STATISTICAL ANALYSIS PLAN

INC STUDY NO.:	1003733
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STUDY TITLE:	Long term follow-up of the following: A marker study of therapeutically transduced CD4+ peripheral blood lymphocytes in HIV discordant identical twins *(Protocol OZ1-HV1-101)* A Phase I trial of autologous CD34+ hematopoietic progenitor cells transduced with an anti-HIV ribozyme *(Protocol OZ1-HV1-102)* A long term follow-up protocol to evaluate the safety and survival of autologous CD34+ hematopoietic progenitor cells transduced with an anti-HIV-1 ribozyme (OZ1) in patients with HIV-1 infection *(Protocol OZ1-HV1-202 Amendment 4)*

Signature Page

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I confirm that I have reviewed this document and agree with the content.

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1. INTRODUCTION

1.1. RESPONSIBILITIES

This document details the proposed tabular and graphical presentations of data collected from long term cell delivered rybozyme gene transfer product (OZ1) follow up studies; OZ1-HV1-101, OZ1-HV1-102 and OZ1-HV1-202. This document also defines the analysis populations and the safety and efficacy endpoints.

This document has been written by INC based on information contained in the study protocols OZ1-HV1-101 amendment 2 dated 23 October 2007, OZ1-HV1-102 amendment 2 dated 23 October 2007, and OZ1-HV1-202 amendment 2 dated 28 August 2007 and OZ1-HV1-202 amendment 4 dated 07 Jun 2017

The production of summary tables, data listings, graphs and statistical analyses will be the responsibility of Biometrics at INC, and will be performed according to INC standard operating procedures (SOPs).

One completed analysis which was reported in 2011 covered data collected from the point of First Patient First Visit (FPFV) in January 2000 until the last subject year 5 follow-up visit (Last Patient Last Visit: LPLV) in February 2011. A separate Statistical Analysis Plan (SAP) was used for this previous analysis (Kendle study 76803). This previous SAP has also been used as a template for this new INC study (1003733).

This SAP had covered an interim analysis in 2016 and will cover a final analysis happened after DBL of study *OZ1-HV1-202*. The interim analysis in 2016 was based on cumulative data collected from the point of First Patient First Visit (FPFV) in January 2000 until the last subject year 10 follow-up visit (Last Patient Last Visit (LPLV) in February 2016. The final analysis expected in 2018 will be based on cumulative data collected from the point of FPFV in January 2000 until the last subject completes the end of study visit by 30-Nov-2017.

The previous Kendle study (76803) database used TrialBase software and the new INC study (1003733) database will use Oracle Clinical software. Data extracts from each database into SAS will be combined to create analysis datasets covering the cumulative data from both databases. The analyses in 2018 covered in this SAP will also be based on clean data.

1.2. GLOSSARY OF ABBREVIATIONS

AE	Adverse event
CBC	Complete blood count
CD	Cluster of differentiation
CRF	Case report form
FDA	United States Food and Drug Administration
FPFV	First Patient First Visit
HIV	Human immunodeficiency virus
LNL6	Moloney murine leukemia virus based retroviral vector
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
n	Number of observations
NSRAE	Non-serious related adverse events
OZ1	Cell delivered rybozyme gene transfer product
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
RCR	Replication competent retrovirus
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard operating procedure

1.3. DEFINTION OF TERMS

The following terms will be used throughout this statistical analysis plan to refer to the three contributing protocols.

101	OZ1-HV1-101 long term follow-up
102	OZ1-HV1-102 long term follow-up
202	OZ1-HV1-202 long term follow-up

The phrase ‘long term follow-up’ used throughout this SAP refers to each individual long term follow-up of 101, 102 and 202.

For the purposes of this SAP the term ‘adverse events’ refers to all serious and non-serious related adverse events only.

All subject ID numbers consist of 6 characters. The following subject ID applies to each of the protocols.

101	0R000X
102	0000XX
202	OZ1XXX

Where X represent the individual subject number.

2. OBJECTIVES

1. To undertake long term safety monitoring for any development of:

    a. Clonal expansion of cells with a predominant OZ1 *(or LNL6 vector)* insertion site

    b. Insertional oncogenesis

2. To archive/store plasma and peripheral blood mononuclear cells (PBMC) samples for other safety testing that may be required.

3. To assess quantitative marking of the gene transfer product in PBMCs over time. The 202 protocol includes the assessment of quantitative marking and expression of the gene transfer product in PBMCs over time.

3. STUDY DESIGN

3.1. OVERVIEW OF STUDY DESIGN

The OZ1-HV1-101, OZ1-HV1-102 and OZ1-HV1-202 studies form the long term follow-up for OZ1. OZ1 comprises a Moloney Murine Leukemia Virus based retroviral vector (LNL6) containing a gene that encodes an anti-human immunodeficiency virus (HIV) ribozyme. It is a recommendation of the United States Food and Drug Administration (FDA) that all individuals receiving retroviral gene transfer products are followed for life.

Patients who participated in the Phase I study "A Marker Study of Therapeutically Transduced CD4+ Peripheral Blood Lymphocytes in HIV discordant twins" were asked to continue long term monitoring under the OZ1-HV1-101 protocol. Patients who participated in the Phase I study "A Phase I Trial of Autologous CD34+ Hematopoietic Progenitor Cells Transduced with an Anti-HIV Ribozyme" were to continued long term monitoring under the OZ1-HV1-102 protocol. Patients who participated in the Phase II study "A randomized Phase II, double blind, controlled trial to evaluate the safety and efficacy of autologous CD34+ hematopoietic progenitor cells transduced with placebo or an anti-HIV ribozyme (OZ1) in patients with HIV-1 infection" continue long term monitoring under the OZ1-HV1-202 protocol. Following completion and unblinding of the Phase II study, patients who were identified as having been enrolled in the placebo arm were subsequently discontinued from the long term follow-up study 202.

