As this study is not powered all p-values and confidence intervals will be nominal.

7.1 Analysis Sets

The planned analyses as described in this SAP will be presented for the Enrolled Set (ES), Intent-To-Treat (ITT) population or the mobilisation set (MS). Definitions of these analysis sets can be found in Table 4.

Table 4 Definition of populations

Population	Label	Definition / Criteria	Analyses Evaluated [1]
ES	Enrolled Set	• All patients for whom informed consent was obtained	Disposition summary table and listing of reasons for withdrawal
ITT	Intent-To-Treat Population	• All patients treated with OTL-103 in this study with data available within the clinical database	• Study Population • Efficacy
MS	Mobilisation Set	• All patients who started peripheral blood stem cell (PBSC) mobilization or bone marrow harvest procedures	• Safety

[1] Additional analyses may be performed on these analysis sets if required (e.g. Safety analyses in ITT set).

7.2 Covariates and Subgroups

No covariates and subgroups are planned to be used in the analyses due to the small sample size.

7.3 Missing Data

Considering the small sample size of the study, missing data will not be imputed unless otherwise indicated. Missing data will be reported as follows:

- These data will be indicated using a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data are excluded from the table.
- Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and will be displayed as such.

For the evaluation of sustained engraftment, if data on peripheral blood (PB) CD3+ is not available, the missing CD3+ value will be imputed as the average of PB CD4+ and CD8+ values obtained from the same sample at that visit.

Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. Partial dates will be displayed as captured in subject listing displays.

Partial dates for adverse events, medical history or concomitant medications records will be imputed for the purpose of assigning phase of onset and in the calculation of duration of adverse events.

The methods for dealing with partial start and stop dates are described below for adverse events and concomitant medications.

The answers to the question "Ongoing?" as recorded on the eCRF pages will also be taken into consideration to determine if the event continued post- gene therapy.

7.3.1 Partial Date Conventions

Partial dates for adverse events and concomitant medications may be imputed for statistical analyses according to the following rules. Imputed dates will not be shown in the listings, but Study Day based on imputation should be displayed.

Reference date of prior and concomitant medications, and adverse events is date of gene therapy. Reference date of adverse events taken from medical history is the date of first signed informed consent.

Imputation of partial start dates:

- If only the month and year are specified and the month and year of reference date is not the same as the month and year of the start date or the reference date is missing, then use the 1st of the month.
- If only the month and year are specified and the month and year of reference date is the same as the month and year of the start date, then use the reference date. If this results in an imputed start date that is after the specified end date and the specified end date is before the date of informed

consent, then use the 1st of the month; else if the specified end date is on or after the date of informed consent, then use the date of informed consent.

- If only the year is specified, and the year of reference date is not the same as the year of the start date or the reference date is missing, then use January 1 of the year of the start date.
- If only the year is specified, and the year of reference date is the same as the year of the start date, then use the reference date. If this results in an imputed start date that is after the specified end date, then use January 1 of the year of start date.
- If the start date is completely unknown, then use the reference date or the date of informed consent if the reference date is missing. If this results in an imputed start date that is after the specified end date, then use January 1 of the year of reference date, the informed consent date or the year of the end date, whichever is earlier.

Imputation of 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 that year.
- For medications: If the stop date is completely unknown, do not impute the stop date. In this case the medication is assumed to be a concomitant medication and would be presented in the outputs as such, but no Study Day will be presented in the listing for stop date.
- For adverse events: If the stop date is completely unknown, do not impute the stop date and do not present Study Day in the listing. Adverse events will be summarised according to the phase in which the AE started.

Imputation of partial date of diagnosis for calculation of the time since diagnosis:

- If only the month and year are specified, use the first day of the month.
- If only the year is specified, use the 1st Jan of that year.
- If either of the above result in a start date that is prior to the subject's date of birth then use the subject's date of birth.

7.4 Interim Analyses

Two interim analyses will be performed to list, tabulate and plot all available data by the planned data cut off to assess the efficacy and safety of the investigation product (OTL-103). The approximate schedules of the interim analyses are as follows:

1. When the first 6 treated subjects complete 3 years of follow up after gene therapy as committed in the European PIP.
2. After the clinical database for marketing authorization application is locked

7.5 Multiple Testing

As the primary and secondary analyses are not powered for, there will be no adjustment for multiplicity across the primary and secondary endpoints.

8 Summary of Study Data

There is only one treatment group and the label used on outputs will be 'OTL-103'.

In general, continuous variables will be summarized using the following descriptive summary statistics: n (non-missing sample size), mean, SD, median, minimum and maximum. However, certain variables will additionally have geometric mean and geometric CV (coefficient of variation) presented.

For categorical measures, the frequency and percentages of observed levels will be reported.

Further details will be specified in a separate shells document. The shell templates provided will describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided in accordance with the recommendations in ICH E3.

Unless otherwise specified, study population and efficacy outputs will use the ITT population and safety outputs will use the mobilisation set.

8.1 Subject Disposition and Protocol Deviations

All subjects who provide informed consent will be accounted for in this study.

Subject disposition and withdrawals, duration of follow-up and protocol deviations, including inclusion and exclusion criteria will be presented for the ITT set.

Summary statistics for the duration of follow-up will be presented and individual durations listed. Listings will be created for reasons for withdrawal, protocol deviations and inclusion/exclusion criteria.

8.2 Demographic and Baseline Variables

Demographic data and other baseline characteristics will be presented for the ITT set.

The following demographic and other baseline characteristics will be summarised and listed for this study:

- Age (years) - calculated relative to date of gene therapy
- Age group
    - 0 to <28 days
    - 28 days to <24 months
    - ≥24 months to 11 years
    - <11 years
- Age group 2
    - < 5 years
    - ≥ 5 years
- Sex
- Race
- Ethnicity
- Height (cm)
- Weight (kg)

- BMI (kg/m^2)
- Body Surface Area (m^2)
- Country of residence
- Time since diagnosis (years) - calculated relative to date of consent
- Derivations for demographic data are included below:
    - BMI (kg/ m^2) = weight (kg)/ height (m)^2
    - Body Surface Area (m^2) = $\sqrt{\frac{weight(kg) \times height\ (cm)}{3600}}$
- Busulfan cumulative AUC (note that busulfan will only be summarised in the conditioning regimen output [see Section 12] and will not be summarised with demographics):
  If subject receives 8 doses of busulfan $(AUC1 + AUC6) \times 4$
  If subject receives 9 doses of busulfan $(AUC1 + AUC6) \times 4 + \frac{AUC6 \times D9}{D5}$
  Where AUC1 = AUC(0-∞) from first dose, AUC6 = AUC(0-6 h) from 5th or 6th dose, D5 is the 5th dose and D9 is the 9th dose

A listing will also be created for the length of hospitalisation for gene therapy.

8.3 Medical Conditions

Medical conditions captured by the relevant Medical History page will be summarised for the ITT set and will be coded using MedDRA version 21.1 or higher. The version will be included in the footnotes of applicable outputs. A flag will be produced to indicate conditions which are ongoing at screening regardless of the onset dates of the medical conditions. They will be summarised by System Organ Class (SOC) and Preferred Term (PT). Relevant medical history will be both tabulated and listed.

Medical conditions of infections or bleeds collected in the 12 months prior to gene therapy that are equivalent to a CTCAE Grade 3, 4 or 5 events will also be summarised and compared to CTCAE Grade 3, 4 and 5 events that occur after gene therapy. See Section 10.2.2.1.

A Listing will be created of WAS condition at screening including WAS mutation, Baseline WASP Expression and WAS severity.

8.4 Prior and Concomitant Medications

Medications will be summarised for the ITT set and coded using the 1st September 2018 version of WHO-DD or higher. The version will be included in the footnotes of applicable outputs.

Concomitant medications excluding conditioning regimen and PBSC mobilisation will be summarised by treatment phase as defined in Table 2 in Section 5.3.5. The number and percentage of subjects receiving concomitant medications will be summarised based on ATC Level 1 codes.

Exposure to conditioning regimen (including pre-conditioning with rituximab and ATG Thymoglobuline, and reduced intensity conditioning with busulfan and fludarabine) will be summarised.

A summary of the terms included in these groupings in included in Appendix 2.

See Section 7.3.1 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e. concomitant.

Prior medication definition:

Prior medications are medications which are started and stopped prior to the gene therapy date.

Concomitant medication definition:

Medications will be labelled as concomitant medications if they satisfy both of the conditions below:

1. The medication is started prior to, on or after gene therapy.
2. The medication ended on or after the date of gene therapy or was ongoing at the end of the study.

Medications will be counted in all treatment phases (as defined in Table 2) for which they are ongoing.

Listings will be created for relevant previous medications at screening, concomitant medications by treatment phase, concomitant medications of special interest (for infections, eczema and autoimmunity) by treatment phase, PBSC mobilisation (including G-CSF and plerixafor) and condition medications.

8.5 Treatment Compliance

As gene therapy is likely to be administered once, compliance to study medication will not be presented.

8.6 Treatment Exposure

Exposure to study medication, which for this study is gene therapy, will be presented for the ITT set. Exposure will be presented through summary statistics (n, mean, SD, median, min and max) of:

- Total volume infused (mL)
- Total nucleated cells (10^6)
- Number of nucleated cells/kg (10^6/kg)
- $CD34^+$ cells/kg (10^6/kg)
- Number of CFU-GM (/ 10^6)
- Transduction Efficiency (CFU-C) (%)
- Vector copy number (VCN/cell)

Data on study medication exposure will also be listed. A listing will also be created of the stem cells collected.

9 Efficacy Analyses

As defined in the protocol, confidence intervals for proportions will be calculated according to the Wilson approach (Brown, 2001):

$$\frac{\left(\hat{p} + \frac{z_{\frac{\alpha}{2}}^2}{2n} \pm z_{\frac{\alpha}{2}}\sqrt{\left(\frac{\hat{p}(1-\hat{p}) + \frac{z_{\frac{\alpha}{2}}^2}{4n}}{n}\right)}\right)}{\left(\frac{1 + z_{\frac{\alpha}{2}}^2}{n}\right)}$$

Where $\hat{p}$ is the proportion with the event, and n is total number and $z_{\frac{\alpha}{2}}$ is the $100\left(1-\frac{\alpha}{2}\right)$ percentile of the standard normal distribution. This can be calculated using the CL=WILSON option within the PROC FREQ procedure in SAS.

An exact Poisson procedure will be adopted for deriving CIs for incidence rates using the below formulas:

$Y_l = \frac{\chi^2_{2Y,\frac{\alpha}{2}}}{2T}$ and $Y_u = \frac{\chi^2_{2(Y+1),1-\frac{\alpha}{2}}}{2T}$

Where Y is the observed number of events, Y_l and Y_u are the lower and upper confidence limits for Y respectively, $\chi^2_{v,a}$ is the chi-squared quantile for the upper tail probability on v degrees of freedom, and T is the person year time at risk.

