

Janssen-Cilag Pty Ltd, Australia

Clinical Protocol

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

BB-IND: 10183

PROTOCOL OZ1-HV1-202

**Amendment 4
PHASE II**

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CONTACT INFORMATION†

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Name _____

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If any Sponsor contact information needs to be changed during the course of the study, written notification will be provided to the Investigator and will not require (a) Protocol amendment(s).

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PROTOCOL VERSION INFORMATION†

Sections of this protocol have been revised. Amendment 1 was issued on 23 June 2006. Amendment 2 was issued on 28 August 2007. Amendment 3 was issued on 15 October 2008. Sections marked “†” have been revised as Amendment 4; 07 June 2017. Please refer to [Appendix 3](#) – Protocol Amendment History for a detailed description of the specific changes.

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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

SYNOPSIS

OBJECTIVE†

The objective of this study is to evaluate the long-term safety of a cell-delivered ribozyme gene transfer product (OZ1) in patients infected with HIV-1. OZ1 comprises a Moloney Murine Leukemia Virus based retroviral vector (LNL6) containing a gene that encodes an anti-HIV ribozyme. It is currently a recommendation of the United States Food and Drug Administration (FDA) and Australian Therapeutic Goods Administration (TGA) that all individuals receiving retroviral gene transfer products are followed to collect data on delayed adverse events.

OVERVIEW OF STUDY DESIGN†

This will be a follow-up study of patients previously enrolled in the OTH/OZ1-INT-1 trial. All patients in this protocol will be reviewed at six monthly intervals until year 5 post infusion. Thereafter all patients will be reviewed annually, on the anniversary of the infusion until withdrawal or study completion. Patients who were enrolled in the placebo arm will be discontinued after OTH/OZ1-INT-1 has been unblinded.

STUDY POPULATION

Participants in the OTH/OZ1-INT-1 Phase II study entitled “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-1 ribozyme (OZ1) in patients with HIV-1 infection” will be asked to consent to continue safety monitoring and gene marking as described in this protocol.

DOSAGE AND ADMINISTRATION

All participants of the OTH/OZ1-INT-1 Phase II study received a single dose of placebo or OZ1 transduced CD34+ cells.

SAFETY EVALUATIONS†

Follow-up will be conducted as per current FDA/Center for Biologics Evaluation and Research (CBER) recommendations. Evaluations will include monitoring for related adverse events such as the development of replication competent retrovirus (RCR), predominant integration sites and insertional oncogenesis. Blood samples will be collected for archival storage for assessment of replication competent retrovirus (RCR) and other safety testing as necessary.

EFFICACY EVALUATIONS

Ongoing analysis of quantitative marking of the gene transfer product (OZ1 and LNL6) in peripheral blood mononuclear cells (PBMC) will be performed as part of the testing of predominant integration sites. These marking data will also be analyzed independently of the integration analysis to detect changes in the number of cells carrying the gene transfer product.

TIME AND EVENTS SCHEDULE

Follow up visits may be part of routine clinic visits where possible, but must be performed as described in the Time and Events Schedule. Additional unscheduled visits will be made if clinical or biological findings, as described in this protocol, require additional evaluation or investigation or as directed by the Investigator.

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TIME AND EVENTS SCHEDULE[†]

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

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

²This 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.

³Blood 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.

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INVESTIGATOR AGREEMENT†

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INVESTIGATOR AGREEMENT†

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Malcolm Handel, BSc(Hons) MB BS PhD FRACP

Institution: Janssen-Cilag Pty Ltd, Australia

Signature: _____ Date: 08 JUN 2017
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

1. INTRODUCTION

1.1 Background[†]

OZ1 is a Moloney Murine Leukemia Virus based retroviral vector (LNL6) containing a gene that encodes an anti-HIV-1 ribozyme directed against the human immunodeficiency virus type 1 (HIV-1) regulatory gene *tat*.^{13,14,15} A Phase I study demonstrated that the introduction of OZ1 into CD34+ cells *ex vivo* is technically feasible and safe.¹ The international, multi-center, Phase II, randomized, double-blind trial, OTH/OZ1-INT-1, was initiated to investigate the safety and efficacy of OZ1-transduced autologous CD34+ cells in patients with HIV-1 infection.⁹ One patient was enrolled in a Phase II protocol comparing the retroviral vector alone (LNL6) and OZ1. In a protocol amendment, OTH/OZ1-INT-1 became a placebo-controlled trial. Of the 74 patients to be enrolled in the placebo controlled protocol, approximately half received a placebo and half OZ1. The primary efficacy end point is the difference in viral load between the two groups at weeks 47 and 48 post-infusion. Patients continue in the OTH/OZ1-INT-1 treatment interruption follow-on phase until week 100 post-infusion as long as the viral load remains below 100,000 copies/ml, the CD4+ cell count is greater than 150 cells/mm³ and there are no other reasons to recommence antiretroviral therapy. At the end of the OTH/OZ1-INT-1 study (week 100 post-infusion), patients are invited to enter this long term follow-up (LTFU) protocol.

1.2 Rationale for Study[†]

Food and Drug Administration (FDA)/Center for Biologics Evaluation and Research (CBER) recommends a 15-year time-period for follow-up observations. However, CBER also recognizes that assessment of risk is a continuous process, and the nature and duration of follow up observations may be revised accordingly.⁴ This follow up protocol is to assess the long-term safety of OZ1/LNL6 gene transfer product in patients who were enrolled in the OTH/OZ1-INT-1 study. Based on the integrated safety analysis of observations up to 10 years in this LTFU study, up to 15 years with the same OZ1/LNL6 gene transfer product in 2 Phase 1 LTFU studies (OZ1-HV1-101 and OZ1-HV1-102), and published reports of adverse events observed with gene therapeutic products using the same type of retroviral vector,^{2,3,5,6,7,8,10,11,12} the sponsor has determined that the risk to OZ1/LNL6 gene transfer product to recipients beyond 10 years post-infusion is minimal. Accordingly, this long term follow up study will conclude by 30 November 2017. This completion date represents a minimum of 10 years follow up following the receipt of OZ1/LNL6-modified CD34+ cells.

2. OBJECTIVES

1. To undertake long term safety monitoring for any development of:
 - a. Clonal expansion of cells with a predominant OZ1 insertion site
 - b. Insertional oncogenesis
2. To archive/store plasma and PBMC samples for other safety testing that may be required.
3. To assess quantitative marking of the gene transfer product in PBMCs over time.

3. OVERVIEW OF STUDY DESIGN

The patients who were enrolled in the OTH/OZ1-INT-1 trial entitled “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-1 ribozyme (OZ1) in patients with HIV-1 infection” will continue to be assessed under this long term follow-up protocol. Where possible follow up visits will coincide with routine clinic visits.

4. COMPLIANCE[†]

1. The semi-annual visit interval is 6 months \pm 6 weeks (for years 2.5-5). The annual visit interval is 12 months \pm 12 weeks (year 5+) except the End-of-Study visit. 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 recipient cannot attend a site visit, a telephonic follow-up will be an acceptable alternative.
2. Complete Blood Count/Differential data will be obtained specifically as part of the follow up procedures.
3. In the event that a recipient dies, irrespective of cause of death or time after the gene transfer procedure, a request will be made by the Principal Investigator to the next of kin for an autopsy to assess for the presence of 1) RCR and 2) LNL6 or OZ1 containing cells. If efforts to obtain permission for an autopsy are unsuccessful or not practicable, failure to undertake an autopsy will not be considered protocol non-compliance. If an autopsy is performed, a copy of the autopsy report will be obtained and the cause of death and any significant observations noted in the Serious Adverse Event report.

4. In the event that the recipient undergoes a biopsy or surgical removal of a tumor, an attempt will be made by the Principal Investigator to obtain a sample of tissue for the assessment of the presence of 1) RCR and 2) LNL6 or OZ1 containing cells. If efforts to obtain a tissue sample are unsuccessful or not practicable, it will not be considered as protocol non-compliance.

5. STUDY POPULATION

5.1 Inclusion Criteria

Patients must satisfy the following criteria before entering the study:

- Received the Final Cell Product infusion in the Phase II trial, OTH/OZ1-INT-1.
- Signed Informed Consent Form for this study.

5.2 Exclusion Criteria

All patients who were enrolled in the OTH/OZ1-INT-1 study and received the final cell product will be invited to participate in this long term follow-up study. After unblinding of the OTH/OZ1-INT-1 study, any patients in the placebo arm will be withdrawn from this protocol.

6. CONCOMITANT THERAPY AND ACTIVITIES

Information on current medications or other therapies will not be collected, unless required for submission of a Serious Adverse Event report.

7. STUDY EVALUATIONS

7.1 Study Procedures By Visit[†]

The Time and Events Schedule included in the Synopsis summarizes the frequency and timing of the various efficacy and safety measurements.

Visit schedules are fixed from the day of the original infusion of autologous CD34+ cells as per the OTH/OZ1-INT-1 protocol. Blood samples may be taken up to 1 week prior to the other assessments.

Table 3: Long term follow-up allowed visit intervals.

Visit interval	Allowed window
6 months	± 6 weeks
12 months*	± 12 weeks*

* Except the End-of-Study visit, which will be scheduled at a date no later than 30 November 2017.

In the event that a subject is unable to attend the clinic within the allowed visit window, a telephone interview can be conducted to collect information on important medical events since the last study visit (or telephone interview). Refer to [Appendix 2](#) for the interview questionnaire. If the clinical trial site is unable to contact the patient directly a nominated secondary contact will be contacted. A patient will be considered to be lost-to-follow-up, at any stage of the clinical trial, after three failed documented attempts (telephone calls, certified letters, e-mail requests) to contact either the patient or a nominated secondary contact. A lost or withdrawn patient may re-enter this long term follow-up protocol at any stage up until 30 November 2017.

2.5 to 5.0 years post-infusion[†]

Visits will be at six monthly intervals from year 2.5 to year 5.0 post-infusion.

The long term follow-up visits at Year 2.5, 3.5 and Year 4.5 post-infusion will have the following assessments:

- Clinical history and physical examination including a detailed record of:
 - exposure to possible mutagenic agents e.g. radiotherapy or chemotherapeutic agents
 - new malignancies
 - new or exacerbated preexisting neurologic, rheumatologic, autoimmune and hematologic disorders
- Complete Blood Count (CBC)/differential and platelet count.
- Testing for clonality of OZ1/LNL6 integration in PBMC samples (PCR) if the percentage of cells marked by the vector (quantitative OZ1 DNA-PCR) is greater than or equal to 1% of the test cell population.
- Analysis of quantitative marking of the gene transfer product (OZ1 and LNL6) in peripheral blood mononuclear cells (PBMC) will be performed as part of the testing of predominant integration sites. These marking data will also be analyzed independently of the integration analysis to detect changes in the number of cells carrying the gene transfer product.
- Recording of AEs.
- Contact details updated for subject and nominated secondary contact.

The long term follow-up visits at Year 3, 4 and 5 post-infusion will have the following assessments:

- Clinical history and physical examination including a detailed record of:

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- exposure to possible mutagenic agents e.g. radiotherapy or chemotherapeutic agents
- new malignancies
- new or exacerbated preexisting neurologic, rheumatologic, autoimmune and hematologic disorders
- Complete Blood Count (CBC), differential and platelet count.
- Archival storage of plasma and PBMC samples for safety testing including Replication-Competent Retrovirus (RCR) as required.
- Testing for clonality of OZ1/LNL6 integration in PBMC samples (PCR) if the percentage of cells marked by the vector (quantitative OZ1/LN6 DNA-PCR) is greater than or equal to 1% of the test cell population.
- Analysis of quantitative marking of the gene transfer product (OZ1 and LNL6) in peripheral blood mononuclear cells (PBMC) will be performed as part of the testing of predominant integration sites. These marking data will also be analyzed independently of the integration analysis to detect changes in the number of cells carrying the gene transfer product.
- Recording of AEs.
- Contact details updated for subject and nominated secondary contact.

Annual Visits Year 5+ post infusion and End-of-Study visit[†]

- Clinical History and Physical Examination including a detailed record of:
 - exposure to possible mutagenic agents e.g. radiotherapy or chemotherapeutic agents
 - new malignancies
 - new or exacerbated preexisting neurologic, rheumatologic, autoimmune and hematologic disorders
- Complete Blood Count (CBC), differential and platelet count.
- Archival storage of plasma and PBMC samples for safety testing including Replication-Competent Retrovirus (RCR) as required.
- Testing for clonality of OZ1/LNL6 integration in PBMC samples (PCR) if the percentage of cells marked by the vector (quantitative OZ1/LNL6 DNA-PCR) is greater than or equal to 1% of the test cell population.
- Analysis of quantitative marking of the gene transfer product (OZ1 and LNL6) in peripheral blood mononuclear cells (PBMC) will be performed as part of the testing of predominant integration sites. These marking data will also be

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analyzed independently of the integration analysis to detect changes in the number of cells carrying the gene transfer product.