All patients in each protocol will be reviewed at 6 month intervals (+/- 6 weeks) until year 5 post infusion. Thereafter, all patients will be reviewed annually (+/- 12 weeks) on the anniversary of their infusion. Given the recommendation to follow patients for life, patients who withdraw from the study or have been lost to follow-up but return for assessments at a later time may be re-instated in their study. Additional unscheduled visits may be made if any clinical or biological findings require further investigation. A schedule detailing the timing of the follow-up visits and the procedures carried out at each visit is presented in Table 1.

Various data and samples have been collected under previous protocol versions. For data consistency across all the long term follow-up protocols only data corresponding to the schedule presented in Table 1 collected on one standardized Case Report Form (CRF) will be included in the data analysis. Additionally, the CRF will collect 'Initial Study Information' which will comprise of demography, significant medical history, treatment details from the respective original studies, and PBMC analysis and complete blood count (CBC)/differential and platelets results obtained 2 years post infusion or the nearest timepoint before starting the respective long term follow-up if 2 years post infusion data is not available.

Table 1 Visit Schedule

Follow-up Visit	Year 2.5	Year 3	Year 3.5	Year 4	Year 4.5	Annual Visit Year 5-15	Annual Visit Year 15+
Clinical history and examination	X	X	X	X	X	X	X
Complete Blood Count (CBC)/Differential and Platelets	X	X	X	X	X	X	
Plasma archive		X		X		X	X
PBMC archive[1]		X		X		X	X
OZ1 integration site polymerase chain reaction (PCR)[2]	X	X	X	X	X	X	
Adverse Events Assessments	X	X	X	X	X	X	X
Contact details updated for patient and nominated secondary contact	X	X	X	X	X	X	X

[1]The PBMCs will be stored as cryopreserved cells and cell pellets for replication competent retrovirus (RCR) and other safety testing as required.

[2]This includes both marking (quantitative OZ1/LNL6 DNA-PCR) and the detection of predominant integration sites. If the percentage of cells marked by the vector (quantitative OZ1/LNL6 DNA-PCR) is less than 1% of the test cell population, the site of integration will not be investigated. If a predominant integration site is detected, the patient will be retested within 3 months to determine if it persists. If so, the site of integration of OZ1 will be sequenced and mapped to the human genome to determine any association with known human oncogene. In all instances that a predominant integration site is present and, particularly when there is expansion of a cellular clone, the patient will be monitored for signs of cancer, so that treatment can be initiated as early as possible. Ongoing analysis of quantitative marking of the gene transfer product will be performed as part of the testing of predominant integration sites. These marking data will also be analyzed independently to detect any changes in the number of cells carrying the gene transfer product.

[3]Blood can be collected up to 1 week prior to the other assessments.

Table 2 Visit Schedule (Study 202)

Follow up visit	Yr 2.5	Yr 3	Yr 3.5	Yr 4	Yr 4.5	Annual Yr 5+ /End-of-Study[4]
Clinical history and examination	X	X	X	X	X	X
Complete Blood Count/Differential and Platelets	X	X	X	X	X	X
Plasma archive		X		X		X
PBMC archive[1]		X		X		X
OZ1 integration site (PCR)[2]	X	X	X	X	X	X
Adverse Events Assessment	X	X	X	X	X	X
Contact details updated for subject and nominated secondary contact	X	X	X	X	X	X
Volume of blood drawn at visit (ml)[3]	**30**	**73**	**30**	**73**	**30**	**73**

[1]The PBMCs will be stored as cryopreserved cells and cell pellets for assessment of replication competent retrovirus (RCR) and other safety testing as required.

[2]This includes both marking (quantitative OZ1/LNL6 DNA-PCR) and the detection of predominant integration sites. If the percentage of cells marked by the vector (quantitative OZ1/LNL6 DNA-PCR) is less than 1% of the test cell population, the site of integration will not be investigated. If a predominant OZ1 integration site is detected, the patient will be retested within 3 months to determine if it persists. If so, the site of integration of OZ1 will be sequenced and mapped to the human genome to determine any association with a known human oncogene. In all instances that a predominant integration site is present and, particularly when there is expansion of a cellular clone, the patient will be monitored for signs of cancer, so that treatment can be initiated as early as possible. Ongoing analysis of quantitative marking of the gene transfer product will be performed as part of the testing of predominant integration sites. These marking data will also be analyzed independently to detect any changes in the number of cells carrying the gene transfer product.

[3]Blood can be collected up to 1 week prior to the other assessments.

[4] End-of-Study assessments will be performed after all ongoing patients have been followed up for least 10 years post-infusion. End-of-Study visits will be completed by 30 November 2017. In the event that a patient cannot attend a site visit, telephonic follow-up will be an acceptable alternative.

3.2. STUDY SAMPLE SIZE

The sample size of the long term follow-up studies is dependant on the number of patients continuing into the long term follow-up phase from the original studies. No formal sample size calculation was performed.

4. POPULATIONS FOR ANALYSIS

Assignment of patients to each of the populations together with a review of the data will take place at a Data Review Meeting to be held immediately prior to database lock. All decisions taken at the Data Review Meeting regarding the analysis populations will be fully documented.

The following listings will be provided for the Data Review Meeting:

Demography	(Listing 16.2.2)
Significant Medical History	(Listing 16.2.3)
Treatment Details	(Listing 16.2.4)
PBMC Analysis	(Listings 16.2.5.1, 16.2.5.2, 16.2.5.3)
Patient Disposition	(Listing 16.2.1.1)
Clinical History	(Listing 16.2.12)
Discontinuation Details	(Listing 16.2.1.2)
Re-instatement Details	(Listing 16.2.1.3)
Adverse Events	(Listings 16.2.8.2, 16.2.8.3)
Death	(Listing 16.2.8.1)
Proposed analysis Populations together with reasons for exclusion	(Listing 16.2.1.4)

Other listings may be provided for the Data Review Meeting as required.