Confidence Intervals for the means or mean changes in continuous variables will be derived with standard parametric methods, if appropriate. Otherwise medians with their corresponding confidence intervals will be presented.

9.1 Primary Efficacy

The primary efficacy analyses will be based on the ITT population, unless otherwise specified. Table 5 provides an overview of the planned efficacy analyses.

Table 5 Overview of Planned Primary Efficacy Analyses

Endpoint/Parameter/ Display Type	Absolute						Change from Baseline						
	Stats Analysis		Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	T	F	F	L	T	F	L	T	F	F	L
Overall Survival	X	X				X							
Engraftment (PCR for transduced cells)			X	X	X	X							
WASP Expression			X	X	X	X				X			X
T-Cell function			X	X	X	X				X	X		X
Antigen specific response to vaccinations			X	X		X							
Platelet count, MPV			X	X	X	X				X			X

T = Table, F = Figure, L = Listing
Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
Individual = Represents FL related to any displays of individual subject observed raw data.
Absolute and change from baseline summaries/listings are combined into a single display.

9.1.1 Overall Survival

Overall survival is defined as the time in days from gene therapy to date of death. Subjects alive at the end of follow-up or having not yet reached the defined follow-up phase will be censored at the latest time point for which vital status information is available. Follow-up will be defined as all data up to the data cut or end of study depending upon availability of data per patient.

The Kaplan-Meier estimate of survival for the entire duration of follow up will be obtained, with 95% confidence interval (CI) if there is any fatal event. The analysis results will be presented in a graph as well as a table. A listing of fatal events will be reported as a safety display.

9.1.2 Engraftment of genetically corrected hematopoietic stem cells in peripheral blood and/or in bone marrow

Adequate engraftment of genetically corrected cells in peripheral blood and/or in bone marrow is defined as ≥0.04 VCN/cell in bone marrow $CD34^+$ or ≥0.1 VCN/cell in peripheral blood T Lymphocytes $CD3^+$ at 1 year after gene therapy.

Missing PB $CD3^+$ values will be imputed using the mean PB $CD4^+$ and PB $CD8^+$ values obtained from the same sample at that visit. If insufficient data are available to determine an adequate engraftment, the response will be set to missing. This includes two scenarios:

a. Neither BM nor PB samples provides data for engraftment assessment;
b. Values are below the threshold for the respective sample matrix (BLQ).

A summary table detailing the number and percentage of subjects who present with adequate engraftment at 1 year after gene therapy will be generated, with the 95% CI of the percentage calculated. PCR transduced cell evaluation in BM and PB will be summarised with descriptive statistics and graphs. Time to adequate engraftment will be plotted and listed based on VCN in BM and PB. The percentage of lentiviral vector (LVV) transduced colony forming units (CFU) in bone marrow cells (%LV in BM) will also be tabulated and plotted.

The longitudinal profile of the PCR transduced cell evaluation in BM and PB over time will be presented in a listing and a plot.

A box plot will be created for engraftment (PB $CD3^+$ and BM $CD34^+$ VCN/cell) by treatment source (BM or PB) at each year post gene therapy.

Scatterplots will be presented of treatment dose (CD34+/kg), busulfan dose (AUC), and age at treatment against engraftment (PB $CD3^+$ and BM $CD34^+$ VCN/cell) at each year post gene therapy.

Line plots will be created for median VCN/cell over time in both the BM and PB cell lineages.

9.1.3 Expression of WASP

Presence of detectable WASP expression (lymphocytes, T Cells, B Cells NK cells, monocytes, platelets) at 1 year after gene therapy by flow cytometry analyses and/or Western Blot.

WASP expression data assessed by flow cytometry will be summarised with descriptive statistics including 95% CI. The mean change from baseline will be calculated with 95% CI. The longitudinal profile over time of WASP expression will be described with a listing for qualitative results from Western Blot if available; and a figure for quantitative results from flow cytometry.

A line plot will be created for median WASP expression values over time. Also a plot of the arithmetic mean WASP expression values with 95% CI over time will be created.

9.1.4 T-cell function

T-cell function is evaluated as part of immunological evaluation: dose response of proliferation to anti-CD3i after anti-CD3i mAb stimulation *in vitro*. Change from baseline in T-cell proliferation upon stimulation with anti-CD3i mAbs will be calculated for each year after OTL-103 administration of gene therapy.

Summary statistics of the absolute values and change from baseline will be calculated along with 95% CI for the mean by level of anti-CD3i stimulation for cells per minute (CPM) and simulation index (SI) separately. A boxplot comparing T-cell function at each year post gene therapy versus baseline will be produced by anti-CD3i levels.

The longitudinal profile over time of the levels of the *in vitro* T-cell proliferation will be described by means of a listing (including observed and change from baseline values) and a plot.

Plots will also be created for the absolute values and change from baseline means and 95% confidence interval of T-Cell proliferation responses over time.

Scatterplots will be presented of treatment dose (CD34+/kg), busulfan dose (AUC), and age at treatment against T-cell response (at 0.01, 0.1 and 1 ug/mL for both SI and CPM) at each year post gene therapy.

A listing will be created for the results from the TCR repertoire results.

9.1.5 Antigen-specific responses to vaccination;

Antigen-specific responses to vaccinations are measured in three ways:

a. Ability to mount a protective humoral response to nominal antigens, including antibodies to at least 4 out of 5 T cell dependent antigens tested (antibodies against Tetanus Toxoid, Diphtheria, Hepatitis B, Pertussis, Haemophilus measured after the end of the vaccination schedule (foreseen >1 year after gene therapy). In case results are available on n<5 antigens, the rule of at least n-1 will be applied for defining success. If there is only 1 available result and this is a protective response, this will also be considered a success.
b. Ability to mount a protective humoral response to unconjugated polysaccharide antigens (Pneumococcus either IgG or IgM), measured after the end of the vaccination schedule (foreseen >1 year after gene therapy).
c. Positive cellular response to Tetanus Toxoid after vaccination, measured by in vitro proliferative response >1 year after gene therapy.

Response to vaccination will only be looked at in subjects who have completed the required schedule for the specific vaccination and have had a period of at least 90 days after their last IVIG infusion. Reference values to define protective or positive responses are summarised below for each specific antigen.

Table 6 Reference values for protective response by antigen

Parameter	Protective response cut-off	Unit
Tetanus Toxoid	820	cpm
Tetanus IgG	0.4	IU/mL
Pneumococcus IgG	200	titer
Pneumococcus IgM	100	titer
Pertussis IgG Antibody	11	Arbitrary U
Hepatitis B Virus Surface Antibody	100	mU/mL
Hemophilus influenzae B Antibody	1	mg/L
Diphtheria IgG Antibody	0.4	IU/mL

A summary of response at any point within the first 3 years after GT as well as over the whole follow-up phase will be produced. In addition, the longitudinal profiles over time of responses to vaccinations will be described together with vaccinations in a listing.

A summary of the number of IVIG infusions per treatment phase will be presented along with the rate of infusions per year of observation.

A summary of time to sustained IVIG discontinuation will be produced for subjects who no longer need IVIG infusions. The cessation of sustained IVIG treatment is defined as a period of 3 months post gene therapy without IVIG treatment. The time to discontinuation will be presented in a table and Kaplan Meier plot including median time to discontinuation and 95% confidence interval.

Separate listings will be produced for patients requiring IVIG infusions and time to IVIG discontinuation (for those subjects who no longer need IVIG infusions).

9.1.6 Platelet counts and Mean Platelet Volume.

Absolute values of platelet count and mean platelet volume (MPV) as well as change from baseline will be calculated according to the planned follow up visits and including platelet count collected for clinical reasons during follow up (in infusion independent subjects). Baseline platelet count will be calculated as the median of the (at least three) determinations performed before beginning of treatment.

Normalization of MPV is defined as MPV within the normal range (MPV ≥ 7.4 fL for children (< 18 years) and MPV ≥ 9.1 fL for adults). Platelet count data obtained within 7 days following platelet infusions will not be considered for evaluation.

Subjects will be also stratified according to the severity of thrombocytopenia before gene therapy in 5 groups (A, B, C, D and E) and the subject will be defined as improved if there is a positive shift (an increase in platelet count) from one group to the subsequent as shown in Table 7. If a subject has no values more than 7 days from a platelet infusion then they are imputed as being in group A.

Table 7 Stratification of platelet count according to severity of thrombocytopenia (count x10^9/L)

A	B	C	D	E
< 20	20- <50	50 - <100	100 – <150	≥150

The percentage of subjects who have improved platelet count over baseline at 1 to8 years (annually) after gene therapy will be calculated with 95% CI.

The means for absolute values and change from baseline will be calculated with 95% CI each year after gene therapy for platelet count and MPV. There will also be accompanying summary statistics.

At 1-8 years after gene therapy the number of subjects with normal MPV will be summarised. The longitudinal profile over time of platelet count and MPV will be described by means of a listing and a plot. The listing will identify which platelet count data points were within 7 days after a platelet infusion as well as thrombocytopenia severity data.

Shift tables of platelet count (as in Table 7) and MPV compared to baseline will be presented for each year after gene therapy.

Median platelet counts will be summarised by baseline WASP expression (Reduced, Absent, Presence of Revertant (>5%)) by means of a bar graph at each year post gene therapy.

Arithmetic mean (and 95% confidence interval) values of platelet count and MPV data will be plotted over time.

A summary of the number of subjects with platelet infusions per treatment phase (See Table 3) will be presented along with the rate of infusions per year of observation.

A summary of time to discontinuation of sustained platelet infusions will be produced for subjects who no longer need platelet infusions. The cessation of sustained infusions is defined as a period of 3 months post gene therapy without a platelet infusion. The time to discontinuation will be presented in a table and Kaplan Meier plot including median time to discontinuation and 95% confidence interval.

Listings of both platelet infusions and time to platelet infusion discontinuation will also be created.

9.2 Secondary Efficacy

The secondary efficacy analyses will be based on the ITT population, unless otherwise specified.

Table 8 provides an overview of the planned efficacy analyses.

As part of the overall efficacy evaluation, an exploratory analysis of platelet activation and morphology will be performed on platelets obtained from peripheral blood. The data from these analyses are captured outside the eCRF, and thus the reporting is not covered in this SAP.