- Recording of AEs.
- Contact details updated for subject and nominated secondary contact.

In the event that a recipient does not report for an in-person End-of-Study visit, a telephonic follow-up will be an acceptable alternative.

Unscheduled Assessments[†]

In addition to the annual follow up visit, unscheduled procedures may be performed in the event of an adverse event or as directed by the Investigator.

7.2 Safety Evaluations

The study will include the following evaluations of safety and tolerability:

- Adverse Events (AEs): AEs will be reported by the patient (or where appropriate by the patient's legally authorized representative) for the duration of the study. Further details on adverse event reporting are provided in Section 10.
- **Clinical Laboratory tests as follows:**

The following testing will be completed as designated in the Time & Events Schedule:

Gene Transfer Product Safety Testing

1. Testing for clonality of OZ1/LNL6 integration in PBMC using PCR.
 - Testing for clonality of OZ1/LNL6 integration in PBMC samples (PCR) will proceed if the percentage of cells marked by the vector (quantitative OZ1/LNL6 DNA-PCR) is greater than or equal to 1% of the test cell population.
 - If a predominant integration site is detected, the patient will be retested within three 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 closely for signs of cancer, so that any potential treatment can be initiated as early as possible.

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- “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 >1% of the test cell population.
 - Any confirmed finding of a predominant integration site, i.e. present on at least two consecutive samples, will be reported as an SAE.
2. PBMC samples will be archived and will be tested for the presence of RCR using primers specific for amphotropic *env* retroviral gene sequences if required.
- PBMC cell pellets and cryopreserved cells will be archived for RCR testing. RCR testing by PCR will be completed on these samples only if there is a clinically relevant adverse event (e.g. neoplasm) or an RCR test during the OTH/OZ1-INT-1 study was positive.
 - Any samples found to be positive for amphotropic *env* sequences will be analyzed further by biological assay to confirm and identify any putative RCR.
 - Any confirmed positive finding of RCR will be reported as a SAE.
3. Archival plasma and PBMC samples will be collected annually for the duration of the long term follow-up protocol.

Hematology

This will include red blood cell count, hemoglobin, hematocrit and platelets, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils).

An Investigator must interpret the laboratory reports. Any clinically significant changes that require an intervention (e.g. concomitant medication or other treatment or investigation) must be recorded in the source documents.

Autopsy

If a patient dies during the long-term follow up, an autopsy will be requested to determine the extent of gene transfer into bone marrow, spleen, lymph nodes and gonadal tissue, as well as any potentially transformed tissues (e.g. lymphomas, leukemia). A separate informed consent for autopsy will be requested. Patients may

sign the consent for autopsy at the time of enrollment. Autopsy will not be required for patients randomized to placebo (after unblinding of the OTH/OZ1-INT-1 trial).

8. PATIENT COMPLETION[†]

Patients will complete long term follow up with an End-of-Study visit to be completed by 30 November 2017.

Patients must be withdrawn from the study if:

- They received placebo in the OTH/OZ1-INT-1 trial. This will only become known when the OTH/OZ1-INT-1 study has been unblinded.
- They withdraw their consent.

If a patient withdraws, the reason for withdrawal is to be documented on the CRF and in the source document. A withdrawn patient or a patient who was lost to follow-up can re-enter this long term follow-up protocol at any time up until 30 November 2017.

9. STATISTICAL METHODS[†]

Statistical analysis of data collected during the long term follow-up study will be performed every 5 years. After patients complete an End-of Study visit, the final analysis of data will be done. The primary focus of analysis will be descriptive summarizing changes over time. Patterns over time will be analysed using appropriate techniques. Factors associated with quantitative changes may be assessed.

9.1 Efficacy Evaluation[†]

Ongoing analysis of quantitative marking of the gene transfer product (OZ1 and LNL6) in peripheral blood mononuclear cells will be performed as part of the testing of OZ1 or LNL6 vector integration sites. These data will be used to independently assess changes in the number of peripheral blood mononuclear cells that carry the gene transfer product over time.

9.2 Safety Evaluations

All AE data will be coded to a System Organ Class and Preferred Term using the current MedDRA coding dictionary.

Clinical history, physical examination findings, CBC and AEs will be listed and summarized in a tabular form. AE data will be summarized annually for regulatory reporting.

10. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures (SOPs) in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical trials sponsored by JC will be conducted in accordance with those procedures.

10.1 Adverse Event Definitions and Classifications[†]

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (Definition per International Conference on Harmonisation [ICH]). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the informed consent until completion of the subject's last study-related procedure.

Serious Adverse Event

A serious adverse event (SAE) as defined by ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- results in death;
- is life-threatening (the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe);
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above; for example, important medical events may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for:

- social reasons in the absence of an adverse event;
- surgery or procedure planned before entry into the study (must be documented in the source documentation and CRF)

In addition to the ICH defined serious adverse events, the following events are to be considered an SAE:

- a confirmed finding of a “predominant integration site”; or
- a confirmed finding of Replication Competent Retrovirus (RCR).

Unlisted (Unexpected) Serious Adverse Event

An SAE which is unlisted, or the nature or severity of which is not consistent with the applicable product information. For an investigational product, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed.

Not related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, e.g. concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative

explanation, e.g. concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely, e.g. concomitant drug(s), concomitant disease(s).

Very likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g. concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

10.2 Procedures

NON-SERIOUS ADVERSE EVENTS

Non-serious adverse events must be recorded using medical terminology in the source document and in the case report form if they have a possible, probable or very likely suspect association to the study drug.

SERIOUS ADVERSE EVENTS

All adverse events meeting the definition of serious, regardless of severity or presumed relationship, must be recorded using medical terminology in the source document and in the case report form. Only SAEs that are “possibly”, “probably” or “very likely” related to the study drug must be reported using the Sponsor Serious Adverse Event Form within 24 hours of knowledge of the event. Exceptions to this include:

- Death, regardless of the cause, is considered a reportable SAE;
- Malignancy (except Basal Cell or Squamous Cell Carcinomas), regardless of causality, is considered a reportable SAE.

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g. cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). Investigators must record in the CRF their opinion concerning the relationship of the SAE to study therapy. All measures required for serious adverse event management must be recorded in the source document.

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Subjects (or their designees, if appropriate) must be provided with a “study card” indicating the name of the investigational product, the study number, the investigator’s name, and a 24-hour emergency contact number.

All reportable SAEs occurring during the study period must be reported to the appropriate sponsor contact person by investigational staff within 24 hours of their knowledge of the event. If the SAE is a death or a life threatening event the Investigator must notify the Sponsor immediately by both telephone and FAX.

Information regarding serious adverse events will be transmitted to the sponsor using the Sponsor Serious Adverse Event Form, which must be signed by a member of the investigational staff. The initial report of a serious adverse event may be made by facsimile (fax) or telephone. It is preferable that serious adverse events be reported via fax. Subsequent to a telephone report of a serious adverse event, a Serious Adverse Event Form must be completed by the investigational staff and transmitted to the sponsor within 24 hours.

All SAEs must be followed until any of the following occurs:

- the event resolves;
- the event stabilizes;
- the event returns to baseline, if a baseline value is available;
- the event can be attributed to agents other than the study drug or to factors unrelated to study conduct; or
- when it becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

The sponsor assumes responsibility for appropriate reporting of serious adverse events to the regulatory authorities. This includes expedited reporting of leukemia (proven or strong clinical suspicion), confirmed positive RCR or predominant integration site. The sponsor will also report to the investigator all serious adverse events that are unlisted and associated with the use of the drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

The sponsor will evaluate any safety information that is spontaneously reported by a subject outside their participation in the formal study program.

PREGNANCY

The investigational staff must report pregnancy within 24 hours of their knowledge of the event using the Sponsor Benefit Risk Management Pregnancy Notification Form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required, and is to be reporting using the Sponsor follow up collection Forms A & B.

Because the study drug may have an effect on sperm, pregnancies in partners of male subjects included in the study will be reported by the investigational staff in the same manner as above. The outcome of the pregnancy and any postnatal sequelae in the infant is also to be reported using the Sponsor pregnancy notification and follow up forms.

Any pregnancy abnormal outcomes (e.g. spontaneous abortion, fetal demise, stillbirth, congenital abnormality, ectopic pregnancy) or pregnancy associated adverse events must be reported as SAEs, as per SAE reporting procedures described above.

10.3 Contacting Sponsor Regarding Safety

The names of the individuals (and corresponding phone numbers) who should be contacted regarding safety issues are listed on the CONTACT INFORMATION page(s) in the front of the protocol.

11. ETHICAL ASPECTS

11.1 Investigator Responsibilities

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the Protocol, the Declaration of Helsinki, current International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements. These documents set forth that the informed consent of the patients is an essential precondition for participation in the clinical study.

11.2 Independent Ethics Committee or Institutional Review Board (IEC/IRB)

This trial will be undertaken only after full approval of the Protocol and adjunctive materials (e.g. informed consent form, advertising) has been obtained from a local IEC/IRB and a copy of this approval has been received by the Sponsor.

The IEC/IRB must be informed of all subsequent Protocol amendments issued by the Sponsor.

The Investigator will submit reports on, and reviews of, the trial and its progress to the IEC/IRB at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines.

11.3 Informed Consent

Each patient (or a legally authorized representative) must give written consent (and sign other locally required documents) according to local requirements after the nature of the study has been fully explained. The consent form must be signed prior to performance of any study-related activity. The consent form that is used must be approved both by the Sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with the current revision of the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and JC policy.

The Investigator must explain to potential patients or their legal representatives the aims, methods, reasonably anticipated benefits and potential hazards of the study and any discomfort it may entail. Patients will be informed that they are free not to participate in the study and that they may withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the Investigator will maintain a patient identification register for the purposes of long-term follow-up if needed and that their records may be examined by competent authorities and authorized persons but that personal information will be treated as strictly confidential and will not be publicly available. Patients must be given the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the patient's or his/her legal representative's dated signature. If a patient and his/her legal representative are unable to read, an impartial witness must be present during the entire informed consent discussion. The signature of the impartial witness will certify the patient's consent. The patient or his/her legal representative will be given a signed and dated copy of the informed consent form.

12 ADMINISTRATIVE REQUIREMENTS

12.1 Protocol Modifications

Neither the Investigator nor Sponsor will modify this Protocol without obtaining the concurrence of the other. All Protocol amendments must be issued by the Sponsor, signed and dated by the Investigator, and should not be implemented without prior IEC/IRB approval, except where necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change in monitor(s), change of telephone number(s)).

Responsibilities for reporting Protocol amendments to IEC/IRBs are further described in the Ethical Aspects section of the Protocol.

In situations requiring a deviation from the Protocol, the Investigator or other physician in attendance will contact the site manager or other appropriate Sponsor representative by FAX or telephone (see Contact Information page). If possible, this contact will be made before implementing any deviation from the Protocol. In all cases, contact with the Sponsor must be made as soon as possible in order to discuss the situation and agree on an appropriate course of action. The CRF and source document will describe any deviation from the Protocol and the circumstances requiring it.

12.2 Regulatory Documentation

Documents that must be provided to the Sponsor prior to study start are as follows:

- A copy of the formal written notification to the Investigator regarding approval of the Protocol by an IEC/IRB that is in compliance with regulatory guidelines. The written notification is to be signed by the chairman or authorized designee and must identify the specific Protocol. In cases where an IEC/IRB member has a known conflict of interest, abstention of that individual from voting should be documented; an Investigator (or sub-Investigator) may be a member of the IEC/IRB, but may not participate in the deliberation or vote on any research in which he or she is involved;
- A copy of the IEC/IRB approved informed consent form and other adjunctive materials (e.g. advertising) to be used in the study, including written documentation of IEC/IRB approval of these items;
- Name and address of the IEC/IRB with a statement that it is organized and operates according to GCP and the applicable laws and regulations, and a current list of the IEC/IRB members. If accompanied by a letter of explanation from the IEC/IRB, a general statement may be substituted for this list;
- Regulatory authority approval or notification, if applicable;
- Applicable local regulatory documentation (e.g. FDA 1572 Form);
- Financial disclosure statement(s) for each Investigator and sub-Investigator;

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- Signed and dated Investigator Agreement page of the final Protocol and, where applicable, amendments;
- Signed and dated trial agreement and financial agreement, if applicable;
- Current *curricula vitae* for each Investigator and sub-Investigator;
- Name and address of any local laboratory conducting tests for the study, a dated copy of the laboratory reference values for tests to be performed during the study and a copy of the certification or other documentation establishing adequacy of the facility.

In addition to the documents required prior to the study, other documentation may be required during the course of the study.