4.1. SAFETY POPULATION

The Safety population will consist of any patient who was enrolled in either of the OZ1-HV1-101, OZ1-HV1-102 or OZ1-HV1-202 studies and continued into the respective long term follow-up protocol.

4.2. PER-PROTOCOL POPULATION

All patients who are eligible for inclusion in the Safety population and received OZ1 or LNL6 or combination OZ1/LNL6.

5. OVERALL CONSIDERATIONS

All summary tables and data listings produced by INC will use the statistical package SAS (v9.2 or a more recent version).

In general, categorical data will be presented using counts and percentages, whilst continuous data will be presented using the descriptive statistics, mean, standard deviation (SD), median, minimum, maximum and number of patients with an observation (n). Minimum and maximum values will be quoted to the number of decimal places as recorded on the CRF; means, medians and SDs will be quoted to one further decimal place. Percentages will be rounded to one decimal place. Percentages smaller than 0.1 will be presented as <0.1. Percentages whose numerator is zero will be reported as zero.

All data recorded on the Case Report Form (CRF) and any derived data will be listed for all patients.

The Safety population will be used to present Adverse Event and death data. The PP population will be used to present all data .

Unless otherwise stated missing data will not be imputed. Patients who withdraw prematurely will have their data summarized at the last attended visit. Repeat assessments will not be summarized unless otherwise indicated but will be fully listed. Similarly, data collected at unscheduled visits will be listed only. Repeat and unscheduled visits will be identified on the data listings.

Where of interest, presentation of data will be pooled to reflect the target cell type, CD4 cells in OZ1-HV1-101 and CD34 cells in OZ1-HV1-102 and OZ1-HV1-202 in addition to presenting separately and overall.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

6.1. DEMOGRAPHIC CHARACTERISTICS

Date of birth, gender and race are recorded on the CRF as part of the initial study information.

Age (years) will be calculated using the formulae below and rounded to 1 decimal place.

Age at Infusion = (Date of Infusion - Date of Birth) / 365.25

Age at Database Lock Cut Off = (Date of cut off* - Date of Birth) / 365.25

* According to the current patient visit schedule this is due 13FEB2016 (window period +/- 6 weeks). If a patient has discontinued or died before the date of cut off, the date of Study Discontinuation will replace date of cut off.

Age will be summarized using descriptive statistics, mean, median, standard deviation (SD), minimum, maximum and n separately for patients in 101, 102, 202 and overall.

The number and percentage of patients within each category for gender and race will be summarized for patients in 101, 102, 202 and overall.

Demography will be summarized for PP population.

6.2. PATIENT DISPOSITION AND WITHDRAWALS

The number and percentage of patients who are ongoing and have never discontinued, discontinued and re-instated, and discontinued and never re-instated will be presented separately for 101, 102, 202 and overall. The primary reason for withdrawal will also be presented for those patients who have discontinued.

A table detailing the visit and date of last visit prior to discontinuation together with the reason for discontinuation of each individual patient who discontinued during the long term follow-up will also be presented.

Patients may be discontinued from the long term follow-up for any of the following reasons:

- Patient request
- Were randomized to the placebo treatment arm (202 only)

- Lost to follow-up
- Regulatory authority request
- Study termination
- Other

Patient disposition and withdrawal data will be summarized for all patients.

The number and percentage of patients assigned to each analysis population will be summarized separately for 101, 102 and 202 and overall.

6.3. SIGNIFICANT MEDICAL HISTORY

Information relating specifically to HIV-1 infection will be recorded in the significant medical history (body system Immunological/Rheumatological) as part of the initial study information.

Time since HIV-1 infection will be summarized by descriptive statistics, mean, median, standard deviation (SD), minimum, maximum and n separately for 101, 102 and 202 and overall for the Safety and PP populations. Time since HIV-1 infection will be derived as follows:

Time since HIV-1 infection (yrs) = Year of diagnosis – (Date of Database lock + 1)

Data recorded for other body systems will be listed only.

6.4. OTHER INITIAL STUDY INFORMATION

Treatment details (date of infusion, dose, treatment and transduced efficiency) from the original studies are recorded as part of the initial study information. Patients in 101 originally received a single dose of transduced CD4+ lymphocytes and patients in 102 and 202 originally received a single dose of CD34+ cells.

Time since infusion (years) will be derived using the following formula:

(Date of Last Visit in Long Term Follow-up – Date of Infusion) / 365.25

Time since infusion, dose, transduction efficiency and calculated dose will be summarized using descriptive statistics, mean, median, standard deviation, minimum, maximum and n by cell type (CD4 or CD34). Calculated dose will be derived as follows:

Dose (CD4+ or CD34+) / 100 x transduction efficiency

7. EFFICACY

7.1. MARKING IN PERIPHERAL BLOOD MONONUCLEAR CELLS

PBMC analysis (OZ1 & LNL6 DNA PCR (marking)) will be performed at 2 years post infusion or the nearest timepoint before starting the long term follow-up and at each 6 monthly visit up to 5 years post infusion and annually there after. Analyzed samples for gene detection will be classified as either not done, not detected or detected. If detected genes are found these will further be classified as to whether they are below the limit of quantification or not. Samples below the limit of quantification will be classified as either 1/3 (genes detected in 1 of the 3 triplicates of the sample), 2/3 (genes detected in 2 of the 3 triplicates of the sample) or 3/3 (genes detected in 3 of the 3 triplicates of the sample). For samples above the limit of quantification the percentage detected will be recorded for OZ1 & LNL6 DNA-PCR.