Table 8 Overview of Planned Secondary Efficacy Analyses

Endpoint/Parameter/Display Type	Absolute[1]				Change from Baseline[1]			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Longitudinal engraftment and WASP expression	X	X	X	X				
Multilineage Engraftment	X	X	X	X				
Frequency of Severe Infections	X	X		X	X			
Frequency of Bleeding episodes	X	X		X	X			
Autoimmunity phenomena[2]	X			X				
Eczema	X		X	X	X			
Quality of life: Social life Requirement of drugs Hospitalization	X		X	X				

T = Table, F = Figure, L = Listing, X = Display generated.
• Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
• Individual = Represents FL related to any displays of individual subject observed raw data.
[1] Absolute and change from baseline summaries/listings are combined into a single display.
[2]. Adverse events potentially related to autoimmunity will be identified via checkbox on the eCRF, "In the opinion of the investigator, is this an autoimmune event?".

9.2.1 Longitudinal Sustained Engraftment and WASP expression

Longitudinal sustained engraftment is defined as the percentage of lentiviral vector (LVV) transduced-colony forming units (CFU) in bone marrow cells (%LVV in BM) over time. WASP expression is described in Section 9.1.39 will be analysed over the whole phase of follow-up.

The longitudinal profile of the transduced cell evaluation in BM and PB over time will be described by means of a listing and a plot.

The %LVV in BM over the time course of the study will also be plotted.

The longitudinal profile over time of WASP expression will be described with a listing for qualitative results from Western Blot if available; and a figure for quantitative results from flow cytometry, as described in Section 9.1.3.

Individual profiles of bone marrow and peripheral blood immunophenotype data will be presented over time in line plots. Listings will be created of bone marrow morphology and karyotype data, bone marrow blood count and immunophenotype data, peripheral blood immunophenotype data, peripheral blood immunophenotype subpopulations outside the normal reference range, serum immunoglobulin data and lymphocyte proliferative response.

9.2.2 Sustained Multilineage Engraftment of Genetically Corrected Cells in Peripheral Blood and Bone Marrow

Adequate engraftment of genetically corrected cells in peripheral blood and/or in bone marrow is defined in Section 9.1.2 and will be analysed over the whole follow-up phase. Adequate engraftment for further subpopulations than BM CD34+ and PB CD3+ will be defined as ≥0.04 VCN/cell.

A summary table detailing the number and percentage of subjects who present adequate engraftment each year after gene therapy will be generated, with the 95% CI of the percentage calculated.

The summary statistics and the longitudinal profile of the genetically corrected cells over time will be described by means of a listing and a plot together with BM $CD34^+$ and PB $CD3^+$ as described in Section 9.1.2.

9.2.3 Frequency of severe infections

Severe infections will be recorded on the Relevant Medical History page, Concomitant Diseases page and Adverse Event page. Severe infections will be identified as infections and infestations graded CTCAE 3 or above. The CTCAE pre-defined criteria are specified in the protocol. Severe infections, unless otherwise stated, will be summarised according to the phases in which the event started. Terms that will be considered as infections are defined in Appendix 2. The number of severe infections will be evaluated comparing post-treatment phases vs. pre-treatment phases as defined in Table 4. Severe infections occurring in the first 12 months prior to gene therapy will be considered for the pre-treatment comparison.

A tabulation of the severe infection events by System Organ Class and Preferred term will be presented. The rate of infections will be estimated pre- and post- treatment as the number of any severe infections per person-year. The number and percent of subjects with severe infections, and the number of severe

infections will be summarised by means of a table and a plot by treatment phase. A listing of all severe infections will be produced.

9.2.4 Bleeding episodes

Bleeding will be recorded on Relevant Medical History page, Concomitant Diseases page and Adverse Event page. Terms that will be considered for bleeding episodes are defined in Appendix 2.

Bleeding episodes will be summarised and listed in the same way as severe infections.

A separate table and plot will be produced to summarise the bleeding episodes by severity and by SOC. Three severity categories will be used for the table: Mild for CTCAE grade 1, Moderate for CTCAE grade 2, and Severe for CTCAE grade 3 or above.

Summaries of severe bleeding events and moderate bleeding events will be created. Each summary will compare the pre-gene therapy phase with the post-gene therapy phase. Rate of events per patient year outcome will be presented along with accompanying confidence interval. A separate summary of the number and rate of bleeding events defined from Haemorrhages (SMQ) will be presented, by treatment phase and severity. All bleeding episodes will be listed.

A plot of the distribution of bleeding events by site (SOC) will be presented as pie charts representing each of the treatment phases defined in Table 2.

9.2.5 Autoimmunity Phenomena

For pre-treatment, autoimmunity events will be determined from a manual review of medical history; additional data will be retrieved from the eCRF for AEs pre-GT (since AEs were not collected pre-GT).

Adverse events related to autoimmunity are identified by the investigator on the eCRF.

Modification of autoimmunity will be evaluated starting from the first year follow-up visit and at day 180 then every year after gene therapy until final assessment (where data are available) and compared to clinical history. Subjects with positive autoimmunity laboratory tests will be listed and summarised over time.

9.2.6 Eczema

The severity of eczema will be assessed by an eczema score as part of the clinical examination. Each subject is assigned one of four scores at each visit: 1 for None, 2 for Transient, 3 for moderate and 4 for severe. Reduction in eczema will be evaluated by the change from baseline in eczema score at each year after gene therapy.

Shift tables will be produced to display the number and percentage of subjects at each eczema score at baseline and the shift at each year after gene therapy. The longitudinal profile over time of the eczema score will be described by means of a listing and a plot.

9.2.7 Quality of life

Quality of life will be assessed according to whether the subject was living in a protected environment, attending school or kindergarten, social ability with peers and participation in sport, as relevant for age.

For subjects who were living in a protected environment at baseline, time to not living in a protected environment will be calculated as:

Time to not living in a protected environment = date of first visit where no longer living in a protected environment – date of baseline visit

For subjects who were not living in a protected environment at baseline, the time will not be calculated.

Lansky play-performance rating (for subjects < 16) or Karnofsky performance status (for subjects ≥16) will also be assessed. A summary table will be produced and individual profiles will be plotted over time. Ratings are assigned based upon the below scale for assessment of play and activity in the previous week:

Table 9 Karnofsky/Lansky Performance Ratings

Rating	Lansky Description	Karnofsky Description
100	Fully active, normal	Normal; no complaints; no evidence of disease.
90	Minor restrictions with strenuous physical activity	Able to carry on normal activity; minor signs or symptoms of disease.
80	Active, but gets tired more quickly	Normal activity with effort; some signs or symptoms of disease.
70	Both greater restriction of, and less time spent in, active play	Cares for self; unable to carry on normal activity or to do active work
60	Up and around, but minimal active play; keeps busy with quieter activities	Requires occasional assistance, but is able to care for most of their personal needs
50	Lying around much of the day, but gets dressed; no active play; participates in all quiet play and activities	Requires considerable assistance and frequent medical care
40	Mostly in bed; participates in quiet activities	Disabled; requires special care and assistance
30	Stuck in bed; needs help even for quiet play	Severely disabled; hospital admission is indicated although death not imminent
20	Often sleeping; play is entirely limited to very passive activities	Very sick; hospital admission necessary; active supportive treatment necessary
10	Does not play nor get out of bed	Moribund; fatal processes progressing rapidly
0	Unresponsive	Dead

The number (and percentage) of subjects living in a protected environment, attending kindergarten/school and practising sport will be summarised.

A listing of complete quality of life assessment will be produced.

Although not a quality of life measure, the Zhu score, a measure of severity of disease, of subjects over time will be presented in a listing.

9.2.8 Hospitalisations

Hospitalisations will be recorded on the Relevant Medical History page, Concomitant Diseases page and Adverse Event page. Days of hospitalisation will be calculated from the admission date and discharge date from the eCRF. Subjects may be hospitalised for multiple AEs. Therefore, overlapping periods of hospitalisation will only be counted once.

The number of days of hospitalisation and rate of hospitalizations per patient year observation will be summarised for the pre-treatment phase (12 months prior to gene therapy), post-treatment phases (as defined in Table 3) and the overall phase post 6 months after gene therapy. Rates will be provided along with confidence intervals. A listing will also be created of hospitalisations.

9.3 Exploratory Efficacy

9.3.1 Analysis of antimicrobial treatment

A summary of the antimicrobial medications per treatment phase (Table 3) will be presented along with the rate of treatments per year of observation.

A summary of time to sustained antimicrobial treatment discontinuation will be produced for subjects who no longer need antimicrobial treatment. The cessation of sustained treatment is defined as a period of 3 months post gene therapy without antimicrobial treatment. The time to discontinuation will be presented in a table and Kaplan Meier plot including median time to discontinuation and 95% confidence interval.

A listing will also be created of positive microbiological evaluations.

9.3.2 Platelet Activation Profile and Morphology

The analysis and reporting of this exploratory endpoint will be detailed in a separate document that will be summarised within and appended to the CSR.

10 Safety Analyses

10.1 All outputs for safety outcomes will be based on the MS Set. Planned Primary Safety Analyses

Table 10 provides an overview of the planned analyses.

Table 10 Overview of Planned Primary Safety Analyses

[Endpoint / Parameter/ Display Type]	Raw Data			
	Summary		Individual	
	T	F	F	L
Safety of reduced conditioning regimen				
Prolonged aplasia based on ANC data	Y		Y	Y
Conditioning regimen related non-hematopoietic toxicity	Y			Y
Safety of LVV gene transfer into HSC				
AEs/SAEs within 2 days from infusion	Y			Y
RCL	Y			Y
ACP				Y

T = Table, F = Figure, L = Listing, Y = Yes display generated.
Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
Individual = Represents FL related to any displays of individual subject observed raw data

10.1.1 Safety of Reduced Conditioning Regimen

Prolonged aplasia will be assessed based on Absolute Neutrophil Count (ANC) data collected at the Day 60 visit together with bone marrow recovery and back-up administration data (recorded in Adverse Event or Concomitant Medications page if there are any) for each subject. A listing of ANC data collected at Day 60 visit by subject will be generated. This will include all ANC data assessed in the visit window for Day 60 (from Day 47 to Day 76, Section 7.3.1). The longitudinal profile of ANC for the whole post treatment phase as well as from baseline to 100 days post treatment will be described by means of two plots of individual patient data.

Regimen related non-hematopoietic toxicity will be assessed based on the clinical and laboratory data collected during the first 100 days post gene therapy (this is based on assessment of AEs with National Cancer Institute (NCI) CTCAE grade ≥ 2 for clinical features and NCI CTCAE grade ≥ 3 for laboratory parameters) for each subject. A summary and listing of clinical features NCI CTCAE grade ≥ 2 and laboratory features NCI CTCAE grade ≥ 3 during the first 100 days after gene therapy will be generated. Events are included based on the onset days from infusion.

To increase the informative clinical value of conditioning-related AEs, the 100 days period will be further stratified in three phases:

- Day 0-30
- Day 31 to Day 60
- Day 61 to Day 100

10.1.2 Safety of Lentiviral (LVV) Gene Transfer into HSC

Short-term safety and tolerability will be evaluated based on adverse event reporting and monitoring of the systemic reactions to cell infusion (fever, tachycardia, nausea and vomiting, joint pain, skin rash). The short-term safety and tolerability of lentiviral-transduced cells infusion will be assessed by the absence of SAEs within 48 hours from infusion. A table of SAEs and AEs starting within 2 days of infusion will be generated by subject.

