COVER PAGE

Official Study Title: Autologous Transplantation of Bone Marrow CD34+ Stem/Progenitor Cells After Addition of a Normal Human ADA Complementary DNA (cDNA) by the EFS-ADA Lentiviral Vector for Severe Combined Immunodeficiency Due to Adenosine Deaminase Deficiency (ADA-SCID)

EFS-ADA Statistical Analysis Plan v4.0. dated 24-Oct-2017

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Statistical Analysis Plan

Study Name: **Autologous Transplantation of Bone Marrow CD34+ Stem/Progenitor Cells after Addition of a Normal Human ADA cDNA by the EFS-ADA Lentiviral Vector for Adenosine Deaminase (ADA)-Deficient Severe Combined Immunodeficiency (SCID)**

Protocol Number: **NCT01852071**

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List of Abbreviations

ADA	Adenosine deaminase
ADA-SCID	Adenosine deaminase deficient severe combined immunodeficiency
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AXP	Total adenine ribonucleotide
AUC	Area under the curve
BM	Bone marrow
BMT	Bone marrow transplant
cDNA	Complementary Deoxyribonucleic Acid
CHLA	Children's Hospital Los Angeles
CI	Confidence interval
CMV	Cytomegalovirus
CNS	Clinically not significant
CS	Clinically significant
dAXP	Adenine deoxyribonucleotide
DFSP	Dermatofibrosarcoma protuberans
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EFS	Elongation Factor 1α Short form
ERT	Enzyme replacement therapy
GOSH	Great Ormond Street Hospital
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSC	Hematopoietic stem cell
HSCT	Hematopoietic stem cell transplant
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IgRT	Immunoglobulin replacement therapy
LV	Lentiviral vector
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
MUD	Matched unrelated donor
NIH	National Institutes of Health
NK	Natural Killer

PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PEG	Polyethylene-glycol
PHA	Phytohemagglutinin
PRP	Polyribosylphosphate
PT	Preferred Term
RBC	Red blood cell(s)
RCL	Replication competent lentivirus
SAE	Serious Adverse Event
SCID	Severe combined immunodeficiency
SI	Stimulation index
SOC	System Organ Class
TCR	T-cell receptor
TD	Transduction
TREC	T-cell receptor excision circle
UCLA	University of California, Los Angeles
WBC	White blood cell(s)

1 Introduction

The trial assesses a new breakthrough therapy composed of *ex vivo* genetically modified $CD34^+$ hematopoietic stem cells (HSC) for the treatment of severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID).

The investigational new drug product, OTL-101, includes autologous bone marrow (BM) $CD34^+$ HSC from ADA-SCID infants, children and adolescents, transduced *ex vivo* with a self-inactivating HIV-1 based lentiviral vector encoding the human ADA cDNA (EFS-ADA LV). OTL-101 is used as fresh cell dispersion for infusion after a single non-myeloablative conditioning.

2 Study Design

This is a historically controlled, open-label, prospective, non-randomized Phase I/II clinical trial to assess the safety and efficacy of OTL-101.

OTL-101 will be compared to an historical control group treated with allogeneic Hematopoietic Stem Cell Transplantation (HSCT), representative of standard of care.

Two centres are involved in this study: UCLA and the National Institute of Health (NIH) in Bethesda, MD. Nineteen subjects have been treated at UCLA and one at the NIH.

3 Study Schedule

Evaluation	Scr	B-L	Pre-op	Infusion	BU	+1d	Months After Procedure												
							1	2	3	4	5	6	8	10	12	15	18	21	24
P.E.	X	X	-		-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
History	X	X	-		-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Metabolic Panel[a]	X	X	X		-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Magnesium, phosphate	X	-	X		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CBC with diff.	X	X	X		-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cytogenet. PB	X	-	-		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pregnancy test*	X	-	-		X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
INR or PT/PTT	X	-	X		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Type and cross	-	-	X		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HIV-1, HepB & C, CMV, B19	X	-	-		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Urinalysis	X	-	X		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECG	X	-	-		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Echo	X	-	-		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CXR	X	-	-		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pulse ox.	X	-	-		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
RBC dAXP	-	X	-		-	-	X	X	X	X	X	X	X	X	X	X	X	X	X
RBC ADA activity	-	X	-		-	-	X	X	X	X	X	X	X	X	X	X	X	X	X
Immune function[b]	-	X	-		-	-	X	X	X	X	X	X	X	X	X	X	X	X	X
TREC, TCRV β panel	-	X	-		-	-	-	-	-	-	-	X	-	-	X	-	X	-	X
PBMC for RCL[c]	-	X	-		-	-	-	-	X	-	-	X	-	-	X	-	-	-	X