7.2. METHODS OF ANALYSIS

7.2.1. Analysis of Marking in Peripheral Blood Mononuclear Cells

For OZ1 & LNL6 DNA-PCR (marking) the number and percentage of patients in each of the categories Not Detected, Detected (1/3 Detected, 2/3 Detected, 3/3 Detected) and Detected (Quantifiable). The number and percentage of patients in each category will be presented at each timepoint for 102/202 combined and overall for the PP population.

Patients who have quantifiable OZ1 & LNL6 DNA-PCR detected will have the value listed and the relationship between the % marking and calculated dose, age at infusion, gender and race explored as described below.

Correlation between OZ1 & LNL6 DNA-PCR (%) and calculated dose will be assessed using PROC CORR in SAS. The number of patients with quantifiable detected and calculated dose data, Spearman's rank correlation co-efficient and its associated p-value will be presented. Similar presentations will be made for OZ1 & LNL6 DNA-PCR (%) versus age and OZ1 & LNL6 DNA-PCR (%) and time since infusion (as defined in Section 6.3).

Association between the number of patients with and without OZ1 & LNL6 DNA-PCR quantifiable detection and gender will be assessed by the Chi-Squared test using PROC FREQ in SAS. The number of patients with data for both parameters, the Chi-Square statistic and its associated p-value will be presented. A p-value of less than 0.05 will indicate an association between the parameters. Similar presentations will be made for OZ1 & LNL6 DNA-PCR versus race and gender. If it is not appropriate to perform the Chi-Square test due to small cell sizes, Fishers Exact test will be performed.

The above analyses will be performed for 102/202 combined and overall at each post infusion timepoint for the PP population providing there are patients with quantifiable data to render the analyses meaningful. A review of the marker data will take place at the Data Review Meeting. All decisions taken regarding the above analyses will be fully documented in the meeting minutes.

The percentage of patients detected with either a quantifiable or non quantifiable OZ1 & LNL6 DNA-PCR result will be plotted over time for 101, 102 and 202 separately, 102/202 combined and overall for the PP population.

8. SAFETY

8.1. COMPLIANCE

Patient compliance to visit attendance will be calculated using the following formula:

$$\frac{\text{Number of Visits Eligible to Attend} - \text{Number of Eligible Visits Not Attended}}{\text{Number of Visits Eligible to Attend}} \times 100$$

Where the number of visits eligible to attend will be derived for each patient from the time of infusion *i.e.* 5 years since infusion = 6 visits in long term follow-up at 2.5, 3, 3.5, 4, 4.5 and 5 years, etc. Repeat or unscheduled visits will not be included in the above calculation.

Visit compliance will be summarized using descriptive statistics, mean, median, standard deviation (SD), minimum, maximum and n separately by time since infusion (≤ 5 yrs, > 5 yrs/≤10yrs and >10yrs) for 101, 102 and 202 and overall for PP population.

8.2. ADVERSE EVENTS

Throughout the long term follow-up, all serious adverse events (SAEs) and non-serious related adverse events (NSRAEs) observed by medical staff, or reported by the patient, will be evaluated by the investigator and noted in the adverse event section of the CRF.

SAEs and NSRAEs will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA). SAEs and NSRAEs will be summarized separately for 101, 102 and 202 and overall by tabulating the frequency of reports for each unique event and by tabulating the number of patients experiencing one or more events. The denominator used for the calculation of percentages will be the number of patients in the Safety population for the respective long term follow-ups. SAEs and NSRAEs will be summarized by MedDRA system order class and preferred term. Separate data listings of all information relating to patient death, SAEs and NSRAEs will be provided.

SAEs are defined as events that have a seriousness category of death, life threatening, initial or prolonged hospitalization, disability, congenital anomaly or other medically important condition such as predominant integration site, positive RCR, malignancy or abnormal pregnancy outcome (*ie* recorded seriousness category of 1, 2, 3, 4, 5 or 6). AEs recorded as non-serious (7) will be defined as non-serious and will only be recorded if they are considered related to the gene transfer product. A related AE is defined as any

AE whose relationship to the gene transfer product is recorded as possible, probable or very likely (coded on CRF as 3, 4, or 5). Severe AEs are defined as any AE recorded in the 'severe' category (coded on CRF as 3). AEs leading to death are defined as any AE in the seriousness category of 'death' (coded on CRF as 1) and/or an outcome category of 'fatal' (coded on CRF as 5). NSRAEs are defined as adverse events (AEs) whose seriousness category is recorded as non-serious but are considered to have a possible, probable or very likely relationship to the gene transfer product.

If the severity or relationship of an SAE/AE is missing a worst case scenario will be assumed (*ie* the AE will be set to severe or very likely, respectively).

The following AE summary tables will be presented101, 102, 202 and overall.

8.2.1. Overall Summary of Adverse Events

The following will be summarized:

Number and percentage of patients with at least one SAE
Number and percentage of patients with at least one related SAE
Number and percentage of patients with at least one severe, related SAE
Number and percentage of patients with at least one NSRAEs
Number and percentage of patients with SAE leading to death

Number of SAEs
Number of related SAEs
Number of severe related SAEs
Number of NSRAEs
Number of SAE/NSRAE leading to death

8.2.2. Summary of SAEs by System Organ Class, Preferred Term, Severity and Relationship

SAEs will be tabulated (n and %) within each severity category (mild, moderate, severe) and overall categories by system organ class and preferred term. In addition, the number of SAEs will be presented by relationship. Related SAEs are defined as those events coded as 'possible', 'probable' or 'very likely'. Non related SAEs are defined as those events coded as not related or doubtful. Counts will be given for both system organ class and preferred term. Each patient experiencing an SAE will be identified within preferred term and shown under the maximum severity relating to the particular preferred term. For overall severity categories, relationship of the AE will take priority over severity *ie* for the same patient a mild related headache will be counted over an unrelated severe headache.