Long-term safety of LVV gene transfer consists of the absence of replication competent lentivirus (RCL) and abnormal clonal proliferation (ACP).

RCL is considered positive if a confirmatory RCL culture test is positive. In protocol amendment 11 (28 May 2020) the strategy for RCL testing was simplified: an HIV p24 antigen detection in the serum by ELISA is performed in the first instance. Should this test be positive, further analyses will be performed, including DNA PCR for VSV-G envelope on cells, and RT- PCR for HIV-pol RNA on serum. If a positive result is obtained from at least one of the additional tests, an appropriate confirmatory test may be performed. Prior to this, a confirmatory test was performed when two of the three screening tests (ELISA for HIV p24 antigen, DNA PCR for VSV-G env, and RT-PCR for HIV-pol RNA) were confirmed as having a positive result. The confirmatory test data will be summarised by visit. A listing of individual test data will be generated by subject together with anti-Human Immunodeficiency Virus (HIV) p24 antibodies and confirmatory RCL Culture test.

Monitoring for ACP requires the clinical review of multiple datasets (e.g., routine clinical and laboratory surveillance, repertoire study, bone marrow examination, integration site analysis). Therefore, no summary tables focused solely on ACP will be produced. Data needed for monitoring of ACP will be displayed in relevant AE and efficacy summaries. The results of the manual clinical review for ACP will be described in the CSR with cross-reference to the relevant study listings and a separate integration site analysis report.

A listing of adverse events with onset within 48 hours of gene therapy will be created.

10.2 Planned Secondary Safety Analyses

Table 12 provides an overview of the planned secondary safety analyses.

Table 11 Overview of Planned Secondary Safety Analyses

[Endpoint / Parameter/ Display Type]	Absolute[5]				Change from Baseline[5]			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Immune response to transgene								
Antibodies to WASP	Y			Y				
Overall safety evaluation								

[Endpoint / Parameter/ Display Type]	Absolute[5]				Change from Baseline[5]			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
AEs[1]/SAEs[2]/Fatal AE/Treatment related AEs	Y			Y				
Clinical and laboratory values [3]								
Routine laboratory tests[3]	Y		Y	Y	Y			Y
Vital signs and physical growth								
Vital signs[4] and physical growth	Y		Y	Y	Y			Y

T = Table, F = Figure, L = Listing, Y = Yes display generated.
Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
Individual = Represents FL related to any displays of individual subject observed raw data
[1] All AEs will be summarised and presented in tables by SOCs and PTs; by PTs only and by Severity (Grade).
[2] Fatal and Non-fatal Serious AEs will be presented in separate listings.
[3] A listing of laboratory data will be produced with values outside normal ranges flagged. The associated reference range of these laboratory tests will also be produced in another listing.
[4] Vital signs are captured as part of clinical examination.
[5] Absolute and change from baseline summaries/listings are combined into a single display.

As part of the overall safety evaluation, a detailed analysis of LVV integrations (ISA analysis) will be performed on PBMC and BM cells, to monitor the nature and distribution vector integration sites. The data from LVV integration site analysis is captured outside the eCRF, and thus the reporting is not covered in this SAP.

10.2.1 Immune Response to Transgene

The lack of immune response towards the transgene will be measured by antibodies to WASP.

A summary table detailing the number and percentage of subjects with present anti-WASP antibodies will be generated with 95% CI of the percentage calculation. The longitudinal profile over time of anti-WASP antibodies will be described with a listing.

10.2.2 Adverse Events

AEs are recorded from screening. All AEs will be coded using version 22.1 of Medical Dictionary for Regulatory Activities (MedDRA) or higher.

10.2.2.1 Summaries of All Adverse Events

Adverse events, unless otherwise stated, will be summarised according to the phase in which the AE started, such that an AE with a duration spanning more than one study phase is only reported once. Adverse event tables will summarise data recorded on Relevant Medical History, Concomitant Diseases and Adverse Event pages. Adverse events that were recorded from day of gene therapy will be recorded on the adverse event page, with prior events recorded on the relevant medical history and concomitant diseases pages.

An overall summary of AEs will be presented including severity, relatedness and seriousness of events. The total number and percentage of subjects reporting AEs will be summarised by MedDRA System Organ Class (SOC), preferred term (PT) and the treatment phase at which they were initially reported. In addition, the total number and percentage of subjects reporting treatment-related AEs during each treatment phase will be summarised by SOC and preferred term. Unexpected adverse reactions (UARs) and suspected unexpected severe adverse reactions (SUSARs) will be summarised by SOC, PT and treatment phase. Expected adverse reactions are listed in protocol section 8.2.4. A separate summary of AEs by severity, SOC and preferred term will be presented.

The total number of AEs, and the number and percentage of AEs with an outcome of recovered/resolved within each treatment phase will be summarised. In addition, a summary of the most frequently reported AEs (defined as rate greater than 1 per year of patient observation in any treatment phase) will be presented by treatment phase and preferred term. A summary will also be presented of AE preferred terms by treatment phase ordered by decreasing frequency.

Clinical events of CTC grade 3 or above that occurred in the 12 months prior to gene therapy will be summarised as part of the pre-treatment medical history next to those that occurred after gene therapy.

A listing of all AEs will be provided. A listing of the relationship between SOC, PTs and verbatim text will also be provided. Based on the PTs, a separate listing will be produced for AEs related to bleeds, infections, autoimmunity, eczema or suspected malignancies to be reviewed together with results from a manual search.

A listing will be created of any events leading to discontinuation.

10.2.2.2 Deaths and Serious Adverse Events

The SAEs recorded for all subjects will be summarised in a table by SOC, PT, and by treatment phase as well as provided in a listing.

All fatal AEs will be reported by PT and verbatim text in a separate listing.

SAEs were only recorded from day 1 and will, therefore, only be reported from the last day of the treatment phase onwards.

10.2.2.3 Analyses of Adverse Events related to bleeds, infections, autoimmunity, eczema or suspected malignancies

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the program and the time of

reporting and/or emerging data from on-going studies may highlight additional adverse events of particular interest to be added to these analyses, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the reviewed list from the latest dictionary in place at the time of reporting. At the time of writing the AEs that will be included are listed in Appendix 2.

Events defined as autoimmunity by the investigator will be summarised by treatment phase.

10.2.3 Clinical Laboratory Evaluations

Clinically relevant abnormal values will be recorded in the Concomitant Disease page or Adverse Events page. Clinical laboratory evaluations will be summarised with descriptive statistics by visit. Any haematology or clinical chemistry test results which are outside the normal ranges will be flagged as high or low relative to the normal range.

The normal range of laboratory test parameters will also be provided in an additional listing as a reference.

Box plots will be generated to provide a graphical overview of the following laboratory parameters over time.

Table 12 Laboratory parameters where box plots will be generated

Chemistry	Haematology	Liver Function Tests (LFTs)
Creatinine	Platelet Count	Aspartate aminotransferase (AST)
	Haemoglobin	Alkaline Phosphatase (ALP)
	Haematocrit	Alanine aminotransferase (ALT)
	White Blood Cell Count (Leukocytes)	Total Bilirubin

In addition to all available data, the box plots will include the maximum post-baseline value for each subject. All data will be presented relative to the upper limit of normal (ULN). In addition, for the haematology parameters only, box plots will also be produced showing the data relative to the lower limit of normal (LLN), including the minimum post-baseline value for each subject. For liver function tests only, a horizontal line will be included in the figures denoting 2xULN.

Individual profiles of LFT, relative to the ULN, over time will be plotted.

Tables will also be created for shifts in parameters with reference to the reference range. Results will be summarised per parameter per visit. Shifts compared to the reference range (low, normal, high) from baseline to minimum value and maximum value post-baseline will be presented for laboratory parameters. Listings of laboratory data outside the normal range and a listing of all laboratory data will be created.

Summary statistics of immunoglobulins (IgA, IgG, IgM, IgE) will be presented over time. IgG evaluations taken within 3 months of IVIG administration will be excluded from the summary.

10.2.4 Vital Signs and Physical Growth

Vital signs captured as part of clinical examinations will be summarised and listed for all the subjects by visit to include body temperature, blood pressure, pulse rate, weight, height, body surface area, and BMI.

A visual summary of physical growth of individual subjects as measured by their height and weight will be presented over time. Height and weight for all subjects will be compared with the World Health Organization (WHO) growth charts as follows:

- https://www.who.int/childgrowth/standards/en/
- https://www.who.int/growthref/en

Height and weight for all subjects will be compared with the WHO length and height charts up to the age of 18 years.

10.2.5 Lentiviral Insertion Site Analysis (ISA)

The analysis and reporting of this exploratory safety endpoint will be detailed in a separate document that will be summarised within and appended to the CSR.

11 Data Not Summarised or Presented

The other variables and/or domains not summarised or presented are:

- Comments

These domains and/or variables will be available in the clinical study database and SDTM datasets.

12 Reporting Conventions

Display of decimals should follow the rules below:

- Minimum and maximum should be displayed to the same accuracy as the original data.
- Median and mean (arithmetic and geometric) and confidence intervals should be displayed to the accuracy of the original data + 1.
- Geometric CV will be reported to 1 decimal place.
- SD should be displayed to the accuracy of the original data + 2.
- For durations that are summarised, use 2 decimal places as the base. List to the same base number of decimal places.
- When summarising age, use 2 decimal places as the base. List to the same base number of decimal places.

Display of summary statistics should follow the rules below.

- There is no minimum n for mean, median, min and max. Present as follows:
  - For n = 1: Mean, median, min, max and geomean (where applicable).
  - For n ≥ 2: All summary stats for n=1, plus SD, LCL, UCL and geoCV (where applicable).

Calculating Geometric Summary Stats

To calculate geometric mean, first take the natural logarithm of the analysis value using the SAS log function, then calculate the mean of this [Mean], then exponentiate the mean: e^([Mean]) using the SAS exp function.

To calculate the geometric CV, first take the natural logarithm of the analysis value using the SAS log function, then calculate the standard deviation [STD], then calculate 100*√(e^(〖[STD]〗^2)-1) using the SAS exp, ** (power), and sqrt functions/operators as appropriate.

13 Technical Details

Statistical evaluation will be performed by Veramed Limited.

The datasets will follow analysis dataset model (ADaM) data specifications.

All analyses will be performed using SAS version 9.4 or higher (SAS Institute, Cary, NC, USA).

14 Summary of Changes to the Protocol

There were two changes in the planned statistical analysis specified in protocol amendment 7 (Dated: 09JAN2015).