Serum for WB to RCL[d]	-	X	-		-	-	-	-	X	-	-	X	-	-	X	-	-	-	X
PBMC for vector[c]	-	X	-		-	-	X	X	X	X	X	X[g]	X	X	X[g]	X	X[g]	X	X[g]
Busulfan PK[e]	-	-	-		X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Myelosupp. Lab[f]	-	-	-			X	X	-	-	-	-	-	-	-	-	-	-	-	-

Scr = screen B-L = Baseline

+1d = day after infusion

BU = Busulfan: See Appendix C for details of administration

X = to be performed, - = not to be performed

*For female subject of child-bearing potential

[a]includes albumin, AST/ALT, alkaline phosphatase, total protein, total bilirubin, creatinine, BUN, glucose, calcium, Na+, K+, Cl-, total CO_2

[b]includes lymphocyte subsets phenotype, quantitative immunoglobulins, antibodies to Tet/PRP (Q 3 months if not receiving IVIg), T cell proliferation to PHA/Tet (only at 6, 12, 18, and 24 months and only to Tet if immunized against tetanus).

[c]At each time, any unused PBMC will be cryopreserved in liquid nitrogen, for possible future studies.

[d]To be banked for possible future studies

[e]Busulfan PK at 0, 1, 2, 4, 8, 13 hours following IV Busulfan administration, done during hospitalization

[f]Myelosuppression Laboratory: Hepatic function tests, CBC/Diff, 2x per week for up to 6 weeks, from day +1 until hospital discharge when neutrophil recovery is observed, or longer as indicated. For subjects who have slow recovery of counts after transplant (beyond Day +30), CBC/Diff will be performed at least once every 7-10 days until ANC is >500 cells/mm.^{3}

[g]According to current FDA guidelines, LAM-PCR samples will be obtained ≈ every 6 months, for 5 years, then annually for an additional 10 years

4 Study Objectives

4.1 Primary Objectives

The primary objectives in this study are:

- to examine the safety of autologous transplantation of bone marrow $CD34^+$ cells transduced with the EFS-ADA lentiviral vector (OTL-101). The safety review will include the identification of grade III/IV serious adverse events (SAE). Subjects will also be monitored for clinical toxicities, replication competent lentivirus, and monoclonal expansion at regular intervals by a clinician, as well as standard blood counts and chemistries.
- to estimate overall and event-free survival by 12 months where failure is defined by one of the following endpoints: death; reinstitution of PEG-ADA; or performance of an allogeneic BMT.

4.2 Secondary Objectives

The secondary objectives will assess the efficacy of OTL-101, engraftment of transduced cells and the extent of ADA expression and immune reconstitution. The secondary outcomes will:

1. Assess overall and event free survival at 24 months,
2. Compare overall survival and event free survival at 24 months between patients treated with OTL-101 and patients treated with allogeneic HSCT,
3. Assess the extent of gene transfer in peripheral blood cells,
4. Assess ADA gene expression by measuring ADA enzymatic activity and adenine nucleotides,
5. Examine the effects of reconstituting ADA gene expression on immune function through serial examination of peripheral blood leukocytes and myeloid cells,
6. Assess immune reconstitution and infection rates, and
7. Assess use of immunoglobulin replacement therapy.

5 Endpoints

5.1 Primary Endpoints

The primary endpoints are:

- Safety: the incidence and severity of serious adverse events (SAEs)
- Efficacy: overall and event-free survival at 12 months, where events are death, reinstitution of PEG-ADA therapy and performance of an allogeneic BMT.

5.2 Secondary Endpoints

Secondary endpoints for this study are:

- Overall survival and event-free survival at 24 months
- Efficacy of gene transfer/engraftment of HSC
- ADA expression: enzyme activity and detoxification

- Effects on ADA reconstitution on immune phenotype and function (the need for IgRT will be assessed under this category)
- Immune reconstitution
- Infection rates

6 Timing of Analyses

The statistical analyses of data from this study will be performed in three stages:

Interim look:

- Performed after all subjects have completed 6 months of follow-up post infusion
- Descriptive statistics for all available data
- Comparisons between OTL-101 treated subjects and HSCT control cohorts of demographics and overall survival

Primary analysis:

- Performed after all subjects have completed 12 months of follow-up post infusion
- Descriptive statistics for all available data
- Comparison to HSCT control cohorts on overall and event-free survival (primary efficacy endpoints), use of immunoglobulin replacement therapy (IgRT) and infection rate (key secondary endpoints).

End of study analysis:

- Performed after all subjects have completed the study (24 months of follow-up post infusion)
- Descriptive statistics for the complete study cohort
- Comparison to HSCT control cohorts on overall and event-free survival (primary efficacy endpoints), use of immunoglobulin replacement therapy (IgRT) and infection rate (key secondary endpoints).

7 Analysis Populations

7.1 Efficacy Population

The primary efficacy population will consist of all patients treated with OTL-101 at UCLA/NIH (current study cohort).

The primary efficacy population from the HSCT historical control cohort will consist of ADA-SCID patients without a medically eligible HLA-matched sibling/family donor and treated with HSCT at either Great Ormond Street Hospital (GOSH) or Duke University from the year 2000 onwards.