12.3 Patient Identification Register

The Investigator agrees to complete a patient identification register, which will be used for the purpose of long-term follow-up. This form will be treated as confidential, and will be filed by the Investigator in the Trial Center File. Otherwise, all reports and communications relating to the study will identify patients by initials, date of birth and assigned number only.

Where applicable, patient specific information required by local regulatory agencies will be provided.

12.4 Record Retention

In compliance with the ICH/GCP guidelines, the Investigator/Institution will maintain all CRFs and all source documents that support the data collected from each patient, and all trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as specified by the applicable regulatory requirement(s). The Investigator/Institution will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least 2 years have elapsed since the formal discontinuation of the long term follow-up study. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained. If an Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, the Institution with which the Investigator is associated must transfer the responsibility to another person within

the Institution. The Sponsor must be notified in writing of the name and address of the new custodian.

12.5 Case Report Form Completion

CRFs are provided for each entered patient. An entered patient is one who has signed the informed consent document.

Data must be entered onto CRFs or Telephone Follow-up Questionnaire in English. All forms must be filled out in blue or black ballpoint pen or typed. The Study Completion Information page of the CRF must be signed and dated by the Investigator. The CRFs are to be completed at the time of the patient's visit, with the exception of results of tests performed outside the Investigator's office, so that they always reflect the latest observations on the patients participating in the trial.

All CRF corrections are to be made by the Investigator or other authorized study site personnel. The Investigator must authorize changes to the recorded safety and efficacy data.

- Completed CRFs will be continuously submitted according to the Sponsor's instructions, and reviewed by the Sponsor to determine their acceptability. If necessary, Data Correction Forms (DCF's) will be generated and transmitted to the study site for resolution.

12.6 Monitoring

The Sponsor will perform on-site monitoring visits annually or more frequently as necessary. Visit intervals will be dependent on both the time post infusion and number of patients at the site. The dates of the visits will be recorded by the monitor in a trial center visit log to be kept at the site. At these visits, the monitor will compare the data entered onto the CRFs with the hospital or clinic records (source documents). At a minimum, source documentation must be available to substantiate patient identification, eligibility and participation, proper informed consent procedures, dates of visits, adherence to Protocol procedures, record of safety and efficacy parameters, adequate reporting and follow-up of adverse events, date of completion and reason. Specific items required as source documents will be reviewed with the Investigator prior to the study. Findings from this review of CRFs and source documents will be discussed with the investigational staff. The Sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related

documents. The monitor will meet with the Investigator on a regular basis during the trial to provide feedback on the trial conduct.

12.7 Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study centers, review of Protocol procedures with the Investigator and associated personnel prior to the study and periodic monitoring visits by the Sponsor. The Sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after their return to JC, and any discrepancies will be resolved with the Investigator or designees, as appropriate. The data will be entered into the clinical trial database and verified for consistency.

12.8 On-Site Audits

Representatives of the Sponsor's Global Clinical Quality Assurance Department may visit the site to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Patient privacy must, however, be respected. Sufficient prior notice will be provided to allow the Investigator to prepare properly for the audit.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study. The Investigator should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

12.9 Use of Information and Publication

All information concerning placebo and OZ1, JC operations, patent application, formulas, manufacturing processes, basic scientific data, and formulation information, supplied by the Sponsor to the Investigator and not previously published, is considered confidential and remains the sole property of JC. The Investigator agrees to use this information only to accomplish this study and will not use it for other purposes without the Sponsor's written consent.

The Investigator understands that the information developed in the clinical study will be used by JC in connection with the continued development of OZ1, and thus may be disclosed as required to other clinical Investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study.

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14. APPENDICES

**Appendix 1:
TOXICITY GRADING TABLE**

TABLE FOR GRADING SEVERITY OF ADULT ADVERSE EXPERIENCES©

**ACTG 285
DIVISION OF AIDS**

ABBREVIATIONS: Abbreviations used in the table:

ULN =	Upper Limit of Normal
LLN =	Lower Limit of Normal
Rx =	Therapy
Req =	Required
Mod =	Moderate
IV =	Intravenous
ADL =	Activities of Daily Living
Dec =	Decreased

ESTIMATING SEVERITY OF GRADE

For abnormalities NOT found elsewhere on the Toxicity Table use the scale below to estimate grade of severity:

GRADE 1 Mild

Transient or mild discomfort; no limitation in activity; no medical intervention/ therapy required

GRADE 2 Moderate

Mild or moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required

GRADE 3 Severe

Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalisations possible

GRADE 4 Life-threatening

Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospital or hospice care probable

Appendix 1:
ATCG Toxicity Grading Table

SERIOUS OR LIFE-THREATENING AE's

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 adverse experience. Clinical events considered to be serious or life-threatening include, but are not limited to:

seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis

PARAMETER	GRADE MILD	GRADE MODERATE	GRADE SEVERE	GRADE POTENTIALLY LIFE-THREATENING
HEMATOLOGY				
Hemoglobin	8.0g/dL - 9.4g/dL	7.0g/dL - 7.9g/dL	6.5g/dL - 6.9g/dL	< 6.5g/dL
Absolute Neutrophil Count	1000 -1500/mm ³	750 -999/mm ³	500 -749/mm ³	< 500/mm ³
Platelets	75,000 - 99,000/mm ³	50,000 - 74,999/mm ³	20,000 - 49,999/mm ³	< 20,000/mm ³
Prothrombin Time (PT)	> 1.0 - 1.25 X ULN	> 1.25 - 1.5 X ULN	> 1.5 - 3.0 X ULN	> 3.0 X ULN
BT	> 1.0 - 1.66 X ULN	> 1.66 - 2.33 X ULN	> 2.33 - 3.0 X ULN	> 3.0 X ULN
Methemoglobin	5.0 - 10.0%	10.0 - 15.0%	15.0 - 20.0%	> 20.0%
CHEMISTRIES				
SODIUM				
Hyponatremia	130 - 135meq/L	123 - 129meq/L	116 - 122meq/L	< 116meq/L
Hypernatremia	146 - 150meq/L	151 - 157meq/L	158 - 165meq/L	> 165meq/L
POTASSIUM				
Hyperkalemia	5.6 - 6.0meq/L	6.1 -6.5meq/L	6.6 - 7.0meq/L	> 7.0meq/L
Hypokalemia	3.0 - 3.4meq/L	2.5 - 2.9meq/L	2.0 - 2.4meq/L	< 2.0meq/L
PHOSPHATE				
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 - 1.9 mg/dL	1.0 - 1.4 mg/dL	< 1.0 mg/dL
CALCIUM				
Hypocalcemia	7.8 - 8.4 mg/dL	7.0 - 7.7 mg/dL	6.1 - 6.9 mg/dL	< 6.1 mg/dL
Hypercalcemia	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL
MAGNESIUM				
Hypomagnesemia	1.2 - 1.4 meq/L	0.9 - 1.1 meq/L	0.6 - 0.8 meq/L	< 0.6 meq/L
BILIRUBIN	> 1.0 - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 x ULN
GLUCOSE				
Hypoglycemia	55 - 64 mg/dL	40 - 54 mg/dL	30 - 39 mg/dL	< 30 mg/dL
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161 - 250 mg/dL	251 - 500 mg/dL	> 500 mg dL
Triglycerides	-----	400 - 750 mg/dL	751 - 1200 mg/dL	> 1200 mg/dL
Creatinine	> 1.0 - 1.5 x ULN	> 1.5 -3.0 x ULN	> 3.0 -6.0 x ULN	> 6.0 x ULN
URIC ACID				
Hyperuricemia	7.5 - 10.0 mg/dL	10.1 - 12.0 mg/dL	12.1 - 15.0mg/dL	>15.0mg/dL

Appendix 1: ATCG Toxicity Grading Table

PARAMETER	GRADE MILD	GRADE MODERATE	GRADE SEVERE	GRADE POTENTIALLY LIFE-THREATENING
LIVER TRANSAMINASE (LFTs)				
AST (SGOT)	1.25 - 2.5 x ULN	2.5 - 5.0 x ULN	5.0 - 10.0 x ULN	> 10.0 x ULN
ALT (SGPT)	0.25 - 2.5 x ULN	2.5 - 5.0 x ULN	5.0 - 10.0 x ULN	> 10.0 x ULN
GGT	1.25 - 2.5 x ULN	2.5 - 5.0 x ULN	5.0 - 10.0 x ULN	> 10.0 x ULN
Alkaline Phosphatase	1.25 - 2.5 x ULN	2.5 - 5.0 x ULN	5.0 - 10.0 x ULN	> 10.0 x ULN
PANCREATIC ENZYMES				
Amylase	> 1.0 - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Pancreatic amylase	> 1.0 - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Lipase	> 1.0 - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
CARDIOVASCULAR				
Cardiac Arrhythmias	-----	Asymptomatic; transient dysrhythmia, no Rx req	Recurrent/persistent dysrhythmia; Rx req	Unstable dysrhythmia; symptomatic; hospitalisation and Rx req
Hypertension	Transient increase > 20mmHg; no Rx	Recurrent; chronic increase > 20mmHg; Rx req	Acute Rx req; outpatient, hospitalisation possible	Hospitalisation req
Hypotension	Transient orthostatic hypotension; no RX	Symptoms correctable with oral fluid Rx	IV fluid req; no hospitalisation req	Hospitalisation req
Pericarditis	Minimal effusion	Mild/mod asymptomatic effusion, no RX	Symptomatic effusion, pain, EKG changes	Tamponade OR pericardiocentesis OR surgery req
Hemorrhage, blood	-----	Mildly symptomatic; no Rx req	gross blood loss OR 1-2 units transfused	Massive blood loss OR > 2 units transfused
GASTROINTESTINAL				
Nausea	Mild Or transient; reasonable intake maintained	Mod discomfort OR intake decreased for > 3 days	Severe discomfort OR minimal intake for ≥3 days	Hospitalisation req
Vomiting	Mild OR transient; 2-3 episodes per day OR mild vomiting lasting < 1 week	Mod OR persistent; 4-5 episodes per day; OR vomiting lasting > 1 week	severe vomiting of all food/fluids in 24 hours OR orthostatic hypotension OR IV Rx req	Hypotensive shock OR hospitalisation req for IV Rx
Diarrhea	Mild OR transient; 3-4 loose stools per day OR mild diarrhea lasting < 1 week	Mod OR persistent 5-7 loose stools per day OR diarrhea lasting ≥ 1 week	Bloody diarrhea OR orthostatic hypotension OR > 7 loose stools/day OR IV Rx req	Hypotensive shock OR hospitalisation req
Oral Discomfort/Dysphagia	Mild discomfort; no difficulty in swallowing	Difficulty swallowing but able to eat drink fluids	Unable to swallow solids; IV fluids req	Unable to drink fluids; severe distension with vomiting

Appendix 1: ATCG Toxicity Grading Table

PARAMETER	GRADE MILD	GRADE MODERATE	GRADE SEVERE	GRADE POTENTIALLY LIFE-THREATENING
RESPIRATORY				
Cough	Transient; no Rx	Treatment associated cough; inhaled bronchodilator	Uncontrolled cough; systemic Rx req	
Bronchospasm	Acute transient; no Rx; FEV1 < 80% - 70% (or peak flow)	Rx req; normalizes with bronchodilator; FEV1 50% - < 70% (or peak flow)	No normalization with bronchodilator; (or FEV1 25% - < 50% or peak flow)	Cyanosis OR retractions; FEV1 < 25% (or intubated peak flow)
Dyspnea	Dyspnea on exertion	Dyspnea with normal activity	Dyspnea at rest	Dyspnea req O ₂ Rx
NEUROLOGIC				
Neuro-cerebellar	Slight incoordination OR dysdiadochokinesia	Intention tremor OR dysmetria OR slurred speech OR nystagmus	Ataxia requiring assistance to walk or arm incoordination interfering with ADLs	Unable to stand
Neuro-psych/mood			Severe mood changes req medical intervention	Acute psychosis req hospitalisation
Paresthesia	Mild discomfort; no Rx req (burning, tingling etc)	Mod discomfort; Rx req with symptomatic improvement	Severe discomfort OR non-narcotic analgesia req	Incapacitating OR narcotic analgesia req; not responsive to non-narcotic analgesia
Neuro-motor	Mild weakness in muscles of feet but able to walk and/or mild decrease in r flexes and/or loss of previously present reflex or development of hyperreflexia and/or unable to do deep knee bends due to weakness	Mod weakness in feet (unable to walk on heels and/or toes); mild weakness in hands, still able to do most tasks	Marked distal weakness (unable to dorsiflex toes or foot drop) and proximal weakness e.g., in hands interfering with ADLs and/or req assistance to walk and/or unable to rise from chair unassisted	Confined to bed or wheel chair because of muscle weakness
Neuro-sensory	Mild impairment (dec sensation e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution	Mod impairment (mod dec sensation e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	Severe impairment (dec or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	Sensory loss involves limbs and trunk