For both system organ class and preferred term, counting will be done by patient and not by event. A patient will only be counted once within each system organ class and preferred term. The maximum severity for an event will be taken for each patient.

8.2.3. Summary of SAEs and Non-Serious Related Adverse Events by System Organ Class, Preferred Term, Outcome and Relationship

SAEs and NSRAEs will be tabulated (n and %) within each outcome category (recovered/resolved, recovering/resolving, not recovered/not resolved, recovered with sequelae, fatal, unknown) by system organ class, preferred term. In addition, the number of SAEs and NSRAEs will be presented by relationship. Related SAEs are defined as those events coded as possible, probable or very likely. Not related SAEs are defined as those events coded as not related or doubtful. Counts will be given for both system organ class and preferred term. Each patient experiencing a related SAE will be identified within preferred term and shown under the outcome relating to the particular preferred term.

For both system organ class and preferred term, counting will be done by patient and not by event. A patient will only be counted once within each system organ class and preferred term.

8.2.4. Summary of Time Adjusted Related SAEs by System Organ Class and Preferred Term

The number of related SAEs will be presented by system organ class and preferred term. In addition, event rate per year will be calculated using the formula below:

Event rate per year = Number of related SAEs / Patient years in long term follow-up

Where patient years in long term follow-up is calculated individually for each patient using the last available date of a safety assessment – (date of infusion + 2 yrs) and summed over all patients.

Each value from the above derivation will be totaled over each body system and preferred term to give a rate at which a particular related SAE may be experienced by a patient in a given year *ie* a patient rate per year of 1 for a particular preferred term is equal to a patient experiencing a related SAE once a year for the particular preferred term.

8.2.5. Correlation between Frequency of SAEs and NSRAE and Time on Study

Correlation between OZ1 & LNL6 DNA-PCR (%) and the frequency of SAEs and NSRAEs will be assessed using PROC CORR in SAS. The number of patients on study and experiencing at least one SAE at the timepoints 2.5, 3, 3.5, 4, 4.5, 5, > 5 to ≤ 10 and > 10

years post infusion will be presented. In addition Spearman's rank correlation co-efficient and its associated p-value overall timepoints will be presented. Similar presentations will be made for patients experiencing at least one NSRAEs.

8.2.6. Summary of Patient Death

AEs where the outcome recorded as 'fatal' and/or seriousness is recorded as 'death' will be tabulated by system organ class and preferred term. Counts will be given for both system organ class and preferred term. Deaths will be identified within the relevant preferred term.

8.3. PREDOMINANT INTEGRATION SITE TEST

Predominant integration site is defined as an integration site which has a density of at least 50% of the total signal detected by PCR , when the percentage of cells marked by the vector (quantitative OZ1/LNL6 DNA PCR) is greater than 1% of the test cell population. Results are recorded as part of the initial study information and at each follow-up visit.

A confirmed finding of a predominant integration site is a finding that is present on at least 2 consecutive samples. A predominant integration site finding will be reported as an SAE. Predominant integration site results will be listed only, no summary tables will be presented.

8.4. CBC/DIFFERENTIAL AND PLATELETS

CBC/differential and platelets (haematocrit, red blood count, haemoglobin, white blood count, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils) will be recorded as part of the initial study information and at each follow-up visit. CBC/ differential and platelets data will be recorded in the units as pre-printed on the CRF. No conversion of these data to Standard International Units will be required.

CBC/differential and platelets values and change from baseline (2 years post infusion or nearest timepoint before starting long term follow-up) values will be summarized overall.

8.5. CLINICAL HISTORY

Individual patient responses (Yes/No/Not Assessed) to the following questions will be recorded at 2.5 years post infusion and all subsequent follow-up visits:

Has the patient,

experienced new or exacerbated haematological disorders (including clinically significant laboratory abnormalities)?

had any new malignancies (including skin cancers)?

been exposed to possible therapeutic or environmental mutagenic agents?

experienced new or exacerbated pre-existing immunological/rheumatologic disorders?

experienced new or exacerbated pre-existing neurological disorders?

undergone a biopsy or surgical removal of a tumour?

For the last question, patient response to 'Was a sample collected for study assessment?' (Yes/No) will be recorded. If the response is 'Yes', the date of collection, will also be recorded. For the preceding questions, patient response to 'Is this possibly related to the gene transfer product will also be recorded?'.

The number and percentage of patients responding 'yes' to the above questions will be tabulated and presented by whether the information was received at a clinical visit, by telephone contact, and overall. The number of patients with clinical history information will also be presented. Percentages within each follow-up visit will be calculated using the number of patients with clinical history information at that visit.

8.6. REPLICATION COMPETENT RETROVIRUS

Blood collected for PBMC archive will be used for Replication Competent Retrovirus (RCR) testing only if there is a clinically relevant AE, such as neoplasm, or an RCR test was positive, or not completed during the original study of the respective long term follow-up.

Positive findings will be analyzed further to confirm and identify any putative RCR. Any confirmed positive RCR finding will be reported as an SAE.

RCR results will be listed only. No summary tables will be presented.

8.7. PHYSICAL EXAMINATION

A physical examination will be performed at each follow-up visit. Patient results (Not Done/Normal/Abnormal) and any description of an abnormal finding will be recorded for each body system (cardiovascular, respiratory, gastrointestinal, haematologic, endocrine, immunologic/rheumatologic, neurologic, dermatologic and other). Patient results will be listed only, no summary tables will be presented.

9. INTERIM ANALYSES

The first interim analysis of Year 5 follow-up data was done in 2011. The second interim analysis of Year 10 follow-up data has been done in 2016 followed by the final analysis expected in 2018.

10. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNNED ANALYSIS

10.1. CHANGES IN THE CONDUCT OF THE STUDY

No changes are planned.