The first is expanding the assessment window. Section 7.2 in the protocol defines a time window of +/- 10% for accepting assessments after day +120; and a time window of +/- 30 days for assessments after 1 year. Section 6.4 in this SAP defines wider assessment windows for reporting purposes. This is driven by the fact that the clinical conditions of subjects and the family travel planning may cause the actual visit date to deviate largely from the planned visit date. In this small study of this ultra-rare disease, all data collected are valuable in contributing to analyses and reporting. The extended assessment windows will potentially allow more evaluation and test results to be included.

The second is designating the day of transduced cells infusion for reporting purposes. Sections 5.2 and 6.9 in the protocol refer to this day as Day 0. Section 6.4 Windowing conventions in this SAP designates this day as Day 1 as required by Study Data Tabulation Model (SDTM) Implementation Guide v3.1.3. The study day value is incremented by 1 for each date following Day 1. Dates prior to Day 1 are decremented by 1, with the date preceding Day 1 designated as Day -1 (there is no Day 0).

In amendment 9 (Dated: 31JAN2018) the following changes that affect the SAP were made:

- The secondary efficacy endpoint of bruising was removed.
- CD61+ was removed from the BM analysis for engraftment (data will still be listed).

- Normalisation of platelet activation profile and morphology was added as an exploratory endpoint but the data will be collected and reported separately and not included in the clinical database. The analysis and results of these data will be reported outside of the CSR so is not detailed in this SAP.
- The addition of an extended long-term follow-up phase. After completion of 8 years of follow-up after gene therapy, subjects will be contacted annually in order to collect long-term safety and selected efficacy data, until a registry/long-term follow-up study is available and subjects have been enrolled in it.

In amendments 11 (dated 28 May 2020) and 11.1 (dated 14 July 2021) the following changes that affect the SAP were made:

Text was amended to allow all subjects to enter a separate observational long-term follow-up (OLTFU) study once it is set up and subjects have been followed up for a minimum of 5 years, not just after subjects enter the (extended long-term follow-up) ELTFU phase. As part of the OLTFU study, patients will continue to be followed up for a total of 15 years from the date of treatment with gene therapy. Text was also amended in this SAP to reflect the change.

The strategy for RCL testing was simplified so text in this SAP was updated to reflect the fact that 2 different RCL testing strategies had been used.

The mention of 'special interest' was removed from the definition of events such as bleeds, infections, autoimmunity, eczema or suspected malignancies, which are disease related and do not meet the criteria for events of special interest in terms for PV safety analysis and reporting. Therefore any mention of 'adverse events of special interest' in this SAP has been replaced with 'adverse events related to bleeds, infections, autoimmunity, eczema or suspected malignancies'.

15 References

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Brown LD, Cai TT, DasGupta A. Interval Estimation for a Binomial Proportion. Statistical Science. 2001;16(2):101-17.

Imai K, Morio T, Zhu Y, et al. Clinical course of patients with WASP gene mutations. Blood. 2004;103(2):456-64.

16 Appendix 1: List of Tables, Figures and Listings

16.1 All outputs detailed in the following sections will be produced for interim and final analyses.Study Population

16.1.1 Tables

Number	Title	Analysis Set
14.1.1.1	Summary of Subject Disposition	ES
14.1.1.2	Summary of Duration of Follow-up	ITT
14.1.2.1	Summary of Demographic Characteristics at Screening/Baseline or on Date of Gene Therapy	ITT
14.1.3.1	Summary of Relevant Medical History	ITT
14.1.4.1	Summary of Concomitant Medications (Excluding PBSC Mobilisation and Conditioning Regimen) by ATC Level 1, Preferred Name and Treatment Phase	MS
14.1.4.2	Summary of Exposure to Conditioning Regimen	ITT
14.1.5.1	Summary of Exposure to Gene Therapy	ITT

16.1.2 Listings

Number	Title	Analysis Set
16.2.1.1	Listing of Reasons for Withdrawal	ES
16.2.1.2	Listing of Duration of Follow-up	ITT
16.2.2.1	Listing of Protocol Deviations	ITT
16.2.2.2	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ITT
16.2.4.1	Listing of Demographic Characteristics at Screening/Baseline or on the Date of Gene Therapy	ITT
16.2.4.2	Listing of Relevant Medical History	ITT
16.2.4.3	Listing of Relevant Previous Medications at Screening	MS
16.2.4.4	Listing of Concomitant Medications by Treatment Phase (PBSC Mobilisation, and Conditioning Regimen Excluded)	MS
16.2.4.5	Listing of Medications for Infections, Eczema, and Autoimmunity by Treatment Phase	MS
16.2.4.6	Listing of PBSC Mobilisation and Conditioning Medications	ITT
16.2.4.7	Listing of Stem Cell Collection	ITT
16.2.4.8	Listing of Mutations, Baseline WASP Expression, and WAS Severity	ITT
16.2.5.1	Listing of Exposure to Gene Therapy	ITT

16.2.5.2	Listing of Duration of Hospitalisation for Gene Therapy	ITT
16.2.5.3	Listing of Patients Requiring Platelet Infusion by Treatment Phase	ITT
16.2.5.4	Listing of Time to Cessation of Maintenance Platelet Infusion, IVIG and Antimicrobial Therapy	ITT

16.2 Efficacy

16.2.1 Tables

Number	Title	Analysis Set
14.2.1.1.1	Summary of Overall Survival	ITT
14.2.1.2.1	Summary of Subjects with Adequate Engraftment Findings Over Time - Bone Marrow CD34+ and Periperal Blood CD3+	ITT
14.2.1.2.2	Summary Statistics of Vector Copy Number Evaluation in BM and PB cells	ITT
14.2.1.2.6	Summary Statistics of Percentage of Lentiviral Vector Transduced-Colony Forming Units in Bone Marrow Cells (%LVV+ CFU in BM) Over Time	ITT
14.2.1.2.12	Summary of Time to Adequate Engraftment	ITT
14.2.1.3.1	Summary Statistics of Cells Expressing WASP Assessed by Flow Cytometry Over Time	ITT
14.2.1.4.1	Summary Statistics of T-Cell Function	ITT
14.2.1.5.1	Summary of Subjects with Positive Antigen-Specific Responses to Vaccinations	ITT
14.2.1.5.2	Summary of Number and Rate of IVIG Treatment Required by Treatment Phase	ITT
14.2.1.5.3	Summary of Time to Cessation of Sustained IVIG Therapy	ITT
14.2.1.6.1	Summary of Subjects with Improved Platelet Count Over Baseline at Each Year Post Gene Therapy	ITT
14.2.1.6.2	Summary Statistics of Platelet Count and MPV Data	ITT
14.2.1.6.3	Summary of Shifts in Categorical Platelet Count Data From Baseline to Each Year Post Gene Therapy	ITT
14.2.1.6.4	Summary of Shifts in MPV From Baseline to Each Year Post Gene Therapy	ITT
14.2.1.6.7	Summary of Number and Rate of Platelet Infusions by Treatment Phase	ITT
14.2.1.6.8	Summary of Time to Cessation of Sustained Platelet Infusion Therapy	ITT
14.2.2.1.1	Summary of Subjects with Adequate Multilineage Engraftment Findings at Each Year Post Gene Therapy	ITT
14.2.2.2.1	Summary of Severe Infections and All Bleeding Events	ITT
14.2.2.2.3	Summary of Number and Rate of Bleeding Events by Treatment Phase and Severity	ITT
14.2.2.2.4	Summary of Number and Rate of Severe Infections Events by Treatment Phase	ITT

14.2.2.2.6	Summary of Number and Rate of Bleeding Events (Defined from Haemorrhages (SMQ)) by Treatment Phase and Severity	ITT
14.2.2.3.1	Summary of Number of Subjects with Positive Autoimmunity Test	ITT
14.2.2.4.1	Eczema Score Shift Table	ITT
14.2.2.5.1	Summary of Social Life Data Over Time	ITT
14.2.2.5.2	Summary Statistics of Lansky/Karnofsky Performance Index	ITT
14.2.2.6.1	Summary of Days and Rate of Hospitalisation by Treatment Phase	ITT
14.2.3.1.1	Summary of Antimicrobial Treatments by ATC Level 1, Preferred Term and Treatment Phase	ITT
14.2.3.1.2	Summary of Number and Rate of Antimicrobial Treatment Required by Treatment Phase	ITT
14.2.3.1.3	Summary of Time to Cessation of Sustained Antimicrobial Treatment Therapy	ITT

16.2.2 Figures

Number	Title	Analysis Set
14.2.1.1.2	Kaplan-Meier Survival Curve	ITT
14.2.1.2.3	Individual Profiles of PCR Transduced Cell Evaluation in BM and PB Over Time	ITT
14.2.1.2.4	Arithmetic Mean (95% CI) Values of PCR Transduced Cell Evaluation in BM and PB	ITT
14.2.1.2.5	Summary of Kaplan-Meier Analysis of Time to Adequate Engraftment	ITT
14.2.1.2.7	Individual Profiles of Percentage of Lentiviral Vector Transduced-Colony Forming Units in Bone Marrow Cells (%LVV+ CFU in BM)	ITT
14.2.1.2.8	Boxplot of Stem Cell Source vs. Engraftment at Each Year Post Gene Therapy	ITT
14.2.1.2.9	Scatterplot of Treatment Dose, Busulfan Exposure, Age at Gene Therapy vs. Engraftment at Each Year Post Gene Therapy	ITT
14.2.1.2.10	Median Values for VCN/cell in Bone Marrow Cell Lineages	ITT
14.2.1.2.11	Median Values for VCN/cell in Peripheral Blood Cell Lineages	ITT
14.2.1.3.2	Median Values of Cells Expressing WASP Assessed by Flow Cytometry Over Time	ITT
14.2.1.3.3	Individual Profiles of WASP+ Cells Assessed by Flow Cytometry Over Time	ITT
14.2.1.3.4	Arithmetic Mean (95% CI) Values of Cells Expressing WASP Assessed by Flow Cytometry Over Time	ITT
14.2.1.4.2	Individual Profiles of T-Cell Proliferation Responses over Time	ITT
14.2.1.4.3	Arithmetic Mean (95% CI) Values of T-Cell Proliferation Responses over Time	ITT