Additional efficacy comparisons will be made with:

- ADA-SCID patients with matched related donors treated with HSCT at either GOSH or Duke University from the year 2000 onwards;
- the complete HSCT historical control cohort consisting of ADA-SCID patients with any type of donor treated with HSCT at either GOSH or Duke University from the year 2000 onwards.

7.2 Safety Population

The safety population will consist of all subjects treated with OTL-101 at UCLA/NIH (current study cohort) and the complete HSCT historical control cohort consisting of ADA-SCID patients with any type of donor treated with HSCT at either GOSH or Duke University from the year 2000 onwards.

8 Statistical Methods

In general, continuous variables will be summarised using the mean, standard deviation, median, minimum, maximum and number of subjects. Categorical variables will be summarised using number of subjects and percentages.

For all summaries, the HSCT controls will be summarised in the groups of those without a matched related donor, those with a matched related donor and all subjects.

8.1 Subject Disposition

8.1.1 Summary of Populations

Number (%) of subjects enrolled (signed informed consent), treated, and in efficacy and safety populations will be summarised for the OTL-101 treated and HSCT control groups. The denominator for the percentages will be the number of subjects enrolled.

Should any subjects be excluded from any of the analysis populations, a listing will be produced for these subjects noting the reason for exclusion.

8.1.2 Summary of Withdrawals

Number (%) of subjects who completed the study period will be summarised along with the reason for study withdrawal. The denominator for the percentages will be the number of subjects treated.

At the interim look and the primary analysis, the number (%) completing the designated follow-up period and ongoing in the study will also be summarized.

Should any subjects have withdrawn from the study, a listing will be produced for these subjects noting the reason for study withdrawal, and the time since infusion at withdrawal.

8.2 Demography and Baseline Characteristics

Demography and baseline characteristics will be summarised for the safety population.

8.2.1 Demography

Age in months for the OTL-101 treated subjects will be calculated as:

12*(date informed consent signed – date of birth)/365.25.

Age in months for the HSCT controls will be captured on the eCRF.

Age in months will be summarized for the OTL-101 treated and HSCT control groups. Sex, race, weight and height at screening will be summarised for the OTL-101 treated group.

8.2.2 Medical History

Medical history was collected on two forms in this study. Each will be summarised separately.

The number (%) of subjects reporting medical history categorized as normal / abnormal clinically non-significant (CNS) / abnormal clinically significant (CS) will be summarised by body system for the OTL-101 treated subjects. Should any subject have an abnormal evaluation with the clinical significance assessment missing, this will be categorized as "abnormal unknown clinical significance" and this category will be added to the summary.

For the skin examination, the number (%) of OTL-101 treated subjects with each of the following will be summarized:

- evidence of active malignant disease other than dermatofibrosarcoma protuberans (DFSP);
- evidence of DFSP expected to require anti-neoplastic therapy within the 5 years following the infusion of genetically corrected cells;
- evidence of DFSP expected to be life limiting within the 5 years following the infusion of genetically corrected cells.

In addition, the number (%) of OTL-101 treated subjects with each of the following will be summarized:

- evidence of active opportunistic infection;
- known sensitivity to busulfan;
- expected survival < 6 months;
- pregnant;
- major congenital anomaly.

In addition, the number (%) of subjects reporting medical history at screening in each category will be summarised for the OTL-101 treated and the HSCT control groups.

8.2.3 ADA Deficiency Diagnosis

Age at diagnosis in months will be calculated for the OTL-101 treated subjects as:

12*(date of diagnosis – date of birth)/365.25.

For the HSCT control groups, the age at diagnosis will be recorded on the eCRF.

Time since diagnosis in months will be calculated as:

12*(date of transplant - date of diagnosis)/365.25,

or, for HSCT control subjects for whom the dates were not recorded, as:

age in months at transplant - age in months at diagnosis.

Age at diagnosis, time since diagnosis and the value used to diagnose ADA deficiency will be summarized using descriptive statistics for the OTL-101 treated subjects. In addition, the number (%) of subjects with each of the following will be summarized:

- ADA deficient as determined by reference laboratory;
- with family history of 1st order relative with ADA deficiency and clinical and laboratory evidence of severe immunologic deficiency;
- with evidence of severe immunologic deficiency prior to institution of immune restorative therapy;
- with no healthy, medically eligible HLA-identical sibling with normal immune function who may serve as an allogeneic bone marrow donor.

Age at diagnosis and time since diagnosis will be summarized using descriptive statistics for the HSCT control groups. In addition, the number (%) of subjects with each method of diagnosis (DNA sequencing/ confirmed absence of <3% enzymatic activity) will be summarized.