10.2. CHANGES TO THE ANALYSES PLANNED IN THE STUDY

No changes to the analyses will be made.

11. REFERENCE LIST

N/A

12. PROGRAMMING CONVENTIONS

Listings will be sorted by long term follow-up study and patient identifier.

The dimensions and margins that will be used for the listings and table output produced via SAS are:

Paper: US letter

Pagesize: 43

Linesize: 132

13. INDEX OF TABLES

Table Number	Table Description
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16.2.13	Physical Examination By Study and Patient All Patients

Patient Disposition
Including Reason for Discontinuation
Summary Statistics: All Patients

	OZ1-HV1-101 (N = X) n (%)	OZ1-HV1-102 (N = XX) n (%)	OZ1-HV1-202 (N = XX) n (%)	Overall (N = XX) n (%)
Patients Ongoing (Never Discontinued)				
Patients Discontinued (and Re-instated)				
Reason				
Patient request				
Randomized to placebo arm in OTH/OZ1-INT-1				
Lost to follow up				
Regulatory authority request				
Study termination				
Other				
Patients Discontinued (Never Re-instated)				
Reason				
Patient request				
Randomized to placebo arm in OTH/OZ1-INT-1				
Lost to follow up				
Regulatory authority request				
Study termination				
Other				

Note: Data summarized in this table are presented in data listing x.x
It is possible that patients may withdraw on more than one occasion.

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Prgm note: Percentage is based on N

Janssen – OZ1-HVI-101/102/202 TABLE 14.1.2 Page x of y

Analysis Populations
Summary Statistics: All Patients

	OZ1-HV1-101 (N = X) n (%)	OZ1-HV1-102 (N = XX) n (%)	OZ1-HV1-202 (N = XX) n (%)	Overall (N=XX) n (%)
Patients entered long term follow-up				
Patients in safety population				
Patients in per protocol population				

Note: Data summarized in this table are presented in data listing x.x

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Janssen – OZ1-HVI-101/102/202 TABLE 14.1.3 Page x of y

Demographic Details
Age, Gender and Race
Summary Statistics: PP Population

			OZ1-HV1-101 (N = X)	OZ1-HV1-102 (N = XX)	OZ1-HV1-202 (N = XX)	Overall (N = XX)
Age(years)	At infusion	Mean				
		Median				
		SD				
		Min				
		Max				
		n				
	At study start (2 years post infusion)	Mean				
		Median				
		SD				
		Min				
		Max				
		n				
	At database lock cut off	Mean				
		Median				
		SD				
		Min				
		Max				
		n				

Note: Data summarized in this table are presented in data listing x.x

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Demographic Details
Age, Gender and Race
Summary Statistics: PP Population

			OZ1-HV1-101 (N = X)	OZ1-HV1-102 (N = XX)	OZ1-HV1-202 (N = XX)	Overall (N = XX)
Gender	Male	n (%)				
	Female	n (%)				
Race	Aboriginal	n (%)				
	African American	n (%)				
	American Indian	n (%)				
	Asian	n (%)				
	Caucasian	n (%)				
	Hispanic	n (%)				
	Maori/Polynesian	n (%)				
	Other	n (%)				

Note: Data summarized in this table are presented in data listing x.x

Programming Note: Overall column will be populated for Race only

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Significant Medical History
Time Since HIV-1 Infection
Summary Statistics: PP Population

Time Since HIV-1 Infection (years)	OZ1-HV1-101 (N = X)	OZ1-HV1-102 (N = XX)	OZ1-HV1-202 (N = XX)	Overall (N = XX)
Mean				
Median				
SD				
Min				
Max				
n				

Note: Data summarized in this table are presented in data listing x.x
Time since HIV-1 infection is derived as Year of diagnosis – (Date of Database lock + 1)

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Treatment Details
Summary Statistics: PP Population

		Cell Type	
		CD4	CD34
Time since infusion (years)	Mean		
	Median		
	SD		
	Min		
	Max		
	n		
Dose (x10^6 cells/kg)	Mean		
	Median		
	SD		
	Min		
	Max		
	n		
Transduction efficiency	Mean		
	Median		
	SD		
	Min		
	Max		
	n		
Calculated dose (1)	Mean		
	Median		
	SD		
	Min		
	Max		
	n		

Note: Data summarized in this table are presented in data listing x.x
(1) Calculated dose = Dose(CD4+ or CD34+)/(100 x transduction efficiency)
Programming note: Please repeat this table for 14.1.5a (Study 202 only)

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Compliance
Visit Attendance
Summary Statistics: PP Population

Time since infusion		OZ1-HV1-101 (N = X)	OZ1-HV1-102 (N = XX)	OZ1-HV1-202 (N = XX)	Overall (N = XX)
≤ 5yrs	Mean				
	Median				
	SD				
	Min				
	Max				
	n				
> 5yrs ≤ 10yrs	Mean				
	Median				
	SD				
	Min				
	Max				
	n				
Repeat for:					
> 10yrs ≤ 15yrs	Mean				
➢ 15 yrs	Median				
	SD				
	Min				
	Max				
	n				

Note: Data summarized in this table are presented in data listing x.x
Compliance is calculated by (Number of Visit Eligible to Attend – Number of Visits Attended)/ Number of Visit Eligible to Attend
Repeat or unscheduled visits are not included in the above calculation.