14.2.1.4.4	Boxplot of T-Cell Proliferation Responses at Baseline and Each Year Post Gene Therapy	ITT
14.2.1.4.5	Scatterplot of Treatment Dose, Busulfan Exposure, Age at Gene Therapy vs. T-Cell Functions at Each Year Post Gene Therapy	ITT
14.2.1.5.4	Summary of Kaplan-Meier Analysis of Time to Cessation of Sustained IVIG Therapy	ITT
14.2.1.6.5	Individual Profiles of Platelet Count and MPV Data Over Time	ITT
14.2.1.6.6	Median Platelet Counts by Subgroups of Baseline WASP Expression	ITT
14.2.1.6.9	Summary of Kaplan-Meier Analysis of Time to Cessation of Sustained Platelet Infusion Therapy	ITT
14.2.1.6.10	Arithmetic Mean (95% CI) Values of Platelet Count and MPV Data over Time	ITT
14.2.2.1.2	Individual Profile of Bone Marrow Immunophenotype Data Over Time	ITT
14.2.2.1.3	Individual Profile of Peripheral Blood Immunophenotype Data Over Time	ITT
14.2.2.2.2	Rate of Severe Infections and Bleeding by Treatment Phase	ITT
14.2.2.2.5	Distribution of Bleeding Event System Organ Class Over Time	ITT
14.2.2.4.2	Individual Profiles of Eczema Score Over Time	ITT
14.2.2.5.3	Individual Profiles of Lansky/Karnofsky Performance Index Over Time	ITT
14.2.3.1.4	Summary of Kaplan-Meier Analysis of Time to Cessation of Sustained Antimicrobial Treatment Therapy	ITT

16.2.3 Listings

Number	Title	Analysis Set
16.2.6.1	Listing of Overall Survival	ITT
16.2.6.2	Listing of PCR Transduced Cell Evaluation in BM and PB	ITT
16.2.6.3	Listing of Time to Adequate Engraftment of Genetically Corrected Cells	ITT
16.2.6.4	Listing of WASP Expression by Flow Cytometry	ITT
16.2.6.5	Listing of WASP Expression by Western Blot	ITT
16.2.6.6	Listing of T-Cell Proliferation Responses	ITT
16.2.6.7	Listing of Vaccinations and Subsequent Immunology Evaluations	ITT
16.2.6.8	Listing of Subjects with Positive Antigen-Specific Responses to Vaccinations	ITT
16.2.6.9	Listing of Platelet Count and MPV Data	ITT
16.2.6.10	Listing of Severe Infections	ITT
16.2.6.11	Listing of Bleeding	ITT

16.2.6.12	Listing of Eczema Score	ITT
16.2.6.13	Listing of Positive Autoimmunity Evaluation Data by Visit	ITT
16.2.6.14	Listing of Quality of Life Data	ITT
16.2.6.15	Listing of Bone Marrow Morphology and Karyotype Data	ITT
16.2.6.16	Listing of Bone Marrow Immunophenotype and Colony Forming Unit Data	ITT
16.2.6.17	Listing of Peripheral Blood Immunophenotype Data	ITT
16.2.6.18	Listing of Peripheral Blood Immunophenotype Subpopulations Outside Normal Reference Ranges	ITT
16.2.6.19	Listing of Serum Immunoglobulin Data	MS
16.2.6.20	Listing of Lymphocyte Proliferative Response	ITT
16.2.6.21	Listing of Patients Requiring IVIG Infusion	ITT
16.2.6.22	Listing of Replication Competent Lentivirus Evaluations	MS
16.2.6.23	Listing of TCR Repertoire by Flow Cytometry	ITT
16.2.6.24	Listing of Immune Response to Transgene	MS
16.2.6.25	Listing of Zhu Clinical Score	ITT
16.2.6.26	Listing of Positive Microbiological Evaluations	ITT
16.2.6.27	Listing of Antibodies to Pathogens	ITT

16.3 Safety

16.3.1 Tables

Number	Title	Analysis Set
14.3.1.1.1	Summary of AEs NCI CTCAE ≥ 2 and Laboratory Features NCI CTCAE ≥ 3 During the First 100 Days after Gene Therapy by SOC and Preferred Term	MS
14.3.1.2.1	Summary of Number of Subjects with an SAE within 48 Hours from Infusion by SOC and PT	MS
14.3.1.3.1	Summary of Subjects with Positive Replication Competent Lentivirus (RCL) Results	MS
14.3.2.1.1	Summary of Subjects with Positive Immune Response to Transgene	MS
14.3.2.2.1	Summary of Number of Subjects with Adverse Events by Treatment Phase	MS
14.3.2.2.2	Summary of All Adverse Events by SOC, Preferred Term and Treatment Phase	MS
14.3.2.2.3	Summary of Related Adverse Events by SOC, Preferred Term and Treatment Phase	MS
14.3.2.2.4	Summary of Serious Adverse Events by SOC, Preferred Term and Treatment Phase	MS
14.3.2.2.5	Summary of Unexpected Adverse Reactions by SOC, Preferred Term and Treatment Phase	MS [1]

Commentato [MS1]: Removed as it is not in TOC

14.3.2.2.6	Summary of Suspected Unexpected Serious Adverse Reactions by SOC, Preferred Term and Treatment Phase	MS [1]
14.3.2.2.7	Summary of All Adverse Events by Severity (Grade), SOC, Preferred Term and Treatment Phase	MS
14.3.2.2.8	Summary of Grade 3, 4, and 5 Adverse Events - 12 Months Pre- vs. Post-Gene Therapy	ITT [2]
14.3.2.2.9	Number and Rate of Most Frequently Reported Adverse Events (Rate ≥ 1 per PYO in Any Treatment Phase) by Preferred Term	MS
14.3.2.2.10	Number (%) of Subjects with Autoimmunity Adverse Events of Special Interest by Preferred Term and Treatment Phase	MS
14.3.2.2.11	Summary of Adverse Events by Preferred Term, Ordered by Decreasing Frequency	MS
14.3.2.2.12	Number (%) of Subjects with Immune Mediated Adverse Events by Preferred Term and Treatment Phase	MS
14.3.2.2.13	Number (%) of Subjects with Eczema and Dermatological Adverse Events by Preferred Term and Treatment Phase	MS
14.3.2.2.14	Number (%) of Subjects with Autoimmunity Adverse Events based on Dictionary Defined Terms by Preferred Term and Treatment Phase	MS
14.3.2.3.1	Summary Statistics for Laboratory Parameters	MS
14.3.2.3.6	Summary of Shifts from Baseline to Maximum and Minimum Values for Lab Parameters	MS
14.3.2.3.7	Summary of Laboratory Data Relative to Normal Range Over Time	MS
14.3.2.3.8	Summary Statistics for Immunoglobulins	MS
14.3.2.4.1	Summary Statistics for Vital Signs	MS

[1] Added for final analysis

[2] Note that this table should be omitted for the final analysis and subsequent numbering updated as appropriate so there is no gap.

Commentato [MS2]: Removed as it is not in TOC

Commentato [MS3]: See comment above

16.3.2 Figures

Number	Title	Analysis Set
14.3.1.1.2	Individual Profiles of ANC from Screening to 100 Days Post-Treatment	MS
14.3.1.1.3	Individual Profiles of ANC from Screening to Last Post-Treatment Follow-Up	MS
14.3.2.3.2	Boxplots of Chemistry and Haematology Data, Relative to the Upper Limit of Normal, by Visit	MS
14.3.2.3.3	Boxplot of Haematology Data, Relative to the Lower Limit of Normal, by Visit	MS
14.3.2.3.4	Boxplot of Liver Function Test Data, Relative to the Upper Limit of Normal, by Visit	MS

14.3.2.3.5	Individual Profiles of LFT Relative to the Upper Limit of Normal Over Time	MS
14.3.2.4.2	Individual Profiles of Physical Growth (Height and Weight) Over Time	MS

16.3.3 Listings

Number	Title	Analysis Set
16.2.7.1	Listing of All Adverse Events	MS
16.2.7.2	Listing of Fatal Adverse Events	MS
16.2.7.3	Listing of All Serious Adverse Events	MS
16.2.7.4	Listing of Adverse Events Leading to Withdrawal from Study	MS
16.2.7.5	Listing of All Adverse Events Onset within 48 Hours from Infusion	MS
16.2.7.6	Listing of Predefined Adverse Event Groupings	MS
16.2.7.7	Listing of Relationship Between System Organ Class, Preferred Term, and Verbatim Text	MS
16.2.7.8	Listing of Adverse Events NCI CTCAE ≥ 2 and Laboratory Features NCI CTCAE ≥ 3 During the First 100 Days after Gene Therapy	MS
16.2.7.9	Listing of Hospitalisations	MS
16.2.8.1	Listing of Laboratory Data Outside Normal Range	MS
16.2.8.2	Listing of Laboratory Data	MS
16.2.8.3	Listing of Laboratory Tests and Associated Reference Ranges	MS
16.2.8.4	Listing of Vital Signs Data	MS
16.2.8.5	Listing of Absolute Neutrophil Count Response	MS

17 Appendix 2: Groupings for Medications, and Adverse Events related to Bleeds, Infections, Autoimmunity, Eczema or Suspected Malignancies

Grouping category	Terms
Medications	
Anti-infectives for systemic use	WHO-DD ATC 1 code J
Antineoplastic and immunomodulating agents	WHO-DD ATC 1 code L
Antimicrobials	WHO-DD coded term of: ACICLOVIR ACYCLOVIR AMOXICILLIN TRIHYDRATE;CLAVULANATE POTASSIUM AMOXICILLIN;CLAVULANATE POTASSIUM AMOXICILLIN;CLAVULANIC ACID AMPHOTERICIN B ANTIBIOTICS ANTIFUNGALS AZITHROMYCIN CEFAZOLIN CEFIXIME CEFTRIAXONE CEFTRIAXONE SODIUM CIPROFLOXACIN CIPROFLOXACIN HYDROCHLORIDE DAPSONE FLUCONAZOLE ITRACONAZOLE LEVOFLOXACIN MICAFUNGIN MICAFUNGIN SODIUM NYSTATIN PENTAMIDINE PENTAMIDINE ISETHIONATE SULFAMETHOXAZOLE;TRIMETHOPRIM VALGANCICLOVIR VALGANCICLOVIR HYDROCHLORIDE VORICONAZOLE
Blood and blood forming organs	WHO-DD ATC 1 code B
Dermatologicals	WHO-DD ATC 1 code D

Vaccines	WHO-DD ATC 2 J07
Infusion of platelets	WHO-DD coded term of PLATELETS, HUMAN BLOOD
Conditioning	WHO-DD coded terms of : RITUXIMAB BUSULFAN FLUDARABINE ANTITHYMOCYTE IMMUNOGLOBULIN
PBSC mobilization	Defined on PBSC eCRF page
IVIG infusion	WHO-DD ATC3 J06B is immunoglobulins.
Adverse Events	
Infections	MedDRA System Organ Class "INFECTIONS AND INFESTATIONS" Higher Level Group "MICROBIOLOGY AND SEROLOGY INVESTIGATIONS" in "INVESTIGATIONS" SOC Lower Level Terms **10003525** and **10022617** from SOC "RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS"