8.2.4 Disease History

Number (%) of OTL-101 treated subjects with each of the following will be summarized:

- Peri-natal complications (Prematurity / Infection / Other);
- Method of diagnosis (Newborn screen / Family History / Infection / Other);
- Siblings (Yes [HLA-Matched] / Yes [HLA-Not Matched] / No);
- Matched unrelated donor (MUD)/cord search performed;
- Pulmonary Complications;
- Feeding History;
- Prior Surgery.

8.2.5 Cytogenetics

Cytogenetics will be assessed at screening and categorised as normal or abnormal, with normal results subcategorised as 46XX/46XY/Other.

The number (%) of OTL-101 treated subjects falling into each category for source (PBMCs, bone marrow, amniotic fluid), result (normal/abnormal), category of normal result (46XX/46XY/Other) will be summarised.

8.2.6 Viral PCR

The number (%) of OTL-101 treated subjects with positive/not detected HIV, hepatitis B, hepatitis C, CMV and parvovirus B19 will be summarised.

8.2.7 Coagulation Tests

Coagulation tests (prothrombin time, partial thromboplastin time and internal normalised ratio) will be evaluated at screening and pre-harvest for the OTL-101 treated subjects.

For each parameter, the actual value will be summarised at each visit using descriptive statistics.

Coagulation tests will be flagged against the normal range as low/normal/high. For each parameter, the number (%) of subjects with evaluations that were low/normal/high relative to the normal range will be summarised by visit.

8.2.8 Urinalysis

Urine protein results will be summarized by visit using the number (%) of OTL-101 treated subjects with results in each category (0, 1+, 2+, 3+, 4+) of urinalysis result. In addition, a shift table from Screening to Pre-Harvest will be produced.

8.2.9 Electrocardiogram (ECG)

An ECG will be taken at screening which will be categorized as normal/ abnormal, not clinically significant/ abnormal, clinically significant. The number (%) of subjects with evaluations falling into each category will be summarised. Should any subject have an abnormal evaluation with the clinical significance assessment missing, this will be categorized as “abnormal unknown clinical significance” and this category will be added to the summary.

8.2.10 Echocardiogram

An echocardiogram will be taken at screening which will be categorized as normal/ abnormal, not clinically significant/ abnormal, clinically significant. The number (%) of OTL-101 treated subjects with evaluations falling into each category will be summarised along with the number (%) of subjects with uncorrected congenital cardiac malformation with clinical symptomatology. Should any subject have an abnormal evaluation with the clinical significance assessment missing, this will be categorized as “abnormal unknown clinical significance” and this category will be added to the summary. Left ventricular ejection fraction will be summarised using descriptive statistics.

In addition, details of any clinically significant findings will be listed.

8.2.11 Chest X-ray

A chest x-ray will be taken at screening which will be categorised as normal/ abnormal, not clinically significant/ abnormal, clinically significant. The number (%) of OTL-101 treated subjects with evaluations falling into each category will be summarised. Should any subject have an abnormal evaluation with the clinical significance assessment missing, this will be categorized as "abnormal unknown clinical significance" and this category will be added to the summary. In addition, the number (%) of OTL-101 treated subjects with active cardiac disease, including clinical evidence of congestive heart failure, cyanosis, hypotension will be summarized.

8.2.12 Pulse Oximetry

Oxygen saturation at screening will be summarized for the OTL-101 treated subjects using descriptive statistics.

8.2.13 Bone Marrow Harvest

The number (%) of OTL-101 treated subjects with each blood type, for whom harvest can be performed, for whom harvest was performed and with central venous access will be summarized.

Total number of $CD34^+$ cells harvested and back-up cells collected will be summarised using descriptive statistics along with the number (%) of OTL-101 treated subjects with each cell type (total nucleated cells / mononuclear cells).

8.2.14 Busulfan Pharmacokinetics

The area under the curve (AUC) for busulfan will be summarised using descriptive statistics for the OTL-101 treated subjects.

8.2.15 OTL-101 Administration

The number (%) of subjects who received OTL-101 will be summarised along with the age in months at transplant and the number of infusions received (1 or 2).

For each infusion, $CD34^+$ pre-TD vector copy number (copy/cell), $CD34^+$ post-TD vector copy number (copy/cell), $CD34^+$ pre-TD ADA enzyme activity (nmol/min/10^8 cells), $CD34^+$ post-TD ADA enzyme activity (nmol/min/10^8 cells), subject weight (kg), total $CD34^+$ cells infused (x 10^6 cells), total $CD34^+$ cells infused / kg, infusion volume (mL), duration of infusion (min) and infusion rate (mL/min) will be summarized using descriptive statistics.

8.2.16 Transplant Details for the HSCT Controls

Age (months) at transplant, number of $CD34^+$ cells/kg transplanted and busulfan dose, if appropriate, will be summarized for each HSCT control group using descriptive statistics.