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Janssen – OZ1-HVI-101/102/202 TABLE 14.2.1.1 Page x of y

OZ1 and LNL6 DNA PCR
Marking Parameters (PBMC)Over Time: Actual Values
Summary Statistics: PP Population

Visit	Result		OZ1-HV1-102 / OZ1-HV1-202 (N = XX)	Overall (N = XX)
2 years post infusion	Analysed Sample	n		
	Not Detected	n (%)		
	1/3 Detected *	n (%)		
	2/3 Detected *	n (%)		
	3/3 Detected *	n (%)		
	Quantifiable OZ1 & LNL6 DNA Detected	n (%)		
2.5 years post infusion	Analysed Sample	n		
	Not Detected	n (%)		
	1/3 Detected *	n (%)		
	2/3 Detected *	n (%)		
	3/3 Detected *	n (%)		
	Quantifiable OZ1 & LNL6 DNA Detected	n (%)		
3 years post infusion	Analysed Sample	n		
	Not Detected	n (%)		
	Etc…			

Note: Data summarized in this table are presented in data listing x.x
* = OZ1 & LNL6 DNA Detected but below the lower quantitative limit of the assay: 1/3 = 1 of the 3 triplicates of the sample were detected; 2/3 = 2 of the 3 triplicates of the sample were detected; 3/3 = 3 of the 3 triplicates of the sample were detected.

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Prgm note: % based on N
Programming note: Please repeat this table for 14.2.1.1a (Study 202 only)

Janssen – OZ1-HVI-101/102/202 TABLE 14.2.1.2 Page x of y

OZ1 and LNL6 DNA PCR
Relationship Between Marking Parameters (PBMC) and Calculated Dose, Age, Time on Study, Gender and Race
Summary Statistics: PP Population

Visit	PBMC versus	Statistic	OZ1-HV1-102 / OZ1-HV1-202 (N = XX)	Overall (N = XX)
2 years post infusion	Calculated Dose	N (1) Rho (2) p-value		
	Age (3)	N (1) Rho (2) p-value		
	Time on Study	N (1) Rho (2) p-value		
	Gender	N (1) Chi-Square (4) p-value		
	Race (5)	N (1) Chi-Square (4) p-value		
2.5 years post infusion Etc…	Calculated Dose	N (1) Rho (2) Etc..		

Note: Data summarized in this table are presented in data listing x.x
(1) N = number of patients with quantifiable OZ1 & LNL6 DNA detected
(2) Rho = Spearman's Rank Correlation co-efficient
(3) = Age at infusion

(4) = Chi-Square statistic
(5) = Race categories (Aboriginal, African American, American Indian, Asian, Caucasian, Hispanic, Maori/Polynesian, Other

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Prgm note: Fishers Exact test may be presented if Chi-Square test is not appropriate
Programming note: Please repeat this table for 14.2.1.2a (Study 202 only)

Janssen – OZ1-HVI-101/102/202 TABLE 14.3.1 Page 1 of x

Overall Summary of Adverse Events
Summary Statistics: Safety Population

	OZ1-HV1-101 (N=xx)	OZ1-HV1-102 (N=xx)	OZ1-HV1-202 (N=xx)	Overall (N=xx)
Number (%) of patients with at least one SAE				
Number (%) of patients with at least one related SAE				
Number (%) of patients with at least one severe related SAE				
Number (%) of patients with least one NSRAE				
Number (%) of patients with SAE/NSRAE leading to death				
Number of SAEs				
Number of related SAEs				
Number of severe related SAEs				
Number of NSRAEs				
Number of SAE/NSRAE leading to death				

Note: Data summarized in this table are presented in data listing x.x
SAE = Serious Adverse Event; NSRAE = Non-serious related adverse event
Drug-related adverse events are those events with a relationship of possible, probable or very likely
Events with missing severity are assumed to be the severe category

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Janssen – OZ1-HVI-101/102/202 TABLE 14.3.2 Page 1 of x

Serious Adverse Events
By System Organ Class, Preferred Term, Severity and Relationship including Patient ID
Summary Statistics: Safety Population

System Organ Class Preferred Term	OZ1-HV1-101 (N=xx)											
	---------Mild---------			-------Moderate-------			--------Severe--------			-------Overall------		
	n (%)	NR	Rel	n (%)	NR	Rel	n (%)	NR	Rel	n (%)	NR	Rel
SYSTEM ORGAN CLASS 1	3 (x.x)	1	2	0	0	0	1 (x.x)	0	1	4 (x.x)	1	3
PREFERRED TERM 1	1 (x.x)	1 R0001	0	0	0	0	0	0	0	1 (x.x)	1	0
PREFERRED TERM 2	1 (x.x)	0	1 R0002	0	0	0	1 (x.x)	0	1 R0004	2 (x.x)	0	2
PREFERRED TERM 3	1 (x.x)	0	1 R0003	0	0	0	0	0	0	1 (x.x)	0	1
SYSTEM ORGAN CLASS A												
PREFERRED TERM 1												
PREFERRED TERM 2												
ETC												

Note: Data summarized in this table are presented in data listing x.x
NR = Not related (those events with a relationship of not related or doubtful
Rel = Drug-related adverse events (those events with a relationship of possible, probable or very likely)
Events with missing severity are assumed to be the severe category

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Prgm note: This table will continue for OZ1-HV1-102, OZ1-HV1-202 and Overall

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<SAP Version: 3.0>

Janssen – OZ1-HVI-101/102/202 TABLE 14.3.3 Page 1 of x

Serious and Non-Serious Related Adverse Events
By System Organ Class, Preferred Term, Outcome and Relationship including Patient ID
Summary Statistics: Safety Population

System Organ Class Preferred Term	OZ1-HV1-101 (N=xx)											
	Recovered\Resolved			Recovering\Resolving			Not Recovered\Not Resolved			Recovered with sequelea		
	n (%)	NR	Rel	n (%)	NR	Rel	n (%)	NR	Rel	n (%)	NR	Rel
SYSTEM ORGAN CLASS 1	3 (x.x)	1	2	0	0	0	1 (x.x)	0	1	4 (x.x)	1	3
PREFERRED TERM 1	1 (x.x)	1 R0001	0	0	0	0	0	0	0	1 (x.x)	1	0
PREFERRED TERM 2	1 (x.x)	0	1 R0002	0	0	0	1 (x.x)	0	1 R0004	2 (x.x)	0	2 R0005 R0006
PREFERRED TERM 3	1 (x.x)	0	1 R0003	0	0	0	0	0	0	1 (x.x)	0	1
SYSTEM ORGAN CLASS A												
PREFERRED TERM 1												
PREFERRED TERM 2												
ETC												