Bleeding	MedDRA Hemorrhage (excl Laboratory Terms) SMQ (Narrow) Abdominal wall haematoma Abdominal wall haemorrhage Abnormal withdrawal bleeding Achenbach syndrome Acute haemorrhagic leukoencephalitis Acute haemorrhagic ulcerative colitis Administration site bruise Administration site haematoma Administration site haemorrhage Adrenal haematoma Adrenal haemorrhage Anal fissure haemorrhage Anal haemorrhage Anal ulcer haemorrhage Anastomotic haemorrhage Anastomotic ulcer haemorrhage Aneurysm ruptured Angina bullosa haemorrhagica Anorectal varices haemorrhage Aortic aneurysm rupture Aortic dissection rupture Aortic intramural haematoma Aortic perforation Aortic rupture Aponeurosis contusion Application site bruise Application site haematoma Application site haemorrhage Application site purpura Arterial haemorrhage Arterial intramural haematoma Arterial perforation Arterial rupture Arteriovenous fistula site haematoma Arteriovenous fistula site haemorrhage Arteriovenous graft site haematoma Arteriovenous graft site haemorrhage Astringent therapy

	Atrial rupture Auricular haematoma Basal ganglia haematoma Basal ganglia haemorrhage Basilar artery perforation Bladder tamponade Bleeding varicose vein Blood blister Blood urine Blood urine present Bloody discharge Bloody peritoneal effluent Bone contusion Bone marrow haemorrhage Brain contusion Brain stem haematoma Brain stem haemorrhage Brain stem microhaemorrhage Breast haematoma Breast haemorrhage Broad ligament haematoma Bronchial haemorrhage Bronchial varices haemorrhage Bursal haematoma Cardiac contusion Carotid aneurysm rupture Carotid artery perforation Catheter site bruise Catheter site haematoma Catheter site haemorrhage Central nervous system haemorrhage Cephalhaematoma Cerebellar haematoma Cerebellar haemorrhage Cerebellar microhaemorrhage Cerebral aneurysm perforation Cerebral aneurysm ruptured syphilitic Cerebral arteriovenous malformation haemorrhagic Cerebral artery perforation Cerebral haematoma Cerebral haemorrhage

	Cerebral haemorrhage foetal Cerebral haemorrhage neonatal Cerebral microhaemorrhage Cervix haematoma uterine Cervix haemorrhage uterine Chest wall haematoma Choroidal haematoma Choroidal haemorrhage Chronic gastrointestinal bleeding Chronic pigmented purpura Ciliary body haemorrhage Coital bleeding Colonic haematoma Conjunctival haemorrhage Contusion Corneal bleeding Cullen's sign Cystitis haemorrhagic Deep dissecting haematoma Diarrhoea haemorrhagic Disseminated intravascular coagulation Diverticulitis intestinal haemorrhagic Diverticulum intestinal haemorrhagic Duodenal ulcer haemorrhage Duodenitis haemorrhagic Dysfunctional uterine bleeding Ear haemorrhage Ecchymosis Encephalitis haemorrhagic Enterocolitis haemorrhagic Epidural haemorrhage Epistaxis Exsanguination Extra-axial haemorrhage Extradural haematoma Extravasation blood Eye contusion Eye haematoma Eye haemorrhage Eyelid bleeding Eyelid contusion

	Eyelid haematoma Femoral artery perforation Femoral vein perforation Foetal-maternal haemorrhage Fothergill sign positive Gastric haemorrhage Gastric ulcer haemorrhage Gastric ulcer haemorrhage, obstructive Gastric varices haemorrhage Gastritis alcoholic haemorrhagic Gastritis haemorrhagic Gastroduodenal haemorrhage Gastrointestinal haemorrhage Gastrointestinal polyp haemorrhage Gastrointestinal ulcer haemorrhage Gastrointestinal vascular malformation haemorrhagic Genital contusion Genital haemorrhage Gingival bleeding Graft haemorrhage Grey Turner's sign Haemarthrosis Haematemesis Haematochezia Haematocoele Haematoma Haematoma evacuation Haematoma infection Haematosalpinx Haematospermia Haematotympanum Haematuria Haematuria traumatic Haemobilia Haemophilic arthropathy Haemophilic pseudotumour Haemoptysis Haemorrhage Haemorrhage coronary artery Haemorrhage foetal Haemorrhage in pregnancy

	Haemorrhage intracranial Haemorrhage neonatal Haemorrhage subcutaneous Haemorrhage subepidermal Haemorrhage urinary tract Haemorrhagic adrenal infarction Haemorrhagic anaemia Haemorrhagic arteriovenous malformation Haemorrhagic ascites Haemorrhagic breast cyst Haemorrhagic cerebral infarction Haemorrhagic cyst Haemorrhagic diathesis Haemorrhagic disease of newborn Haemorrhagic disorder Haemorrhagic erosive gastritis Haemorrhagic hepatic cyst Haemorrhagic infarction Haemorrhagic necrotic pancreatitis Haemorrhagic ovarian cyst Haemorrhagic stroke Haemorrhagic thyroid cyst Haemorrhagic transformation stroke Haemorrhagic tumour necrosis Haemorrhagic urticaria Haemorrhagic vasculitis Haemorrhoidal haemorrhage Haemostasis Haemothorax Henoch-Schonlein purpura Hepatic haemangioma rupture Hepatic haematoma Hepatic haemorrhage Hereditary haemorrhagic telangiectasia Hyperfibrinolysis Hyphaema Iliac artery perforation Iliac artery rupture Iliac vein perforation Immune thrombocytopenic purpura Implant site bruising

	Implant site haematoma Implant site haemorrhage Incision site haematoma Incision site haemorrhage Increased tendency to bruise Induced abortion haemorrhage Inferior vena cava perforation Infusion site bruising Infusion site haematoma Infusion site haemorrhage Injection site bruising Injection site haematoma Injection site haemorrhage Instillation site bruise Instillation site haematoma Instillation site haemorrhage Internal haemorrhage Intestinal haematoma Intestinal haemorrhage Intestinal varices haemorrhage Intra-abdominal haematoma Intra-abdominal haemorrhage Intracerebral haematoma evacuation Intracranial haematoma Intracranial tumour haemorrhage Intraocular haematoma Intrapartum haemorrhage Intraventricular haemorrhage Intraventricular haemorrhage neonatal Iris haemorrhage Joint microhaemorrhage Kidney contusion Lacrimal haemorrhage Large intestinal haemorrhage Large intestinal ulcer haemorrhage Laryngeal haematoma Laryngeal haemorrhage Lip haematoma Lip haemorrhage Liver contusion Lower gastrointestinal haemorrhage

	Lower limb artery perforation Lymph node haemorrhage Mallory-Weiss syndrome Mediastinal haematoma Mediastinal haemorrhage Medical device site bruise Medical device site haematoma Medical device site haemorrhage Melaena Melaena neonatal Meningorrhagia Menometrorrhagia Menorrhagia Mesenteric haematoma Mesenteric haemorrhage Metrorrhagia Mouth haemorrhage Mucocutaneous haemorrhage Mucosal haemorrhage Muscle contusion Muscle haemorrhage Myocardial haemorrhage Myocardial rupture Naevus haemorrhage Nail bed bleeding Nasal septum haematoma Neonatal gastrointestinal haemorrhage Nephritis haemorrhagic Nipple exudate bloody Ocular retrobulbar haemorrhage Oesophageal haemorrhage Oesophageal intramural haematoma Oesophageal ulcer haemorrhage Oesophageal varices haemorrhage Oesophagitis haemorrhagic Optic disc haemorrhage Optic nerve sheath haemorrhage Oral contusion Oral mucosa haematoma Osteorrhagia Ovarian haematoma

	Ovarian haemorrhage Palpable purpura Pancreatic haemorrhage Pancreatitis haemorrhagic Papillary muscle haemorrhage Paranasal sinus haematoma Paranasal sinus haemorrhage Parathyroid haemorrhage Parotid gland haemorrhage Pelvic haematoma Pelvic haematoma obstetric Pelvic haemorrhage Penile contusion Penile haematoma Penile haemorrhage Peptic ulcer haemorrhage Pericardial haemorrhage Perineal haematoma Periorbital haematoma Periorbital haemorrhage Periosteal haematoma Peripartum haemorrhage Peripheral artery aneurysm rupture Peripheral artery haematoma Perirenal haematoma Peritoneal haematoma Peritoneal haemorrhage Periventricular haemorrhage neonatal Petechiae Pharyngeal haematoma Pharyngeal haemorrhage Pituitary haemorrhage Placenta praevia haemorrhage Polymenorrhagia Post abortion haemorrhage Post procedural contusion Post procedural haematoma Post procedural haematuria Post procedural haemorrhage Post transfusion purpura Postmenopausal haemorrhage

	Postpartum haemorrhage Post-traumatic punctate intraepidermal haemorrhage Premature separation of placenta Procedural haemorrhage Proctitis haemorrhagic Prostatic haemorrhage Pulmonary alveolar haemorrhage Pulmonary contusion Pulmonary haematoma Pulmonary haemorrhage Puncture site haemorrhage Purpura Purpura fulminans Purpura neonatal Purpura non-thrombocytopenic Purpura senile Putamen haemorrhage Radiation associated haemorrhage Rectal haemorrhage Rectal ulcer haemorrhage Renal artery perforation Renal cyst haemorrhage Renal haematoma Renal haemorrhage Respiratory tract haemorrhage Respiratory tract haemorrhage neonatal Retinal aneurysm rupture Retinal haemorrhage Retinopathy haemorrhagic Retroperitoneal haematoma Retroperitoneal haemorrhage Retroplacental haematoma Ruptured cerebral aneurysm Scleral haemorrhage Scrotal haematocoele Scrotal haematoma Shock haemorrhagic Skin haemorrhage Skin neoplasm bleeding Skin ulcer haemorrhage Small intestinal haemorrhage

	Small intestinal ulcer haemorrhage Soft tissue haemorrhage Spermatic cord haemorrhage Spinal cord haematoma Spinal cord haemorrhage Spinal epidural haematoma Spinal epidural haemorrhage Spinal subarachnoid haemorrhage Spinal subdural haematoma Spinal subdural haemorrhage Spleen contusion Splenic artery perforation Splenic haematoma Splenic haemorrhage Splenic varices haemorrhage Splinter haemorrhages Spontaneous haematoma Spontaneous haemorrhage Stoma site haemorrhage Stomatitis haemorrhagic Subarachnoid haematoma Subarachnoid haemorrhage Subarachnoid haemorrhage neonatal Subchorionic haematoma Subchorionic haemorrhage Subclavian artery perforation Subclavian vein perforation Subcutaneous haematoma Subdural haematoma Subdural haematoma evacuation Subdural haemorrhage Subdural haemorrhage neonatal Subgaleal haematoma Subgaleal haemorrhage Subretinal haematoma Superior vena cava perforation Testicular haemorrhage Thalamus haemorrhage Third stage postpartum haemorrhage Thoracic haemorrhage Thrombocytopenic purpura