Number (%) of subjects with each type of transplant cells, transplant donor type, conditioning type, receiving enzyme replacement therapy (ERT) prior to the transplant, receiving ERT after the transplant, receiving IgRT prior to the transplant, receiving IgRT after the transplant and receiving gene therapy after the transplant will be summarized for each HSCT control group.

8.2.17 Exposure

Duration of follow-up in months will be calculated for the OTL-101 treated subjects as:

12*(date of final evaluation – date of infusion + 1)/365.25.

For the HSCT controls, the duration of follow-up will be recorded on the eCRF.

Duration of follow-up will be summarized for the OTL-101 treated and the HSCT control groups using descriptive statistics. In addition, the total subject-years of follow-up in each treatment group will be presented.

8.3 Efficacy Evaluations

The primary comparison for all efficacy analyses will be between the OTL-101 treated subjects and the allogeneic HSCT controls treated at either GOSH or Duke University without a matched related donor.

Secondary comparisons will be between:

- the OTL-101 treated subjects and the HSCT controls treated at either GOSH or Duke University with a matched related donor;
- the OTL-101 treated subjects and the total group of HSCT controls.

8.3.1 Primary Efficacy Endpoints

8.3.1.1 Overall Survival at 12 Months

Overall survival will be evaluated using the time in months from transplant to either the subject's death or their last evaluation calculated as:

12*(date of death/last evaluation – date of transplant)/365.25,

or, for HSCT control subjects for whom the dates were not recorded, as:

age in months at death/end of follow-up - age in months at transplant.

The number (%) of subjects who were still alive at 12 months post-transplant will be summarised. For the purpose of this analysis, any subject who withdrew from the study prior to 12 months, who was known to be alive at the last evaluation, will have a status of "unknown". The proportion and exact 95% confidence interval (CI) for survivors at 12 months post-transplant will be calculated for the OTL-101 treated and each of the HSCT control groups along with the difference in proportions (with 95% CI) between the OTL-101 treated and each of the control groups, excluding those with unknown status.

Overall survival in each treatment group will also be presented using a Kaplan-Meier curve for time to death. For the purpose of this analysis, any subject who withdrew from the study prior to 12 months and was known to be alive at the last evaluation will be censored at the date of their last evaluation. If appropriate, the proportion alive at 12 months and the associated 95% confidence interval will be estimated for each treatment group from the Kaplan-Meier curve along with the median survival time (and interquartile range), if they can be estimated from the data.

If there is at least one event in each group, the log-rank test will be used to compare the difference in survival curves between the OTL-101 treated subjects and each of the HSCT control groups.

In addition, a Bayesian analysis will be carried out. The prior distribution for the rate of survivors in each treatment group will be set to Beta(α=1, β=1) (a conservative non-informative prior). The number of survivors in each group (X) will be estimated and the posterior distribution for the rate of survivors in each group will be updated to Beta(α=1 + X, β=1 +N - X), where N is the total number of subjects in the group. Histograms will be presented for the posterior distributions for each treatment group.

A posterior distribution for the difference between the survival rate in the OTL-101 treated group and each of the HSCT control groups will be estimated empirically via simulation with 10,000 replications. Based on the distribution above, posterior probabilities for the following will be calculated:

- rate on OTL-101 > rate on control (superiority like test);
- rate on OTL-101 > rate on control – 10% (non-inferiority like test).

8.3.1.2 Event-free Survival at 12 Months

Event-free survival will be evaluated using the time in months from transplant to either the first event or their last evaluation calculated as:

12*(date of event/last evaluation – date of transplant)/365.25,

or, for HSCT control subjects for whom the dates were not recorded, as:

age in months at death/end of follow-up - age in months at transplant.

For the purpose of this analysis, the events of interest are:

- death;
- reinstitution of PEG-ADA ERT;
- requirement for a second transplant.

Event-free survival will be summarized in the same way as overall survival described in Section 8.3.1.1.

In addition, if there are any events (other than death), the time to each event will be summarized in a similar manner to the overall event-free survival.

8.3.2 Secondary Efficacy Endpoints

8.3.2.1 Overall and Event-free Survival at 24 Months

Overall and event-free survival at 24 months will be summarized in the same way as for the analyses at 12 months described in Sections 8.3.1.1 and 8.3.1.2.

8.3.2.2 Use of Immunoglobulin Replacement Therapy

The number (%) of subjects receiving immunoglobulin replacement therapy (IgRT) will be summarised by visit for the OTL-101 treated subjects.

The time to cessation of IgRT will be calculated (in months) as:

12*(stopping date of IgRT – date of transplant) /365.25,

or, for HSCT control subjects for whom the dates were not recorded, as:

age in months when IgRT stopped – age in months at transplant.

Time to cessation of IgRT will be summarised for the OTL-101 treated and HSCT control groups using descriptive statistics and, if appropriate, estimated from a Kaplan-Meier curve in which subjects who are still receiving IgRT will be censored at the time of their last visit.