Note: Data summarized in this table are presented in data listing X.X.X.X
NR = Not related (those events with a relationship of not related or doubtful
Rel = Drug-related adverse events (those events with a relationship of possible, probable or very likely)

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Prgm note: This table will continue for Fatal and Unknown categories and for OZ1-HV1-102, OZ1-HV1-202 and Overall

Janssen – OZ1-HVI-101/102/202 TABLE 14.3.4 Page 1 of x

Time Adjusted Serious Adverse Events
By System Organ Class, Preferred Term
Summary Statistics: Safety Population

System Organ Class Preferred Term	OZ1-HV1-101	OZ1-HV1-102	OZ1-HV1-202	Overall
SYSTEM ORGAN CLASS 1				
Number of events				
Event rate per year				
PREFERRED TERM 1				
Number of events				
Event rate per year				
PREFERRED TERM 2				
Number of events				
Event rate per year				
SYSTEM ORGAN CLASS 2				
Number of events				
Event rate per year				
PREFERRED TERM 1				
Number of events				
Event rate per year				
ETC				

Note: Data summarized in this table are presented in data listing X.X.X.X
Event rate per year = Number of related SAEs / Patient years in long term follow-up

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Janssen – OZ1-HVI-101/102/202 TABLE 14.3.5 Page 1 of x

Serious and Non-Serious Related Adverse Events
Relationship Between Time on Study and Related Serious and Non Serious Adverse Events
Summary Statistics: Safety Population

Visit		Statistic	OZ1-HV1-102 / OZ1-HV1-202 (N = XX)	Overall (N = XX)
2.5 years post infusion	SAE	N (1) Rho (2) p-value		
	NSRAE	N (1) Rho (2) p-value		
3 years post infusion	SAE	N (1) Rho (2) p-value		
	NSRAE	N (1) Rho (2) p-value		
3.5 years post infusion	N (1) Rho (2) p-value	SAE		
Etc…	Etc…	Etc…		

Note: Data summarized in this table are presented in data listing x.x
(1) N = number of patients experiencing at least one event
(2) Rho = Spearman's Rank Correlation co-efficient

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Janssen – OZ1-HVI-101/102/202 TABLE 14.3.6 Page 1 of x

Patient Death
By System Organ Class, Preferred Term including Patient ID
Summary Statistics: Safety Population

System Organ Class Preferred Term	OZ1-HV1-101 (N=xx)	OZ1-HV1-102 (N=xx)	OZ1-HV1-202 (N=xx)	Overall (N=xx)
SYSTEM ORGAN CLASS 1	2	1	2	5
PREFERRED TERM 1	1 R0001	1 R0002	1 R0003	3
PREFERRED TERM 2	1 R0004	0	1 R0005	2
SYSTEM ORGAN CLASS 2	1	0	0	1
PREFERRED TERM 1	1 R0004	0	0	1
PREFERRED TERM 2	etc..			
ETC				

Note: Data summarized in this table are presented in data listing X.X.X.X
Death is defined as an AE outcome recorded as fatal and/or a AE seriousness recorded as death

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Suggest add footnote to define how these are selected (AEs with outcome='fatal')?

Clinical History
Experienced new or exacerbated pre-existing haematological disorders
(including clinically significant laboratory abnormalities)?
Summary Statistics: PP Population

Long Term Follow-up Visit	Response	Clinical Visit (N = XX) n (%)	Telephone Contact (N = XX) n (%)	Overall (N = XX) n (%)
2.5 yrs post infusion	N*			
	Yes			
	Related			
	Not Related			
	No			
	Not Assessed			
3 yrs post infusion	N*			
	Yes			
	Related			
	Not Related			
	No			
	Not Assessed			
3.5 yrs post infusion	N*			
Etc…	Etc…			

Note: Data summarized in this table are presented in data listing X.X.X.X
N* represents the number of patients responding at each visit and is used as the denominator to calculate percentage

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Similar tables will appear for:
Had any new malignancies (including skin cancers)?
Been exposed to possible therapeutic or environmental mutagenic agents?
Experienced new or exacerbated pre-existing immunologic/rheumatologic disorders?

Experienced new or exacerbated pre-existing neurological disorders?
Undergone a biopsy or surgical removal of a tumor?

<Protocol: Janssen OZ1-HV1-101/102/202>

<INC code: 1003733>

<SAP Version: 3.0>

CBC/Differential and Platelets
Parameter (units)
Summary Statistics: PP Population

	Overall											
Post infusion Visit	Result						Change from Baseline					
	mean	std	median	min	max	n	mean	std	median	min	max	n
2 years												
2.5 years												
3 years												
3.5 years												
4 years												
4.5 years												
5 years												
Etc…												

Note: Data summarized in this table are presented in data listing x.x
Baseline is the 2 year post infusion visit or nearest timepoint before start of long term follow-up

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Below is an example of a typical listing ie Protocol, Treatment, Dose and Patient ID will appear on all listings. For some lisitings this may mean that space is restricted for other data and the listing may be split over more than one page.

Data Listing 16.2.X
Listing Description
All Patients

Protocol	Treatment	Dose	Patient ID	*Listed data1*	*Listed data2*	*Listed data3*	*Listed data4*
ie OZ1-HIV-1-101 or OZ1-HIV-1-102 or OZ1-HIV-1-202	OZI or LNL6 or OZ1&LNL6 or placebo	CD4 or CD34					