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Appendix 1: ATCG Toxicity Grading Table

PARAMETER	GRADE MILD	GRADE MODERATE	GRADE SEVERE	GRADE POTENTIALLY LIFE-THREATENING
URINALYSIS				
Proteinuria - spot urine 24 hr urine	+1 200mg - 1g loss/day OR < 0.3% OR < 3 g/L	2-3 + 1-2 g loss/day OR 0.3-1.0% OR 3- 10g/L	+4 2 - 3.5g loss/day OR >1.0% OR > 10g/L	Nephrotic syndrome Nephrotic syndrome OR > 3.5g loss/day
Gross Hematuria	Microscopic only	Gross; no clots	Gross plus clots	Obstructive
MISCELLANEOUS				
Fever (oral > 12 hours)	37.7 - 38.5°C OR 100.0 - 101.5°F	38.6 - 39.5°C OR 101.6 - 102.9°F	39.6 40.5°C OR 103 -105°F	> 40.5°C OR > 105°F
Headache	Mild; no Rx req	Mod; or non- narcotic analgesia Rx	Severe; OR responds to initial narcotic Rx	Intractable; OR req repeated narcotic Rx
Allergic Reaction	Pruritus without	Localized urticaria	Generalised urticaria; angioedema	Anaphylaxis
Cutaneous/Rash/Der matitis	Erythema, pruritus	Diffuse maculopapular rash OR dry desquamation	Vesiculation OR moist desquamation OR ulceration	ANY ONE: mucous membrane involvement, suspected Stevens- Johnson (TEN), erythema multiforme, necrosis req surgery, exfoliative dermatitis
Local Reaction (2° parenteral Rx)	Erythema	Induration < 10mm OR inflammation OR phlebitis	Induration >10mm OR ulceration	Necrosis of skin
Fatigue	Normal activity reduced < 25%	Normal activity reduced 25-50%	Normal activity reduced >50%; cannot work	Unable to care for self

Appendix 2:[†]
TELEPHONE FOLLOW-UP QUESTIONNAIRE
FOR SEMI-ANNUAL, ANNUAL, OR END-OF-STUDY REVIEW OF CLINICAL HISTORY

Instructions for Interviewer: This interview will be conducted over the phone by a study investigator only if a patient is unable to be reviewed in the clinic.

SUBJECT NAME:

Date of Birth: |__|_| - |__|_|_|_| - |__|_|
 DD MMM YY

INTERVIEWER SIGNATURE:

Date of Interview: |__|_| - |__|_|_|_| - |__|_|
 DD MMM YY

Study Physician: Circle all appropriate answers for PARTS A, B & C. If respondent answers 'yes' to any of the PART A questions, complete sub-sections and add any additional comments.

All questions refer to the time since the since the last study visit or interview.

PART A: Targeted Review of Clinical History

Please elicit a history to determine whether the subject currently has or has experienced any of the following diseases/conditions (new or exacerbation of existing) since the last review.

Disease, condition or problem	<i>Approximately when did they FIRST notice this condition?</i>	<i>Over the past 12 months have they seen a health care provider for this condition?</i>	<i>Over the past 12 months, have they been hospitalized for this condition?</i>	Study Physician's Comments including Diagnosis
<p>1. New or exacerbated hematologic disorders including laboratory abnormalities?</p> <p><input type="checkbox"/> No (skip to Q2)</p> <p><input type="checkbox"/> Yes</p>	<div style="border: 1px solid black; width: 100%; height: 20px; margin-bottom: 5px;"></div> <div style="display: flex; justify-content: space-between; font-size: small;"> dd mm yy </div>	<p>No.....</p> <p>Yes...</p>	<p>No</p> <p>Yes: <i>(record hospital name)</i></p>	<p>.....</p> <p>.....</p> <p>.....</p>
<p>2. New malignancies including skin cancer?</p> <p><input type="checkbox"/> No (skip to Q3)</p> <p><input type="checkbox"/> Yes</p>	<div style="border: 1px solid black; width: 100%; height: 20px; margin-bottom: 5px;"></div> <div style="display: flex; justify-content: space-between; font-size: small;"> dd mm yy </div>	<p>No.....</p> <p>Yes...</p>	<p>No</p> <p>Yes: <i>(record hospital name)</i></p>	<p>.....</p> <p>.....</p> <p>.....</p>
<p>3. Exposure to possible therapeutic or environmental mutagenic agents including radiotherapy or chemotherapy?</p> <p><input type="checkbox"/> No (skip to Q4)</p> <p><input type="checkbox"/> Yes</p>	<div style="border: 1px solid black; width: 100%; height: 20px; margin-bottom: 5px;"></div> <div style="display: flex; justify-content: space-between; font-size: small;"> dd mm yy </div>	<p>No.....</p> <p>Yes...</p>	<p>No</p> <p>Yes: <i>(record hospital name)</i></p>	<p>.....</p> <p>.....</p> <p>.....</p>

Disease, condition or problem	<i>Approximately when did they FIRST notice this condition?</i>	<i>Over the past 12 months have they seen a health care provider for this condition?</i>	<i>Over the past 12 months, have they been hospitalized for this condition?</i>	Study Physician's Comments including Diagnosis
<p>4. New or exacerbated immunologic/rheumatologic disorder</p> <p><input type="checkbox"/> No (skip to Q5)</p> <p><input type="checkbox"/> Yes</p>	<div style="border: 1px solid black; padding: 2px; display: inline-block;"> ____-____-____ dd mm yy </div>	<p>No....</p> <p>Yes...</p>	<p>No</p> <p>Yes: <i>(record hospital name)</i></p>	<p>.....</p> <p>.....</p>
<p>5. New or exacerbated neurologic disorder</p> <p><input type="checkbox"/> No (skip to Q6)</p> <p><input type="checkbox"/> Yes</p>	<div style="border: 1px solid black; padding: 2px; display: inline-block;"> ____-____-____ dd mm yy </div>	<p>No....</p> <p>Yes...</p>	<p>No</p> <p>Yes: <i>(record hospital name)</i></p>	<p>.....</p> <p>.....</p>
<p>6. Adverse Events other than covered above?</p> <p><input type="checkbox"/> No (skip to PART B)</p> <p><input type="checkbox"/> Yes (complete Q7)</p>	<div style="border: 1px solid black; padding: 2px; display: inline-block;"> ____-____-____ dd mm yy </div>	<p>No....</p> <p>Yes...</p>	<p>No</p> <p>Yes: <i>(record hospital name)</i></p>	<p>.....</p> <p>.....</p>

Disease, condition or problem	<i>Approximately when did they FIRST notice this condition?</i>	<i>Over the past 12 months have they seen a health care provider for this condition?</i>	<i>Over the past 12 months, have they been hospitalized for this condition?</i>	Study Physician's Comments including Diagnosis
<p>7. Was this adverse event serious?</p> <p><input type="checkbox"/> No (skip to PART B)</p> <p><input type="checkbox"/> Yes (complete Q8)</p> <p>Physician must complete SAE Notification Form</p>	<div style="border: 1px solid black; padding: 2px; display: inline-block;"> ____-____-____ dd mm yy </div>	<p>No.....</p> <p>Yes...</p>	<p>No</p> <p>Yes: <i>(record hospital name)</i></p>	<p>.....</p> <p>.....</p> <p>.....</p>
<p>8. For any serious adverse events, list new medications or treatments etc</p>				

PART B: Contact Information

1. Please read subject current address and phone contact details. Is contact information correct?

Yes (skip to Q2)

No: Record updated contact details:
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.....

2. Please read name, address and phone contact details for subjects NOMINATED SECONDARY CONTACT PERSON. Is contact information correct?

Yes (skip to PART C)

No: Record updated contact details:
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PART C: Further Follow-Up

1. Do any findings noted during the interview warrant review of the subject's medical records?

No (skip to Q2)

Yes: specify details:
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2. Do any findings noted during the clinical history interview warrant further safety testing?

No (skip to Q3)

Yes: specify details:
.....

3. Is authorization for the release of medical records to be obtained?

No

Yes: specify details:
.....

Investigator's Signature: _____

Date: |_|_|-|_|_|_|-|_|_|

Appendix 3: PROTOCOL AMENDMENT HISTORY

Amendment 1; 23 June 2006

Applicable sections	Original Text	New/Revised Text	Description and Rationale
SYNOPSIS	OVERVIEW OF STUDY DESIGN: This will be a follow-up study of patients who complete the OTH/OZ1-INT-1 trial.	OVERVIEW OF STUDY DESIGN: This will be a follow-up study of patients previously enrolled in the OTH/OZ1-INT-1 trial.	To include all patients 'enrolled' in the trial, rather than only patients that 'complete' the trial.
SYNOPSIS	New text	POPULATION Participants of the OTH/OZ1-INT-1 Phase II study entitled "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-1 ribozyme (OZ1) in patients with HIV-1 infection" will be asked to consent to continued safety monitoring and gene marking as described in this protocol.	To further clarify the trial population and the means by which they will enter this protocol.
SYNOPSIS	New text	DOSAGE AND ADMINISTRATION All participants of the OTH/OZ1-INT-1 Phase II study received a single dose of transduced CD34+ cells.	To clarify that the dosage and administration of the transduced CD34+ cells relates to a separate protocol.
SYNOPSIS	EFFICACY EVALUATIONS: In addition to safety evaluations, patients may elect to have ongoing analysis of quantitative marking and expression of the gene transfer product in peripheral blood mononuclear cells.	EFFICACY EVALUATIONS: Ongoing analysis of quantitative marking of the gene transfer product (OZ1 and LNL6) in peripheral blood mononuclear cells will be performed as part of the testing of predominant integration sites. This marking data will also be analyzed independently of the integration analysis to detect changes in the number of cells carrying the gene transfer product. In addition to safety evaluations, patients may elect to have ongoing analysis of quantitative expression of the gene transfer product in peripheral blood mononuclear cells.	To specify the level of analysis to be undertaken of the quantitative marking of the gene transfer product in the peripheral blood mononuclear cells as part of integration.
SYNOPSIS	The Time and Events Schedule for this study is shown on the following page.	TIME AND EVENTS SCHEDULE: Follow up visits may be part of routine clinic visits where possible, but must be performed as described in the Time & Events Schedule. Additional unscheduled visits will be made if clinical or biological findings, as described in this protocol, require additional evaluation or investigation. <i>Note: Time and Events Schedule inserted</i>	To clarify procedures associated with visits, both scheduled and unscheduled.