The number (%) of subjects who have stopped treatment with IgRT at 12, 18 and 24 months without restarting at any subsequent time point will be summarized for the OTL-101 treated and HSCT control groups (data permitting).

In addition, serum immunoglobulin levels (IgG, IgA and IgM) will be measured at each visit for the OTL-101 treated subjects. Levels of IgG, IgA and IgM and changes from baseline will be summarised by visit using descriptive statistics. In addition, plots of the median value and range over time on a logarithmic scale will be produced for each parameter along with individual plots for each subject which will include age-dependent normal ranges provided by the study sites.

8.3.2.3 Rate of Severe Infections

Infections will be recorded as adverse events. The infections of interest in this study are severe infections or opportunistic infectious episodes, defined as infections requiring hospitalization or prolonging hospitalization and/or documented infections by opportunistic pathogens (e.g. interstitial pneumonia, intractable diarrhoea).

The number (%) of subjects reporting severe infections or opportunistic infectious episodes along with the number of events reported will be summarized for the OTL-101 treated and

HSCT control groups (data permitting). In addition, the infection rate will be calculated as the number of infections/the total follow-up time. The rate will be calculated both within each treatment group and for each individual subject. The subject infection rate will be summarized by treatment group using descriptive statistics. In addition to the rate for the entire follow-up period, the rate will be calculated for both the first 12 months following transplant and for the remaining study period.

8.3.2.4 Immune Reconstitution

Immune reconstitution will be assessed using lymphocyte subsets. Absolute numbers and percentages of CD3+, CD4+, CD8+ CD4+CD45RA+, CD4+CD45RO+ T-lymphocytes, CD19+ B-lymphocytes and CD16+CD56+ NK cells will be measured.

For each of the lymphocyte subsets, the actual value and change from baseline will be summarized by visit for the OTL-101 treated subjects. The median value and range will be plotted over time on a logarithmic scale and individual counts will be plotted along with the age-dependent normal ranges reported in Table 2.

In addition, statistical testing of the change from baseline to 6 and 12 months will be performed. If the difference is normally distributed, a paired t-test will be used. Otherwise, the Wilcoxon signed rank test will be used.

The trend over time will be examined for each count separately, using mixed models for repeated measures (MMRM) with visit and baseline count as fixed effects, and subject as a random effect, utilizing the compound-symmetry covariance structure. If counts are approximately normally distributed they will be analysed on the original scale. If the distribution is found to be skewed to the right and a log transformation can normalize the data, statistical analysis will be performed on log-transformed data. If the data are still not normal, the data will be ranked in ascending order of magnitude and the analysis will be performed on the ranks.

8.3.2.5 T Cell Receptor Excision Circles (TREC) in the PB

TREC levels will be summarised for OTL-101 treated subjects at each visit using descriptive statistics. Plots of the median and range over time on a logarithmic scale will be produced. In addition, individual subject plots of TREC levels over time will be produced.

8.3.2.6 Engraftment

Engraftment of transduced cells will be assessed using vector gene marking in granulocytes and PBMC.

The vector copy numbers in each type of cell will be summarised for OTL-101 treated subjects by visit using descriptive statistics. In addition, for each cell type, plots of the median and

range for copy numbers over time on a logarithmic scale will be produced along with individual subject plots.

8.3.2.7 ADA Expression, Enzyme Activity and Detoxification

RBC ADA activity, AXP, dAXP and %dAXP will be summarized by visit for the OTL-101 treated subjects. The median value and range will be plotted over time on a logarithmic scale as will the values for individual subjects.

In addition, statistical testing of the change in %dAXP from baseline to 6 and 12 months will be performed. If the difference is normally distributed, a paired t-test will be used. Otherwise, the Wilcoxon signed rank test will be used.

If the %dAXP values are approximately normally distributed, the trend over time will be examined using MMRM with visit and baseline count as fixed effects, and subject as a random effect, utilizing the compound-symmetry covariance structure (if it produces an acceptable fit).

8.3.2.8 T Cell Receptor Vβ Panel Results

For each cell type (CD4 and CD8), each of the Vβ results will be summarised for OTL-101 treated subjects at each visit using descriptive statistics. A panel of plots of the median and range over time on a logarithmic scale will also be produced.

8.3.2.9 Lymphocyte Proliferative Responses Stimulation Index (SI)

Lymphocyte proliferative response to PHA, Tetanus, and Candida were collected. Early in the study, these responses were provided by Quest laboratories. At a later date, these analyses were moved to the in-house immunogenetics laboratories at each study site. Since the results from the in-house laboratories are not comparable with those from Quest, they will be summarized separately.

The stimulation index will be calculated for each parameter as the sample response/control response. Stimulation indices will be summarized for the OTL-101 treated subjects by visit for each parameter, separately for the data from the Quest and in-house laboratories. In addition, for each parameter, the median and range will be plotted on a logarithmic scale over time. These stimulation indices will be compared with the normal reference ranges provided by the study sites and the number (%) of subjects with responses above and below the normal range will be summarized by visit as well as at any time post infusion.