	Thrombotic thrombocytopenic purpura Thyroid haemorrhage Tongue haematoma Tongue haemorrhage Tonsillar haemorrhage Tooth pulp haemorrhage Tooth socket haemorrhage Tracheal haemorrhage Traumatic haematoma Traumatic haemorrhage Traumatic haemothorax Traumatic intracranial haematoma Traumatic intracranial haemorrhage Tumour haemorrhage Ulcer haemorrhage Umbilical cord haemorrhage Umbilical haematoma Umbilical haemorrhage Upper gastrointestinal haemorrhage Ureteric haemorrhage Urethral haemorrhage Urinary bladder haemorrhage Urogenital haemorrhage Uterine haematoma Uterine haemorrhage Vaccination site bruising Vaccination site haematoma Vaccination site haemorrhage Vaginal haematoma Vaginal haemorrhage Varicose vein ruptured Vascular access site bruising Vascular access site haematoma Vascular access site haemorrhage Vascular access site rupture Vascular graft haemorrhage Vascular pseudoaneurysm ruptured Vascular purpura Vascular rupture Vein rupture Venous haemorrhage

	Venous perforation Ventricle rupture Vertebral artery perforation Vessel puncture site bruise Vessel puncture site haematoma Vessel puncture site haemorrhage Vitreous haematoma Vitreous haemorrhage Vulval haematoma Vulval haematoma evacuation Vulval haemorrhage Withdrawal bleed Wound haematoma Wound haemorrhage

Eczema/ dermatological	MedDRA defined terms list Acute generalized exanthematous pustulosis Administration site dermatitis Administration site eczema Administration site hypersensitivity Administration site rash Administration site recall reaction Administration site urticaria Administration site vasculitis Allergic eosinophilia Allergic granulomatous angiitis Allergic oedema Allergic otitis externa Allergic transfusion reaction Allergy alert test positive Allergy test positive Allergy to immunoglobulin therapy Allergy to vaccine Anaphylactic reaction Anaphylactic shock Anaphylactic transfusion reaction Anaphylactoid reaction Anaphylactoid shock Anaphylaxis treatment Angioedema Antiallergic therapy Anti-neutrophil cytoplasmic antibody positive vasculitis Application site dermatitis Application site eczema Application site hypersensitivity Application site rash Application site recall reaction Application site urticaria Application site vasculitis Atopy Blepharitis allergic Blood immunoglobulin E abnormal Blood immunoglobulin E increased Bromoderma Catheter site dermatitis Catheter site eczema Catheter site hypersensitivity Catheter site rash

	Catheter site urticaria Catheter site vasculitis Circumoral oedema Contact stomatitis Contrast media allergy Contrast media reaction Cutaneous vasculitis Dennie-Morgan fold Dermatitis Dermatitis acneiform Dermatitis allergic Dermatitis atopic Dermatitis bullous Dermatitis contact Dermatitis exfoliative Dermatitis exfoliative generalised Dermatitis herpetiformis Dermatitis infected Dermatitis psoriasiform Dialysis membrane reaction Documented hypersensitivity to administered product Drug cross-reactivity Drug eruption Drug hypersensitivity Drug provocation test Drug reaction with eosinophilia and systemic symptoms Eczema Eczema infantile Eczema nummular Eczema vaccinatum Eczema vesicular Eczema weeping Epidermal necrosis Epidermolysis Epidermolysis bullosa Erythema multiforme Erythema nodosum Exfoliative rash Eye allergy Eye oedema Eye swelling Eyelid oedema Face oedema

	Giant papillary conjunctivitis Gingival oedema Gingival swelling Gleich's syndrome Haemorrhagic urticaria Hand dermatitis Henoch-Schonlein purpura Henoch-Schonlein purpura nephritis Heparin-induced thrombocytopenia Hereditary angioedema Hypersensitivity Hypersensitivity vasculitis Idiopathic angioedema Idiopathic urticaria Immediate post-injection reaction Immune thrombocytopenic purpura Immune tolerance induction Implant site dermatitis Implant site hypersensitivity Implant site rash Implant site urticaria Incision site dermatitis Incision site rash Infusion site dermatitis Infusion site eczema Infusion site hypersensitivity Infusion site rash Infusion site recall reaction Infusion site urticaria Infusion site vasculitis Injection site dermatitis Injection site eczema Injection site hypersensitivity Injection site rash Injection site recall reaction Injection site urticaria Injection site vasculitis Instillation site hypersensitivity Instillation site rash Instillation site urticaria Interstitial granulomatous dermatitis Intestinal angioedema Iodine allergy

	Kaposi's varicelliform eruption Limbal swelling Lip oedema Lip swelling Mast cell degranulation present Medical device site dermatitis Medical device site eczema Medical device site hypersensitivity Medical device site rash Medical device site recall reaction Medical device site urticaria Mouth swelling Mucocutaneous rash Multiple allergies Nephritis allergic Nikolsky's sign Nodular rash Oculomucocutaneous syndrome Oculorespiratory syndrome Oedema mouth Oral allergy syndrome Oropharyngeal blistering Oropharyngeal spasm Oropharyngeal swelling Palatal oedema Palatal swelling Palisaded neutrophilic granulomatous dermatitis Palpable purpura Pathergy reaction Periorbital oedema Pruritus allergic Radioallergosorbent test positive Rash Rash erythematous Rash follicular Rash generalised Rash macular Rash maculo-papular Rash maculovesicular Rash morbilliform Rash neonatal Rash papulosquamous Rash pruritic

	Rash pustular Rash rubelliform Rash scarlatiniform Rash vesicular Reaction to azo-dyes Reaction to colouring Reaction to drug excipients Reaction to preservatives Red man syndrome Scrotal oedema Serum sickness Serum sickness-like reaction Skin necrosis Skin reaction Skin test positive Solar urticaria Solvent sensitivity Stevens-Johnson syndrome Stoma site hypersensitivity Stoma site rash Swelling face Swollen tongue Toxic epidermal necrolysis Toxic skin eruption Type I hypersensitivity Type II hypersensitivity Type III immune complex mediated reaction Type IV hypersensitivity reaction Urticaria Urticaria cholinergic Urticaria chronic Urticaria contact Urticaria papular Urticaria physical Urticaria pigmentosa Urticaria vesiculosa Vaccination site dermatitis Vaccination site eczema Vaccination site exfoliation Vaccination site hypersensitivity Vaccination site rash Vaccination site recall reaction Vaccination site urticaria

	Vaccination site vasculitis Vaccination site vesicles Vaginal exfoliation Vaginal ulceration Vasculitic rash Vessel puncture site rash Vulval ulceration Vulvovaginal rash Vulvovaginal ulceration
Autoimmunity	Investigator decision on eCRF page

18 Appendix 3: Schedule of Events

Pre and post-treatment evaluation (up to 36 months after gene therapy)

Parameter / ***Time point***	Clinical Exam.***	Routine Lab. N° 1	Routine Lab. N° 2	Bone Marrow+ qPCR	Microbiology N° 1	Microbiology N° 2	Microbiology N° 3	Immunology N° 1	Immunology N° 2	Immunology N° 3	Immunology N° 4	Immunology N° 5	Zhu score	HLA typing and donor search	WASP Expression**	Autoimmunity	PCR Transduced cells (PB)	Archiving Blood/BM sample	Specialist Examination	Imaging N° 1	Imaging N° 2	AEs/SAEs recording	Platelet activation and morphology
Screening	X	X		X*			X		X				X	X	X			X					
Baseline	X	X	X		X	X			X	X	X	X	X		X	X		X	X	X	X		
Day -14	X	X						X															
Day 0	X	X						X										X				X	
+ 7 days	X	X			X													X				X	
+ 14 days	X	X			X			X									X	X				X	
+ 21 days	X	X			X													X				X	
+ 30 days	X	X		X	X	X			X						X		X	X				X	
+ 60 days	X	X			X				X						X		X	X				X	
+ 90 days	X	X	X	X	X	X			X	X					X		X	X				X	
+ 180 days	X	X	X		X				X	X	X				X	X	X	X				X	
+ 1 y	X	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X		X	
+ 1,5 y	X	X	X						X						X		X	X				X	
+ 2 y	X	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X		X	
+ 2,5 y	X	X	X						X						X		X	X				X	
+ 3 y	X	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X[P]

***** if the qPCR is not performed at this time point it may be performed on bone marrow collected for back up or harvested for preparation of medical product**.**
** WAS mutation search carried out at screening if not available
*** Eczema will be evaluated as part of the clinical examination (according to Imai, 2004)
[P] Platelet activation and morphology will be assessed at at least one time point ≥ 3y post-GT

Long-term follow up evaluation

Parameter / ***Time point***	Clinical Exam. ***	Routine Lab. N° 1	Routine Lab. N° 2	Bone Marrow+ qPCR	Microbiology N° 1	Microbiology N° 2	Microbiology N° 3	Immunology N° 2	Immunology N° 3	Immunology N° 4	Immunology N° 5	Zhu score	WASP Expression	Autoimmunity	PCR Transduced cells (PB)	Archiving Blood/BM sample	Specialist Examination	Imaging N° 3	Imaging N° 4	AEs/SAEs recording	Platelet activation and morphology
+ 4 y	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X		X	X	X[P]
+ 5 y	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X[P]
+ 6 y	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X		X	X	X[P]
+ 7 y	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X		X	X	X[P]
+ 8 y	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X[P]

*** Eczema will be evaluated as part of the clinical examination (according to Imai, 2004)
[P] Platelet activation and morphology will be assessed at at least one time point ≥ 3y post GT

Extended Long-Term Follow Up evaluation

Parameter	***Year 9+ p.a. (+/- 3 months)***
Social Life Is the patient living in a protected environment? Is the patient attending kindergarten/school or in employment (according to age)? - *Please comment.* How is the patient's social ability with peers (if applicable for age)? - *If abnormal please specify.* Does the patient practice any sport (if applicable for age)? - *Please comment.*	X
General Number of platelet infusions per year Complete Blood Count (CBC) including Platelet count/MPV	X
Specialist laboratory assessments Integration Site Analysis (ISA)	X
Safety* SAEs AEs (related to bleeds, infections, autoimmunity, eczema, suspected malignancies)	X
Ig usage** Intravenous Ig Subcutaneous Ig	X

* SAE and AE's related to bleeds, infections, autoimmunity, eczema or suspected malignancies will be forwarded to TIGET as per current practice by the physician overseeing the patient in their home country. This includes the event, labs, and any other relevant data. In addition patients/family may also provide such information directly to TIGET. All such AEs should be entered into the eCRF within 30 days of awareness. SAEs, and any suspected malignancies, should be reported within 24 hours of awareness.
** Frequency to be specified if possible.