<p>INTRODUCTION 1.2 Toxicology</p>	<p>New text</p>	<p>Viruses like LNL6 have been tested extensively in animal models. (Brenner <i>et al.</i>, 1993; Dunbar <i>et al.</i>, 1995; Economou <i>et al.</i>, 1996; Emmons <i>et al.</i>, 1997; Huhn <i>et al.</i>, 1999). Leukemia has been reported in one bone marrow transplantation study (Li <i>et al.</i> 2002; Baum <i>et al.</i>, 2005) in mice where the blood progenitor cells were infected ex-vivo with a retrovirus containing the nerve growth factor receptor and then re-introduced to the same animal. No hematopoietic alterations were observed in the 5 mice so treated. However, when bone marrow cells were later taken from these mice, pooled and transplanted into secondary irradiated mice, the cells gave rise to hematopoietic disorders in all 10 recipient animals (1 animal showed extramedullary hematopoiesis, 3 had pre-leukemia and 6 developed overt acute myeloid leukemia). The transformed cells of these animals were clonal and retroviral integration was found in a gene (ecotropic viral integration site-1, <i>Evi-1</i>) that may have cooperated with the nerve growth factor receptor to cause leukemia. Several subsequent bone marrow transplantation studies have shown co-operation between insertional mutagenesis of a host gene and a growth promoting gene introduced by the retroviral vector (Du <i>et al.</i>, 2005a and b Modlich <i>et al.</i>, 2005)</p> <p>In another study one of seven rhesus macaque monkeys developed a solid tumor in the kidney approximately five years after transplantation with retrovirally transduced blood progenitor cells (Seggewiss <i>et al.</i>, 2006). Insertional mutagenesis has not been seen previously in approximately 80 large animals followed long-term (Kiem <i>et al.</i>, 2004; Seggewiss <i>et al.</i>, 2006). Confounding factors in this monkey study include the relatively old age of the affected animal, and the fact that it had gone through multiple cycles of blood progenitor cell mobilization, progenitor cell growth outside the animal and <i>in vivo</i> drug selection of the transduced cells. In studies of bone marrow transplantation in mice and non-human primates predominant clones with vector insertions have been seen in genes apparently linked to enhanced hematopoietic cell proliferation, but have not resulted in disease (Seggewiss <i>et al.</i>, 2006; Klein <i>et al.</i>, 2004; Kusticova <i>et al.</i>, 2005; Du <i>et al.</i>, 2005; Nienhuis <i>et al.</i>, 2006) and in the case of 2 patients with Chronic Granulomatous Disease this enhanced expansion appeared to be therapeutic (Ott <i>et al.</i>, 2006)</p>	<p>Inclusion of new data.</p>
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<p>1.3 Clinical Experience</p>	<p>New text</p>	<p><u>Phase I CD4+ Cell Study</u></p> <p>This 'proof of principle' study conducted at St. Vincent's Hospital, Sydney, Australia, involved identical twins discordant for HIV infection. Lymphocytes were collected by apheresis from the HIV-negative twin, purified by CD8+ depletion to yield CD4+ cells and stimulated to expand in cell culture with OKT3 and IL-2 to in excess of 1×10^9 cells. Approximately half of the cells were transduced with LNL6 and the other half with OZ1.</p> <p>Both batches of cells were mixed and infused into the HIV-positive twin (Cooper <i>et al.</i>, 1999). The aim of the study was to determine the feasibility and safety of transduction and infusion of LNL6- and OZ1-containing CD4+ cells and the length of time the cells were detectable thereafter. Preferential survival of OZ1-transduced CD4+ cells was also assessed by semi-quantitative PCR assay.</p> <p>Table 1 presents the cell number and transduction efficiency for the four patients in the CD4+ cell trial. All patients were receiving combination ART while on study. The gene transfer approach was shown to be feasible and safe. The number of transduced CD4+ cells detected post-infusion was very low, < 0.01%, but marked cells are persisting in the peripheral blood at 3.5 years (latest time point censored to date) and continue to express the gene constructs (Cooper <i>et al.</i>, unpublished data). No preferential survival for OZ1 transduced cells is evident.</p> <p>All four patients have been followed for up to 6.5 years. None of the patients experienced any Serious Adverse Events (SAEs) related to the gene transfer procedure either during the 6 months study period or, to date, in the long-term follow-up. Patient R0005 died 5.7 years post infusion due to CMV related pneumonia due to progression of HIV infection. There was no report of malignancy at the time of death. Patient R003 developed an SAE, a basal cell carcinoma, unrelated to the gene transfer product, during the follow up period of the study.</p> <p><i>(Table 1 inserted)</i></p> <p>There were no gene transfer-related adverse events reported. Importantly, there was no evidence of transmission of any infection from donor to recipient. The infusion of CD4+ cells was associated with some minimal light-headedness, headache and pruritus. There was no evidence of graft versus host disease. The changes in plasma HIV RNA (viral load) and CD4+ cell counts</p>	<p>To provide background on other OZ1 Phase I studies.</p>
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		<p>are consistent with those for HIV-infected patients on ART. Replication competent retrovirus (RCR) polymerase chain reaction (PCR) assay of patient samples showed no detectable RCR.</p> <p><u>Phase I CD34+ Cell Study</u></p> <p>This Phase I study was conducted at the University of California Los Angeles (UCLA), California, USA, in 10 patients, using autologous CD34+ cells collected from HIV-1 infected patients. Patients were not myeloablated. Following G-CSF mobilization and apheresis, the CD34+ cells were purified using a CD34+ specific antibody. The CD34+ cells were then introduced into culture with the growth factors Stem Cell Factor (SCF) and Megakaryocyte Growth and Development Factor. Approximately half the cells were transduced with LNL6 and half with OZ1. Both batches of cells were mixed and re-infused. Table 2 presents the purity, total number CD34+ infused (number/kg body weight), percent transduction and number of transduced (LNL6 + OZ1) cells. The first three patients treated received between 0.4%-4% mixture of LNL6- and OZ1-transduced cells. A modification to the transduction procedure was introduced, and retronectin (RN – a recombinant cell adhesion protein) was used to enhance transduction efficiency. The remaining seven patients received cells with transduction efficiencies ranging between 7 - 57 %.</p> <p>(Table 2 inserted)</p> <p>Patients were recruited over the period February 1998 to January 2000. The last three patients were enrolled substantially later (November 1999 to January 2000) than the first seven (February 1998 to October 1998). The time period since infusion for all ten patients ranges from approximately 4 to 6 years. Six patients completed the 3-year study period and 8 patients are participating in long-term follow up. Results to date show gene marking in bone marrow and peripheral blood mononuclear cells, specifically, purified T-cells, monocytes and granulocytes, and in purified naïve and memory CD4+ and CD8+ cells (Amado <i>et al.</i>, 2004). The presence of gene marked cells with the naïve phenotype (CD45RA+/CD62L+) is direct evidence for the production of mature T-cells from the infused CD34+ cells (Amado <i>et al.</i>, 2004, Tough <i>et al.</i>, 1995; Aguila <i>et al.</i>, 1997; McFarland <i>et al.</i>, 2000). Thus, the transduced CD34+ cells have contributed to relevant hematopoietic lineages.</p>	
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		<p>The factors that affected the degree of cell marking in the ten patients in this study were:</p> <ul style="list-style-type: none"> The percentage of CD34+ cell transduction Number of transduced CD34+ cells infused Total number of CD34+ cells infused <p>No gene transfer-related SAEs were reported for any of the treated patients. One patient developed Kaposi's sarcoma, an Adverse Event (AE) reported to be related to the underlying Acquired Immunodeficiency Syndrome (AIDS) rather than the gene transfer product. There were five patients who experienced AEs definitely or possibly related to the G-CSF mobilization procedure. There were two cases of severe bone pain, one case of headache, one of moderate back pain, and one of mild bone pain with mild myalgia and chest pain. In addition, 3 patients experienced a transient mild thrombocytopenia, on or after the infusion procedure; however, only one was reported as related to the G-CSF treatment. There was one report of moderate anxiety related to the apheresis procedure. Only three AEs were possibly related to the re-infusion of the CD34+ cells; one patient developed sweating and one reported nausea, and a third patient developed hypotension during the infusion. All three were categorized as mild. No RCR has been detected by PCR. Long-term follow up and collection of archival samples is ongoing as per the current FDA/CBER recommendations.</p>	
<p>1.4 Clinical Toxicology</p>	<p>To date, LNL6 or similar retroviral vectors have been used in more than 1800 patients in 254 gene transfer clinical trials worldwide (www.wiley.co.uk/genmed). Serious Adverse Events (SAEs) reported in a gene transfer study for X-linked Severe Combined Immunodeficiency (SCID-X1) have led to specific changes to the long term monitoring protocols for recipients of retroviral gene transfer products. In the study of patients with SCID-X1 in whom the gamma common chain gene is absent or defective, eleven children received autologous CD34+ cells transduced with Moloney-derived retroviral vector containing the gamma common chain gene. A clinical response was evident in nine children, two of whom developed T cell leukemia at</p>	<p>To date, LNL6 or similar retroviral vectors have been used in more than 1800 patients in 250 gene transfer clinical trials worldwide (www.wiley.co.uk/genmed). The <i>neo^R</i> gene product, neomycin phosphotransferase, has not been shown to be antigenic in humans (Riddell <i>et al.</i>, 1996). There may be a greater potential risk of an antigenic response in the OZ1 group in the current study because the number of transduced cells will be greater than in the Phase I trials. Therefore blood samples will be analyzed for cytotoxic T-lymphocyte response to neomycin phosphotransferase (<i>neo^R</i> specific CTLs). Any patient who develops a CTL response to the <i>neo^R</i> gene product may be ineligible to receive future infusions of any gene transfer products that express neomycin phosphotransferase.</p> <p>SAEs reported in a gene transfer study for X-linked Severe Combined Immunodeficiency (SCID-X1) have led to specific</p>	<p>Inclusion of new safety data.</p>

<p>approximately 3 years after infusion of the transduced CD34+ cells (Baum <i>et al.</i>, 2003; Buckley <i>et al.</i>, 2002; Cavazzana-Calvo <i>et al.</i>, 2000 & 2004; Check 2003; Dave <i>et al.</i>, 2004; Fischer 2000; Hacein-Bey-Abina <i>et al.</i>, 2002 & 2003; Kaiser 2003; Williams & Baum 2003).</p> <p>The leukemic clones in both children, contained a single copy of the intact retroviral vector near or within the LMO2 gene. The LMO2 protein is known from previous work (primarily in mice) to act as a bridge molecule in transcriptional factor complexes. Abnormal expression of the LMO2 gene appears to increase susceptibility to leukemia by blocking T cell differentiation (Drynan <i>et al.</i>, 2001; McCormack and Rabbitts 2004; Orkin 1995; Rabbitts 2001). Retroviral insertion into LMO2 has been found in a third patient from the same study. This patient, who has not shown any signs of leukemia, is being monitored closely (McCormack and Rabbitts 2004).</p> <p>Expression of the introduced gamma common chain is essential to the T cell reconstitution in these children but also may be a factor in the development of the leukemias. The rapid increase in T cells that results from expression of the introduced gamma common chain gene does not occur normally in embryonal and early childhood hematopoiesis. Thus it has been speculated that the dysregulated hematopoiesis associated with abnormal expression of LMO2 and the considerable survival advantage conferred by the introduced gamma common chain gene to cells in the T lymphocyte lineage are the main factors that contributed to the development of leukemias. (Baum <i>et al.</i>, 2003; Buckley <i>et al.</i>, 2002; Cavazano-Calvo <i>et al.</i>, 2004; Dave <i>et al.</i>, 2004; Hacein-Bey-Abina <i>et al.</i>, 2003; Kaiser .2003; Leonard 2000; McCormack and Rabbitts 2004; Williams & Baum 2003;).</p> <p>Other possible contributing factors to the</p>	<p>changes to the long term monitoring protocols for recipients of retroviral gene transfer products. In that study, eleven children with SCID-X1 received autologous CD34+ cells transduced with Moloney-derived retroviral vector containing the cytokine gamma common chain gene. A clinical response was evident in nine children. In 2002 two of the children, both who of whom had responded well to the procedure, developed T cell leukemia approximately 3 years after infusion of the transduced CD34+ cells (Baum <i>et al.</i>, 2003; Buckley <i>et al.</i>, 2002; Cavazzana-Calvo <i>et al.</i>, 2000 & 2004; Check. 2003; Dave <i>et al.</i>, 2004; Fischer 2000; Hacein-Bey-Abina <i>et al.</i>, 2002 & 2003 Kaiser 2003; Williams & Baum 2003). One of the children with leukemia died in October 2004, but the other child continues to respond to treatment. The leukemic clones in all three of the children contained a copy of the intact retroviral vector near or within the LMO2 gene (Frederickson, 2005). The LMO2 protein is known from previous work (primarily in mice) to act as a bridge molecule in transcriptional factor complexes. Abnormal expression of the LMO2 gene appears to increase susceptibility to leukemia by blocking T cell differentiation (Drynan <i>et al.</i> 2001; McCormack and Rabbitts 2004; Orkin 1995; Rabbitts 2001). (). The relevant regulatory agencies continue to monitor these studies closely.</p> <p>Expression of the introduced gamma common chain is essential to the T cell reconstitution in these children but also may be a factor in the development of the leukemias. The rapid increase in T cells that results from expression of the introduced gamma common chain gene does not occur normally in embryonal and early childhood hematopoiesis. Thus it has been speculated that the dysregulated hematopoiesis associated with abnormal expression of LMO2 and the considerable survival advantage conferred by the introduced gamma common chain gene to cells in the T lymphocyte lineage are the main factors that contributed to the development of leukemias. (Baum <i>et al.</i>, 2003; Buckley <i>et al.</i>, 2002; Cavazzana-Calvo <i>et al.</i>, 2004; Dave <i>et al.</i>, 2004; Hacein-Bey-Abina <i>et al.</i>, 2003; Kaiser .2003; Leonard 2000; McCormack and Rabbitts 2004; Williams & Baum 2003). Investigations in mice have indicated an apparent cooperation between LMO2 and the gamma common chain gene (Berns, 2004; Woods <i>et al.</i>, 2006)</p> <p>Other possible factors contributing to the development of leukemia are the disease background including the unusual</p>	
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	<p>development of leukemia in these children are the disease background including the unusual properties of the bone marrow derived CD34+ cells in young children and the high numbers of CD34+ cells that were transduced and infused (approximately 2×10^7 cells/kg) (Cavazano-Calvo <i>et al.</i>, 2004; Dave <i>et al.</i>, 2004; Hacein-Bey-Abina <i>et al.</i>, 2003; McCormack and Rabbitts 2004; Williams & Baum 2003).</p> <p>The two cases of insertional oncogenesis led to the FDA/CBER requirements to include the number and any clonality of vector integration sites in peripheral blood mononuclear cells (Schmidt <i>et al.</i>, 2001 & 2002). If a predominant integration site is detected, a second test will be conducted 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 confirmed, and particularly when there is expansion of a cellular clone, the patient will be monitored closely for signs of oncogenesis, so that treatment can be initiated as early as possible.</p>	<p>properties of the bone marrow derived CD34+ cells in young children and the high numbers of CD34+ cells that were transduced and infused (approximately 2×10^7 cells/kg) (Cavazzana-Calvo <i>et al.</i>, 2004; Dave <i>et al.</i>, 2004; Hacein-Bey-Abina <i>et al.</i>, 2003; McCormack and Rabbitts 2004; Williams & Baum 2003).</p> <p>In contrast to the studies by Fischer and colleagues, a similar trial for SCID-X1 by Thrasher and colleagues in the United Kingdom have not shown these SAEs (Gaspar <i>et al.</i>, 2004; Gaspar and Thrasher, 2005).</p> <p>The initial two cases of insertional oncogenesis led to the FDA/CBER requirements to extend the monitoring for patients in this study to include the number and any clonality of vector integration sites in peripheral blood mononuclear cells (Schmidt <i>et al.</i>, 2001 & 2002). If a predominant integration site is detected, a second test will be conducted 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 confirmed, and particularly when there is expansion of a cellular clone, the patient will be monitored closely for signs of oncogenesis, so that treatment can be initiated as early as possible. This recommendation was not modified by the third case (Baum, 2005; Check, 2005).</p>	
<p>2. OBJECTIVES</p>	<p>1. To undertake long term safety monitoring for any development of:</p> <ol style="list-style-type: none"> a. Replication Competent Retrovirus (RCR) b. Clonal expansion of cells with a predominant OZ1 or LNL6 vector insertion site c. Insertional oncogenesis <p>2. To assess quantitative marking and expression of the gene transfer product in peripheral blood mononuclear cells over time.</p>	<p>1. To undertake long term safety monitoring for any development of:</p> <ol style="list-style-type: none"> a. Replication Competent Retrovirus (RCR) b. Clonal expansion of cells with a predominant OZ1 or LNL6 vector insertion site c. Insertional oncogenesis <p>2. To archive/store plasma and PBMC samples for other safety testing as maybe required.</p> <p>3. To assess quantitative marking and expression of the gene transfer product in peripheral blood mononuclear cells over time.</p>	<p>To define the use of stored samples, should additional safety testing be required.</p>
<p>3. OVERVIEW OF STUDY DESIGN</p>	<p>New text</p>	<p>The patients who were enrolled in the OTH/OZ1-INT-1 trial entitled “A randomized Phase II, double blind, controlled trial to evaluate the safety and efficacy of autologous CD34+ hematopoietic cells transduced with placebo or an anti-HIV-1 ribozyme (OZ1) in patients with HIV-1 infection” will continue to</p>	<p>To further clarify the trial population and the means by which they will enter this protocol.</p>