8.3.2.10 Antibody Responses

Antibody responses to Tetanus and Polyribosylphosphate (PRP) were evaluated.

The response to each of the antibodies will be summarized for the OTL-101 treated subjects using descriptive statistics.

8.3.3 Additional Efficacy Endpoints

8.3.3.1 Use of PEG-ADA Enzyme Replacement Therapy

The time to withdrawal of PEG-ADA ERT will be calculated (in months) as:

12*(stop date of PEG-ADA ERT – date of transplant) /365.25,

or, for HSCT control subjects for whom the dates were not recorded, as:

age in months when PEG-ADA stopped – age in months at transplant.

Time to withdrawal of PEG-ADA ERT will be summarised for the OTL-101 treated and HSCT control groups using descriptive statistics and, if appropriate, estimated from a Kaplan-Meier curve in which subjects who are still receiving PEG-ADA ERT will be censored at the time of their last visit.

8.3.4 Sensitivity Analyses

Protocol violations in this study will be reviewed prior to database lock in order to determine whether any major violations have occurred that could have influenced the outcome of the study. In the event that such violations have occurred, sensitivity analyses will be carried out in order to assess the impact of these violations on the efficacy results.

Sensitivity analyses will be carried out for:

- Overall and event free survival (descriptive statistics and Kaplan-Meier analyses)
- Lymphocyte subsets (descriptive statistics and plots)
- Measures of engraftment (descriptive statistics and plots)

8.4 Safety Evaluations

8.4.1 Adverse Events

All adverse events will be coded using MedDRA version 20.0

8.4.1.1 Definition of Treatment-emergent Adverse Events

Adverse events (AEs) will be summarised on the basis of treatment emergence. An adverse event is considered to be treatment emergent if it occurred on or after the date and time of the start of the OTL-101 infusion. If the start time of the event is not present, any event starting on the same day as the infusion will be considered to be treatment emergent. If the start date of the adverse event is partial or missing, it will be considered to be treatment emergent if:

- the day is missing, the month and year are present and are the same as or after the month and year of the infusion and the end date is missing or is not before the date of infusion,
- the day and month are missing, the year is present and is the same as or after the year of the infusion and the end date is missing or is not before the date of infusion,

- the entire date is missing and the end date is missing or is not before the date of infusion.

8.4.1.2 Serious Adverse Events

The primary safety parameter in this study is the incidence and severity of serious adverse events (SAEs).

Incidence and frequency of treatment emergent SAEs will be summarised by system organ class (SOC) and preferred term (PT):

- overall,
- by maximum severity,
- by maximum relationship to treatment
- treatment related SAEs.

In each table, if the same SOC or PT is reported on multiple occasions for a single subject, it will be included only once in the summary. In the table by maximum severity, only the most severe occurrence for each SOC and PT for each subject will be included in the summary. In the table by relationship, only the most related occurrence for each SOC and PT for each subject will be included in the summary.

Any SAEs that are not treatment emergent (occurred prior to the infusion) will be listed.

If there are any deaths, the details will be listed.

8.4.1.3 Adverse Events

Treatment emergent adverse events will be summarised in an overall summary presenting the number (%) of subjects with:

- any AE,
- AE grade 2 or higher (at least moderate in severity),
- AE grade 3 or higher (at least severe in severity),
- treatment related AE,
- AE leading to study withdrawal,
- any serious adverse event (SAE),
- treatment related SAE,
- SAE leading to death.

Incidence and frequency of treatment emergent AEs will be summarised by system organ class (SOC) and preferred term (PT):

- overall,
- by maximum severity,
- by maximum relationship to treatment,
- treatment related AEs,

- AEs leading to study withdrawal (if sufficient events).

In addition, a summary table for the most frequently reported treatment emergent adverse events (those reported in 2 or more subjects) will be presented by PT in descending order of incidence and frequency.

In each table, if the same SOC or PT is reported on multiple occasions for a single subject, it will only be included once in the summary. In the table by maximum severity, only the most severe occurrence for each SOC and PT for each subject will be included in the summary. In the table by maximum relationship, only the most related occurrence for each SOC and PT for each subject will be included in the summary.

Any adverse events that are not treatment emergent (occurred prior to the infusion) will be listed.

8.4.2 Concomitant Medications

Concomitant medications taken during the study will be listed.

8.4.3 RCL Testing

Number (%) of OTL-101 treated subjects testing positive for RCL will be summarised by visit and at any time.

8.4.4 Laboratory Evaluations

8.4.4.1 Haematology

Haematology parameters (red blood cell (RBC) count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell (WBC), neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelet count) will be evaluated over time for the OTL-101 treated subjects. The baseline evaluation for each parameter will be the final evaluation prior to the OTL-101 infusion.

For each parameter, the actual value and change from baseline will be summarised at each visit using descriptive statistics.

Haematology evaluations will be flagged against the normal range as low/normal/high. For each parameter, the number (%) of subjects with evaluations that were low/normal/high relative to the normal range will be summarised by visit. In addition, shift tables will be constructed comparing the flags at the baseline evaluation with those at each post-infusion evaluation and the minimum and maximum evaluation post-baseline. Out of range values will be assessed for their clinical significance. The number (%) of subjects with any clinically significant abnormal values will be summarized by visit and at any time post-infusion.

8.4.4.2 Biochemistry

Biochemistry parameters (Urea Nitrogen, creatinine, total bilirubin, sodium, potassium, chloride, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, albumin, total protein, glucose, magnesium, phosphorus, total CO2) will be evaluated over time for the OTL-101 treated subjects. The baseline evaluation for each parameter will be the final evaluation prior to the OTL-101 infusion.

For each parameter, the actual value and change from baseline will be summarised at each visit using descriptive statistics.

Biochemistry evaluations will be flagged against the normal range as low/normal/high. For each parameter, the number (%) of subjects with evaluations that were low/normal/high relative to the normal range will be summarised by visit. In addition, shift tables will be constructed comparing the flags at the baseline evaluation with those at each post-infusion evaluation and with the minimum and maximum evaluation post-infusion. Out of range values will be assessed for their clinical significance. The number (%) of subjects with clinically significant abnormal values will be summarized by visit and at any time post-infusion.

8.4.5 Vital Signs, Height and Weight

Vital signs (temperature, heart rate, respiratory rate, systolic and diastolic blood pressure), height and weight are measured over time for the OTL-101 treated subjects.

The baseline evaluation for each of the vital signs, height and weight will be the final evaluation prior to the OTL-101 infusion.

For each parameter, the actual value and change from baseline will be summarised at each visit using descriptive statistics.

Each subject's vital signs be categorized as normal, abnormal not clinically significant or abnormal clinically significant at each visit. The number (%) of subjects with clinically significant evaluations will be summarised by visit and at any time post-infusion.

8.4.6 Physical Examination

Physical examinations will be performed over time for the OTL-101 treated subjects. The number (%) of subjects with evaluations categorized as normal / abnormal clinically non-significant / abnormal clinically significant will be summarized by body system at each visit. Should any subject have an abnormal evaluation with the clinical significance assessment missing, this will be categorized as "abnormal unknown clinical significance" and this category will be added to the summary. An overall summary will also be produced for each body system showing the number (%) of subjects with normal evaluations at all pre-treatment evaluations who had one or more abnormal evaluations post-treatment, these will be categorized as abnormal clinically non-significant / abnormal clinically significant with the worst case being used for the summary.

9 Analysis Software

All summaries and analyses will be carried out using SAS version 9.4.

10 Changes in Statistical Analysis Plan

10.1 Changes in Version 3.0

Since Statistical Analysis Plan version 2.0 was signed off on 14th March, 2017, Version 10.0 of the protocol has been signed off, so a number of modifications were needed to this SAP in order to account for the changes in the protocol.

In addition to these changes, the document has been restructured in order to improve the flow and the understandability. In particular, the description of any derivations of the endpoints has been added to the statistical methods section instead of being with the list of endpoints. Also, some of the details relating to programming specifications have been removed and will be added to the programming documentation.

Changes of note are:

- Study objectives and endpoints have been reworded to match protocol version 10.0.
- The age at entry and transplant will be expressed in months rather than years as this is more appropriate for the subjects enrolled.
- The calculation of durations in months has been changed from days/30 to 12*days/365.25 to be consistent with calculations of age.
- Inclusion/exclusion criteria will no longer be summarized, but will be listed.
- A summary of the busulfan AUC has been added.
- The plots of parameters over time will no longer present the mean +/- 2SE, but the median and range as this was more appropriate for the parameters being presented.
- The infection summaries have been reworded to match the definition of severe infections from the protocol.
- Additional adverse event summaries have been added and it has been explicitly stated that all summaries will only include treatment emergent adverse events.
- Summaries of laboratory evaluations using descriptive statistics have been added.
- Plots of vital signs over time have been removed as they were not considered to be useful.
- Plots of antibody responses over time and summaries by visit have been removed as the data will not be collected over time for individual subjects.

10.2 Changes in Version 4.0

Since version 3.0 of the Statistical Analysis Plan was signed off, the sponsor has received regulatory approval to include further HSCT control data from Duke University, so this SAP has been updated to include these data.

The following additional changes have been made:

- Details added to clarify the calculation of time to event for subjects in the HSCT control group who do not have the dates of events recorded.
- Tables of reference ranges have been deleted to allow the most up to date ranges received from the study sites to be used in the analyses.
- The summary of coagulation data has been moved from the safety section to the baseline section as these data are only collected prior to the transplant.
- The MedDRA version to be used has been updated to 20.0.