		be assessed under this Long Term Follow-Up Protocol. Where possible follow up visits will coincide with routine clinic visits.	
4. COMPLIANCE	New text	<p>1.The semi-annual visit interval is 6 months ± 6 weeks (for years 2.5-5). The annual visit interval is 12 months ± 12 weeks (year 6+).</p> <p>2.CBC/Differential data will be obtained specifically as part of the follow up procedures for a total of fifteen (15) years following the time of the infusion in the original phase II study. After this date, CBC/Differential data obtained as part of routine clinic assessments will be collected in the study CRF on an unscheduled basis (as per the unscheduled visit in the Time & Events Schedule). Failure to obtain this data will <u>not</u> be considered protocol non-compliance.</p> <p>3.In the event that a Recipient dies, irrespective of cause of death or time after the gene transfer procedure, a request will be made by the Principal Investigator to the next of kin for an autopsy to assess for the presence of 1) RCR and 2) LNL6 or OZ1 containing cells. If efforts to obtain permission for an autopsy are unsuccessful or not practicable, it will not be considered as protocol non-compliance. If an autopsy is performed, a copy of the autopsy report will be obtained and the cause of death and any significant observations noted in the Serious Adverse Event report.</p> <p>4. In the event that the Recipient undergoes a biopsy or surgical removal of a tumor, an attempt will be made by the Principal Investigator to obtain a sample of tissue for the assessment of the presence of 1) RCR and 2) LNL6 or OZ1 containing cells. If efforts to obtain a tissue sample are unsuccessful or not practicable, it will not be considered as protocol non-compliance.</p>	To be consistent with the other OZ1 long-term follow-up protocols.
6. CONCOMITANT THERAPY AND ACTIVITIES	Information regarding medications (prescriptions and/or over-the-counter) or therapies being taken or administered will be collected if the subject has a serious adverse event.	Information on current medications or other therapies will not be collected, unless required for submission of a Serious Adverse Event report.	To further define which concomitant medications will be collected.
7. STUDY EVALUATIONS	The Time and Events Schedule included in the Synopsis summarizes the frequency and timing of the various efficacy and safety measurements. Visit schedules are fixed from the day of the original infusion of autologous CD34+ cells as per the OTH/OZ-1-INT-1 protocol. <u>Allowed Visit Intervals</u>	The Time and Events Schedule included in the Synopsis summarizes the frequency and timing of the various efficacy and safety measurements. Visit schedules are fixed from the day of the original infusion of autologous CD34+ cells as per the OTH/OZ-1-INT-1 protocol. <u>Allowed Visit Intervals</u> Visit interval: 6 months	A breakdown of years 2-5, 5-15, 15+ and unscheduled visits has been included.

<p>Visit interval: 6 months Allowed window: 6 months \pm 6 weeks Visit interval: 12 months Allowed window: 12 months \pm 612 weeks. The following assessments and evaluations will be completed as described in the Time & Events Schedule during the various phases of the study: Complete Blood Count (CBC), differential and platelet count. Archival storage of plasma and PBMC samples. PCR analysis of PBMCs for the presence of Replication-Competent Retrovirus (RCR) using primers specific for amphotropic <i>env</i> retroviral gene sequences. Optional quantitative analysis of OZ1 DNA (PCR) in total PBMC Optional quantitative analysis of OZ1 RNA (RT-PCR) in total PBMC if OZ1 DNA is detected Testing for clonality of OZ1 integration in PBMC samples (PCR). Recording of serious adverse events (SAEs). 2 to 5 years post-Infusion <u>Visits will be at six monthly intervals from year 2 to year 5 post-infusion.</u> The Long Term Follow-up visits at Year 2.5, 3.5 and Year 4.5 post-infusion, will have the following assessments : CBC, differential and platelet count. Testing for clonality of OZ1 integration sites in PBMC samples (PCR). Recording of Serious Adverse Events (SAEs). The Long Term Follow-up visits at Year 3, 4 and 5 post-infusion the following assessments will be completed: CBC, differential and platelet count. Testing for clonality of OZ1 integration sites in</p>	<p>Allowed window: 6 months \pm 6 weeks Visit interval: 12 months Allowed window: 12 months \pm 12 weeks. The following assessments and evaluations will be completed as described in the Time & Events Schedule during the various phases of the study: 2 to 5 years post-Infusion <u>Visits will be at six monthly intervals from year 2 to year 5 post-infusion.</u> The Long Term Follow-up visits at Year 2.5, 3.5 and Year 4.5 post-infusion, will have the following assessments: Clinical History and Physical Examination including a detailed record of: -exposure to possible mutagenic agents eg radiotherapy or chemotherapeutic agents -new malignancies -new or exacerbated preexisting neurologic, autoimmune and hematologic disorders. Complete Blood Count (CBC), differential and platelet count. Testing for clonality of OZ1/LNL6 integration in PBMC samples (PCR) including gene marking (quantitative OZ1 DNA-PCR). Recording of adverse events (AEs). The Long Term Follow-up visits at Year 3, 4 and 5 post-infusion the following assessments will be completed: Clinical History and Physical Examination including a detailed record of: -exposure to possible mutagenic agents eg radiotherapy or chemotherapeutic agents -new malignancies -new or exacerbated preexisting neurologic, autoimmune and hematologic disorders. Complete Blood Count (CBC), differential and platelet count. Archival storage of plasma and PBMC samples for Replication-Competent Retrovirus (RCR) and other safety testing as required Testing for clonality of OZ1/LNL6 integration in PBMC samples (PCR) including gene marking (quantitative OZ1 DNA-PCR). Quantitative analysis of PBMC sample for OZ1 RNA (RT PCR) if</p>	
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	<p>PBMC samples (PCR). Archival storage of plasma and PBMC samples. PBMC archive for PCR analysis for the presence of Replication-Competent Retrovirus (RCR) using primers specific for amphotropic <i>env</i> retroviral gene sequences. Both PBMC cell pellets and cryopreserved cells are required for archive. Recording of SAEs Year 5+ <u>Annual Visits</u> Annual visits will include all assessments listed in the 2-5 year annual visits above. If the full blood count/differential and clonality of OZ1 integration in PBMC show no significant abnormality during the first 15 years post-infusion for patients receiving OZ1, these tests will no longer be performed for the remaining Long Term Follow-up Protocol. It is currently required that all other assessments continue for the lifetime of the patient.</p>	<p>OZ1 DNA is detected. Recording of adverse events (AEs). Annual Visits Year 5-15 post infusion Clinical History and Physical Examination including a detailed record of: -exposure to possible mutagenic agents eg radiotherapy or chemotherapeutic agents -new malignancies -new or exacerbated preexisting neurologic, autoimmune and hematologic disorders. Complete Blood Count (CBC), differential and platelet count. Archival storage of plasma and PBMC samples for Replication-Competent Retrovirus (RCR) and other safety testing as required Testing for clonality of OZ1/LNL6 integration in PBMC samples (PCR) including gene marking (quantitative OZ1 DNA-PCR). Quantitative analysis of PBMC sample for OZ1 RNA (RT PCR) if OZ1 DNA is detected. Recording of adverse events (AEs). Annual Visits Year 15+ post infusion Clinical History and Physical Examination including a detailed record of: -exposure to possible mutagenic agents eg radiotherapy or chemotherapeutic agents -new malignancies -new or exacerbated preexisting neurologic, autoimmune and hematologic disorders. Archival storage of plasma and PBMC samples for Replication-Competent Retrovirus (RCR) and other safety testing as required Recording of adverse events (AEs). If the full blood count/differential and platelet count and the clonality of OZ1 integration in PBMC show no significant abnormality during the first 15 years post-infusion these tests will no longer be performed for the remaining Long Term Follow-up Protocol. It is currently required that all other assessments continue for the lifetime of the patient. Unscheduled Assessments In addition to the annual follow up visit, unscheduled procedures may be performed in the event of an adverse event.</p>	
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7.2 Optional Efficacy Evaluation	<p>Patients will have the option of consenting to the collection of additional blood samples for the ongoing assessment of OZ1. The following efficacy assessments will continue as detailed in the Time & Events Schedule: Quantitative analysis of PBMC sample for OZ1 DNA (PCR) and OZ1 RNA (RT PCR)</p>	<p>Patients will have the option of consenting to the collection of additional blood samples for the ongoing assessment of OZ1 expression (OZ1 RNA- RTPCR).</p>	<p>Specific efficacy assessments included.</p>
7.3 Safety Evaluations	<p><u>Gene Transfer Product Safety Testing</u> Testing for clonality of OZ1 integration in PBMC using PCR. If a predominant integration site is detected, the patient will be retested within three 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 dominant integration site is present and, particularly when there is expansion of a cellular clone, the patient will be monitored closely for signs of cancer, so that any potential treatment can be initiated as early as possible. Any confirmed finding of a predominant integration site will be reported as a serious adverse event (SAE). “Predominant integration site” is defined as an integration site which has a density of at least 50% of the total signal detected by PCR.</p>	<p><u>Gene Transfer Product Safety Testing</u> Testing for clonality of OZ1 integration in PBMC using PCR. If a predominant integration site is detected, the patient will be retested within three 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 dominant integration site is present and, particularly when there is expansion of a cellular clone, the patient will be monitored closely for signs of cancer, so that any potential treatment can be initiated as early as possible. 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 % of cells marked by the vector (quantitative OZ1 DNA PCR) is >1% of the test cell population. Any confirmed finding of a predominant integration site i.e. present on at least two consecutive samples will be reported as a serious adverse event (SAE)</p>	<p>General rewording. Specify additional SAE reporting requirements.</p>
9.1 Efficacy Evaluation	<p>There will be ongoing assessment of quantitative marking and expression of the gene transfer product in PBMC</p>	<p>Ongoing analysis of quantitative marking of the gene transfer product (OZ1 and LNL6) in peripheral blood mononuclear cells will be performed as part of the testing of OZ1 or LNL6 vector integration sites. This data will be used to independently assess changes in the number of peripheral blood mononuclear cells that carry the gene transfer product over time. Patients will have the option of consenting to the collection of additional blood samples for the ongoing assessment of OZ1 expression (OZ1 RNA- RTPCR).</p>	<p>To clarify the use of the data obtained from this analysis.</p>
9.2 Safety Evaluations	<p>Serious Adverse Event data will be assigned a body system and preferred term using the MedDRA coding dictionary, Version 6.0. All Serious Adverse Events (SAEs) will be</p>	<p>Serious Adverse Event data will be assigned a body system and preferred term using the current MedDRA coding dictionary. All Serious Adverse Events (SAEs) will be recorded with respect to severity as per the ACTG 285 Toxicity Table (See Appendix 1).</p>	<p>The current version of the MedDRA dictionary will be used. Description of safety</p>

	<p>recorded with respect to severity as per the ACTG 285 Toxicity Table (See Appendix 1). Serious Adverse Events will be summarized either in a tabular form, or via data listings. Data will be summarized annually for regulatory reporting.</p>	<p>Serious Adverse Events will be summarized either in a tabular form, or via data listings. Data will be summarized annually for regulatory reporting.</p>	<p>evaluations expanded to include all clinical observations.</p>
<p>10.2 Procedures Serious Adverse Events</p>	<p>Only Serious Adverse Events (SAEs) that are “possibly”, “probably” or “very likely” related to the study drug that occur from two years after infusion will be reported on a SAE form by the Investigator. Death or malignancies (except Basal Cell or Squamous Cell Carcinomas) should be reported, regardless of causality assessment. All other SAEs (unrelated to the drug) will be recorded in the CRF as a summary of the event. SAEs may be reported by the patient to the site at the 6 monthly or annual follow up visits or via spontaneous reporting between follow up visits. For each serious adverse event reported, the Investigator should obtain all the information required to complete the Serious Adverse Event Form (if applicable), in accordance with the guidelines that accompany it. All measures required for serious adverse event management must be recorded in the source document and reported according to Sponsor instructions. Patients (or their designee, if appropriate) must be provided with a “trial card” indicating the name of the investigational product, the trial number, the Investigator’s name and a 24-hour emergency contact number. All serious adverse events occurring during clinical trials must be reported to the appropriate Sponsor contact person by investigational staff within 24 hours of their knowledge of the event. Information regarding serious adverse events will be transmitted to JJR using the Serious Adverse Event Form, which must be signed by a member of the investigational staff. The initial report of a serious adverse event may be made by telephone or facsimile (FAX). A telephone report of a serious</p>	<p>Only Serious Adverse Events (SAEs) that are “possibly”, “probably” or “very likely” related to the study drug that occur from two years after infusion will be reported on a SAE form by the Investigator. Death or malignancies (except Basal Cell or Squamous Cell Carcinomas) should be reported, regardless of causality assessment. All other SAEs (unrelated to the drug) will be recorded in the CRF as a summary of the event. SAEs may be reported by the patient to the site at the follow up visits or via spontaneous reporting between follow up visits. For each serious adverse event reported, the investigational staff should obtain all the information required to complete the Serious Adverse Event Form (if applicable), in accordance with the guidelines. All measures required for serious adverse event management must be recorded in the source document and reported according to Sponsor instructions. All reportable serious adverse events must be reported to the appropriate Sponsor contact person by investigational staff within 24 hours of their knowledge of the event. If the SAE is a death or a life threatening event the Investigator must notify the Sponsor immediately by both telephone and FAX. The completed SAE form must be transmitted by FAX to JJR within 24 hours of knowledge of the event. The Investigator must provide the following minimal information: Protocol number, patient’s initials and date of birth, patient number or medication code number, date of treatment, nature of the adverse event and Investigator’s attribution. All serious adverse events must be followed until any of the following occurs: the event resolves; the event stabilizes; the event returns to baseline, if a baseline value is available; or the event can be attributed to agents other than the study drug or to factors unrelated to study conduct. The cause of death of a patient in a clinical trial, whether the event is expected or associated with the investigational agent, is</p>	<p>To define specific SAE and pregnancy reporting responsibilities.</p>

	<p>adverse event must be followed by a completed Serious Adverse Event Form from the investigational staff within one working day. The Investigator must provide the following minimal information: Protocol number, patient's initials and date of birth, patient number or medication code number, period of intake, nature of the adverse event and Investigator's attribution.</p> <p>All serious adverse events must be followed until any of the following occurs:</p> <ul style="list-style-type: none"> the event resolves; the event stabilizes; the event returns to baseline, if a baseline value is available; or the event can be attributed to agents other than the study drug or to factors unrelated to study conduct. <p>The cause of death of a patient in a clinical trial, whether the event is expected or associated with the investigational agent, is considered a serious adverse event.</p> <p>If there is evidence of leukemia (proven or strong clinical suspicion), RCR or a predominant integration site the Sponsor assumes responsibility for reporting these serious adverse events to the relevant regulatory authorities in an expedited manner.</p> <p>The Sponsor will also report to the Investigator all serious adverse events that are unlisted and associated with the use of the drug. The Investigator must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) in accordance with local regulations.</p> <p>Any event requiring hospitalisation (or prolongation of hospitalisation) that occurs during the course of a patient's participation in a clinical study must be reported as a serious adverse event, except hospitalisations for:</p> <ul style="list-style-type: none"> social reasons in absence of an adverse event; surgery or procedure planned prior to entry into the 	<p>considered a reportable serious adverse event.</p> <p>If there is evidence of leukemia (proven or strong clinical suspicion), RCR or a predominant integration site the Sponsor assumes responsibility for reporting these serious adverse events to the relevant regulatory authorities in an expedited manner.</p> <p>The Sponsor will also report to the Investigator all serious adverse events that are unlisted and associated with the use of the drug.</p> <p>The Investigator must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) in accordance with local regulations.</p> <p>Any event requiring hospitalisation (or prolongation of hospitalisation) that occurs during the course of a patient's participation in a clinical study is a serious adverse event, except hospitalisations for:</p> <ul style="list-style-type: none"> • social reasons in absence of an adverse event; • surgery or procedure planned prior to entry into the study. <p>Pregnancy</p> <p>Pregnancy must be reported by the investigational staff within 24 hours of their knowledge of the event using the JJR SAE Notification Form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.</p> <p>In the event that, while enrolled in the trial, a male patient impregnates his partner, the Sponsor should be notified by completion of a Pregnancy Notification Form faxed to the Sponsor. The outcome of the pregnancy and any postnatal sequelae in the infant should also be required.</p>	
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	<p>study.</p> <p>PREGNANCY Any pregnancy occurring during clinical studies must be reported by the investigational staff within 1 working day of their knowledge of the event using the Pregnancy Notification Form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required. In the event that, while enrolled in the trial, a male patient impregnates his partner, the Sponsor should be notified by completion of a Pregnancy Notification Form faxed to the Sponsor. The outcome of the pregnancy should also be reported.</p>		
<p>12.9 Use of Information and Publication</p>	<p>All information concerning placebo and OZ1, JJR operations, patent application, formulas, manufacturing processes, basic scientific data, and formulation information, supplied by the Sponsor to the Investigator and not previously published, is considered confidential and remains the sole property of JJR. The Investigator agrees to use this information only to accomplish this study and will not use it for other purposes without the Sponsor's written consent. The Investigator understands that the information developed in the clinical study will be used by JJR in connection with the continued development of OZ1, and thus may be disclosed as required to other clinical Investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study. Guidelines regarding publication and presentation of study data are outlined in the study Investigator Agreement.</p>	<p>All information concerning placebo and OZ1, JJR operations, patent application, formulas, manufacturing processes, basic scientific data, and formulation information, supplied by the Sponsor to the Investigator and not previously published, is considered confidential and remains the sole property of JJR. The Investigator agrees to use this information only to accomplish this study and will not use it for other purposes without the Sponsor's written consent. The Investigator understands that the information developed in the clinical study will be used by JJR in connection with the continued development of OZ1, and thus may be disclosed as required to other clinical Investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study.</p>	<p>Guidelines regarding publication and presentation of study data have been provided elsewhere in study documentation.</p>

<p>13. REFERENCES</p>	<p>16. REFERENCES</p>	<p>Bahner, I., C. Zhou, X. J., Yu, Q. L. Hao, J. C. Guatelli and D. B. Kohn. Comparison of trans-Dominant inhibitory mutant human immunodeficiency virus type-1 genes expressed by retroviral vectors in human T-Lymphocytes. <i>J Virol</i>, 1993; 67: 3199-3207</p> <p>Baum, C. A Balanced Decision? Regulatory Reaction to the “Third Child”. <i>Molecular Therapy</i> 2005; 11(6): 819-820.</p> <p>Berns, A Good News for Gene Therapy. <i>N Engl J Med</i>, 2004; 350(16): 1679-1680</p> <p>Boyd, K.E., Xiao, Y.Y., Poholek, A., Copeland, N.G., Jenkins, N.A. and Perkins, A.S. <i>Sox4</i> cooperates with <i>Evi1</i> in AKXD-23 myeloid tumors via transactivation of proviral LTR. <i>Blood</i>, 2006; 107 (2): 733-741.</p> <p>Du, Y., Jenkins, N.A. and Copeland, N.G. Insertional mutagenesis identifies genes that promote the immortalization of primary bone marrow progenitor cells. <i>Blood</i>, 2005; 106 (12): 3932-3939.</p> <p>Bahner, I., C. Zhou, X. J., Yu, Q. L. Hao, J. C. Guatelli and D. B. Kohn. Comparison of trans-Dominant inhibitory mutant human immunodeficiency virus type-1 genes expressed by retroviral vectors in human T-Lymphocytes. <i>J Virol</i>, 1993; 67: 3199-3207</p> <p>Baum, C. A Balanced Decision? Regulatory Reaction to the “Third Child”. <i>Molecular Therapy</i> 2005; 11(6): 819-820.</p> <p>Berns, A Good News for Gene Therapy. <i>N Engl J Med</i>, 2004; 350(16): 1679-1680</p> <p>Boyd, K.E., Xiao, Y.Y., Poholek, A., Copeland, N.G., Jenkins, N.A. and Perkins, A.S. <i>Sox4</i> cooperates with <i>Evi1</i> in AKXD-23 myeloid tumors via transactivation of proviral LTR. <i>Blood</i>, 2006; 107 (2): 733-741.</p> <p>Du, Y., Jenkins, N.A. and Copeland, N.G. Insertional mutagenesis identifies genes that promote the immortalization of</p>	<p>Addition of new references</p>
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		<p>Du, Y., Spence, S.E., Jenkins, N.A. and Copeland, N.G. Cooperating cancer-gene identification through oncogenic-retrovirus-induced insertional mutagenesis. Blood, 2005; 106(7): 2498-2505.</p> <p>Fischer, A., Hacein-Bey-Abina and Cavazanna-Calvo, M. Gene therapy for metabolic diseases. J Inherit Metab Dis, 2006; 29: 409-412.</p> <p>Frederickson RM. Report from the 2nd Stem Cell Clonality and Genotoxicity Retreat. Mol Ther 2005; 12: 379-383</p> <p>Gaspar, H.B., Parsley, K.P., Howe, S., King, D., Gilmour, K.C., Sinclair, J., Brouns, G., Schmidt, M., Von Kalle, C., Barington, T., Jacobsen, M.A., Christensen, H.O., Ghoniaum, A.A., White, H.N., Smith, J.L., Levinsky, R.J., Ali, R.R., Kinnon, C. and Thrasher, A.J. Gene Therapy of X-linked severe combined immunodeficiency by use of a pseudotyped gammaretroviral vector. The Lancet, 2004; 364: 2181-2187.</p> <p>primary bone marrow progenitor cells. Blood, 2005; 106 (12): 3932-3939.</p> <p>Du, Y., Spence, S.E., Jenkins, N.A. and Copeland, N.G. Cooperating cancer-gene identification through oncogenic-retrovirus-induced insertional mutagenesis. Blood, 2005; 106(7): 2498-2505.</p> <p>Fischer, A., Hacein-Bey-Abina and Cavazanna-Calvo, M. Gene therapy for metabolic diseases. J Inherit Metab Dis, 2006; 29: 409-412.</p> <p>Frederickson RM. Report from the 2nd Stem Cell Clonality and Genotoxicity Retreat. Mol Ther 2005; 12: 379-383</p> <p>Gaspar, H.B., Parsley, K.P., Howe, S., King, D., Gilmour, K.C., Sinclair, J., Brouns, G., Schmidt, M., Von Kalle, C., Barington, T., Jacobsen, M.A., Christensen, H.O., Ghoniaum, A.A., White, H.N., Smith, J.L., Levinsky, R.J., Ali, R.R., Kinnon, C. and Thrasher, A.J. Gene Therapy of X-</p>	
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Amendment 2; 28 August 2007

Applicable sections	Original Text	New/Revised Text	Description and Rationale
SYNOPSIS	It is currently a requirement of the United States Food and Drug Administration (FDA) that all individuals receiving retroviral gene transfer products are followed indefinitely.	It is currently a requirement of the United States Food and Drug Administration (FDA) that all individuals receiving retroviral gene transfer products are followed for the life.	Clarification regarding the lifetime follow-up of individuals receiving retroviral gene transfer products
Time and Events Schedule	New Text	<p>Contact details updated for subject and nominated secondary contact</p> <p>If the percentage of cells marked by the vector (quantitative OZ1 DNA-PCR) is less than 1% of the test cell population, the site of integration will not be investigated.</p>	<p>Addition of scheduled review of contact details to facilitate long term follow-up</p> <p>Clarification regarding the analysis of the site of integration</p>
2. Objectives	a. Replication Competent Retrovirus	Deleted	RCR assessment undertaken as safety testing under item 2.
7. STUDY EVALUATIONS 7.1 Study Procedures by Visit	<p>New Text</p> <p>new or exacerbated preexisting neurologic, autoimmune and hematologic disorders</p>	<p>In the event that a subject is unable to attend the clinic within the allowed visit window, a telephone interview can be conducted to collect information on important medical events since the last study visit (or telephone interview). Refer to Appendix 2 for the interview questionnaire.</p> <p>new or exacerbated preexisting neurologic, rheumatologic, autoimmune and hematologic disorders</p>	<p>Addition of a Telephone Questionnaire to facilitate long term follow up</p> <p>Addition of “rheumatologic”.</p>
7.3 Safety Evaluations Gene Transfer Product Safety Testing	New Text	Testing for clonality of OZ1/LNL6 integration in PBMC samples (PCR) will proceed if the percentage of cells marked by the vector (quantitative OZ1 DNA-PCR) is greater than or equal to 1% of the test cell population.	Clarification regarding the analysis of the site of integration

<p>9. STATISTICAL METHODS</p>	<p>Statistical analysis of data collected during the Long Term Follow-up Trial will be performed annually.</p>	<p>Statistical analysis of data collected during the Long Term Follow-up Trial will be performed every 5 years.</p> <p>Clinical history, physical examination findings, CBC and AEs will be listed and summarized in a tabular form. AE data will be summarized annually for regulatory reporting.</p>	<p>Interval between statistical analyses increased to allow the accumulation of sufficient data</p> <p>Description of safety evaluations expanded to include all clinical observations.</p>
<p>9.2 Safety Evaluations</p>	<p>Serious Adverse Event data will be assigned a body system and preferred term using the current MedDRA coding dictionary. All Serious Adverse Events (SAEs) will be recorded with respect to severity as per the ACTG 285 Toxicity Table (See Appendix 1). Serious Adverse Events will be summarized either in a tabular form, or via data listings. Data will be summarized annually for regulatory reporting.</p>	<p>All AE data will be coded to a body system and preferred term using the current MedDRA coding dictionary. Clinical history, physical examination findings, CBC and AEs will be listed and summarized in a tabular form. AE data will be summarized annually for regulatory reporting.</p>	<p>Description of safety evaluations expanded to include all clinical observations.</p>

<p>10. ADVERSE EVENT REPORTING</p> <p>10.2 PROCEDURES ADVERSE EVENTS</p>	<p>Only Serious Adverse Events (SAEs) that are “possibly”, “probably” or “very likely” related to the study drug that occur from two years after infusion will be reported on a SAE form by the Investigator. Death or malignancies (except Basal Cell or Squamous Cell Carcinomas) should be reported, regardless of causality assessment. All other SAEs (unrelated to the drug) will be recorded in the CRF as a summary of the event. SAEs may be reported by the patient to the site at the follow up visits or via spontaneous reporting between follow up visits.</p> <p>For each serious adverse event reported, the investigational staff should obtain all the information required to complete the Serious Adverse Event Form (if applicable), in accordance with the guidelines. All measures required for serious adverse event management must be recorded in the source document and reported according to Sponsor instructions.</p> <p>All reportable serious adverse events must be reported to the appropriate Sponsor contact person by investigational staff within 24 hours of their knowledge of the event.</p> <p>If the SAE is a death or a life threatening event the Investigator must notify the Sponsor immediately by both telephone and FAX. The completed SAE form must be transmitted by FAX to JJR within 24 hours of knowledge of the event. The Investigator must provide the following minimal information: Protocol number, patient’s initials and date of birth, patient number or medication code number, date of treatment, nature of the adverse event and Investigator’s attribution.</p> <p>All serious adverse events must be followed until any of the following occurs:</p> <ul style="list-style-type: none"> the event resolves; the event stabilizes; the event returns to baseline, if a baseline value is 	<p><u>Non-Serious Adverse Events</u></p> <p>Non-serious adverse events must be recorded using medical terminology in the source document and in the case report form if they have a possible, probable or very likely suspect association to the study drug.</p> <p><u>Serious Adverse Events</u></p> <p>All adverse events meeting the definition of serious, regardless of severity or presumed relationship, must be recorded using medical terminology in the source document and in the case report form. Only SAEs that are “possibly”, “probably” or “very likely” related to the study drug must be reported using the Sponsor Serious Adverse Event Form within 24 hours of knowledge of the event. Exceptions to this include:</p> <p>Death, regardless of the cause, is considered a reportable SAE;</p> <p>Malignancy (except Basal Cell or Squamous Cell Carcinomas), regardless of causality, is considered a reportable SAE.</p> <p>Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”).</p> <p>Investigators must record in the CRF their opinion concerning the relationship of the SAE to study therapy. All measures required for serious adverse event management must be recorded in the source document.</p> <p>Subjects (or their designees, if appropriate) must be provided with a “study card” indicating the name of the investigational product, the study number, the investigator’s name, and a 24-hour emergency contact number.</p> <p>All reportable SAEs occurring during the study period must be reported to the appropriate sponsor contact person by investigational staff within 24 hours of their knowledge of the event. If the SAE is a death or a life threatening event the Investigator must notify the Sponsor immediately by both telephone and FAX.</p>	<p>Change to reflect updates to company safety reporting requirements clarify reporting requirements and expand safety reporting requirements to include non-serious, associated adverse events.</p>
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	<p>available; or</p> <p>the event can be attributed to agents other than the study drug or to factors unrelated to study conduct.</p> <p>The cause of death of a patient in a clinical trial, whether the event is expected or associated with the investigational agent, is considered a reportable serious adverse event.</p> <p>If there is evidence of leukemia (proven or strong clinical suspicion), RCR or a predominant integration site the Sponsor assumes responsibility for reporting these serious adverse events to the relevant regulatory authorities in an expedited manner.</p> <p>The Sponsor will also report to the Investigator all serious adverse events that are unlisted and associated with the use of the drug. The Investigator must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) in accordance with local regulations.</p> <p>Any event requiring hospitalisation (or prolongation of hospitalisation) that occurs during the course of a patient’s participation in a clinical study is a serious adverse event, except hospitalisations for:</p> <ul style="list-style-type: none"> • social reasons in absence of an adverse event; • surgery or procedure planned prior to entry into the study. 	<p>Information regarding serious adverse events will be transmitted to the sponsor using the Sponsor <u>Serious Adverse Event Form</u>, which must be signed by a member of the investigational staff. The initial report of a serious adverse event may be made by facsimile (fax) or telephone. It is preferable that serious adverse events be reported via fax. Subsequent to a telephone report of a serious adverse event, a Serious Adverse Event Form must be completed by the investigational staff and transmitted to the sponsor within 1 working day.</p> <p>All SAEs must be followed until any of the following occurs:</p> <ul style="list-style-type: none"> the event resolves; the event stabilizes; the event returns to baseline, if a baseline value is available; the event can be attributed to agents other than the study drug or to factors unrelated to study conduct; or when it becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts) <p>The sponsor assumes responsibility for appropriate reporting of serious adverse events to the regulatory authorities. This includes expedited reporting of leukemia (proven or strong clinical suspicion), confirmed positive RCR or predominant integration site. The sponsor will also report to the investigator all serious adverse events that are unlisted and associated with the use of the drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.</p> <p>The sponsor will evaluate any safety information that is spontaneously reported by a subject outside their participation in the formal study program.</p> <p>Pregnancy</p> <p>The investigational staff must report pregnancy within 24 hours of their knowledge of the event using the Sponsor</p>	
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<p>12. ADMINISTRATIVE REQUIREMENTS</p> <p>12.4 Record Retention</p>	<p>If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility.</p>	<p>If an Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, the Institution with which the Investigator is associated must transfer the responsibility to another person within the Institution.</p>	<p>Clarification of responsibilities in the event that an Investigator is no longer involved with the study.</p>
<p>Appendix 2</p>	<p>New Text</p>	<p>See Questionnaire</p>	<p>Addition of a Telephone Questionnaire to facilitate long term follow up</p>

Amendment 3; 15 October 2008			
Applicable sections	Original Text	New/Revised Text	Description and Rationale
<p>Global change</p>	<p>Johnson & Johnson Research JJR</p>	<p>Janssen Cilag Pty Ltd JC</p>	<p>Change to indicate change in Sponsor, effective 01/01/09</p>

SYNOPSIS Efficacy evaluations	<p>Ongoing analysis of quantitative marking of the gene transfer product (OZ1 and LNL6) in peripheral blood mononuclear cells (PBMC) will be performed as part of the testing of predominant integration sites. These marking data will also be analyzed independently of the integration analysis to detect changes in the number of cells carrying the gene transfer product. In addition to safety evaluations, patients may elect to have ongoing analysis of quantitative expression of the gene transfer product in peripheral blood mononuclear cells on an annual basis.</p>	<p>Ongoing analysis of quantitative marking of the gene transfer product (OZ1 and LNL6) in peripheral blood mononuclear cells (PBMC) will be performed as part of the testing of predominant integration sites. These marking data will also be analyzed independently of the integration analysis to detect changes in the number of cells carrying the gene transfer product.</p>	<p>Removal of OZ1 expressions analysis as the assay no longer available.</p>
TIME & EVENTS SCHEDULE	<p>Table</p> <p>Footnotes</p>	<p>Table – row deleted</p> <p>Footnotes – amended to remove footnote 3</p>	<p>Removal of OZ1 expressions analysis as the assay no longer available.</p> <p>Update numbering of footnotes.</p>
1. INTRODUCTION	<p>1.1 Background 1.2 Toxicology 1.3 Clinical Experience 1.4 Rationale for Study</p>	<p>1.1 Background 1.2 Rationale for Study</p>	<p>Sections 1.2 (Toxicology) and 1.3 (Clinical Experience) removed as they are covered more fully in the Investigators Brochure.</p> <p>Section 1.4 renumbered to 1.2</p>
OBJECTIVES	<p>3. To assess quantitative marking and expression of the gene transfer product in PBMCs over time.</p>	<p>3. To assess quantitative marking of the gene transfer product in PBMCs over time.</p>	<p>Removal of OZ1 expressions analysis as the assay no longer available.</p>
STUDY EVALUATIONS <u>2 to 5 years post- Infusion</u> Annual Visits Year 5-15 post infusion	<p>Quantitative analysis of PBMC sample for OZ1 RNA (RT PCR).</p> <p>Quantitative analysis of PBMC sample for OZ1 RNA (RT PCR).</p>	<p>Deleted</p> <p>Deleted</p>	<p>Removal of OZ1 expressions analysis as the assay no longer available.</p>
7.2 Optional Efficacy	<p>Patients will have the option of consenting to the collection of additional blood samples for the ongoing</p>	<p>Deleted section</p>	<p>Removal of OZ1 expressions analysis as the</p>

Evaluation	assessment of OZ1 expression (OZ1 RNA- RTPCR).		assay no longer available.
7.2 Safety Evaluation	7.3 Safety Evaluations	7.2 Safety Evaluations	Renumbered section in line with above deletion
STATISTICAL METHODS 9.1 Efficacy Evaluation	Ongoing analysis of quantitative marking of the gene transfer product (OZ1 and LNL6) in peripheral blood mononuclear cells will be performed as part of the testing of OZ1 or LNL6 vector integration sites until year 15 post infusion. These data will be used to independently assess changes in the number of peripheral blood mononuclear cells that carry the gene transfer product over time. Patients will have the option of consenting to the collection of additional blood samples for the ongoing assessment of OZ1 expression (OZ1 RNA- RTPCR).	Ongoing analysis of quantitative marking of the gene transfer product (OZ1 and LNL6) in peripheral blood mononuclear cells will be performed as part of the testing of OZ1 or LNL6 vector integration sites until year 15 post infusion. These data will be used to independently assess changes in the number of peripheral blood mononuclear cells that carry the gene transfer product over time.	Removal of OZ1 expressions analysis as the assay no longer available.

Amendment 4; 07 June 2017			
Applicable sections	Original Text	New/Revised Text	Description and Rationale
CONTACT INFORMATION	Contact details for the sponsor, serious adverse event reporting, and appropriate sponsor contact personnel.	For the Sponsor: address was updated, central emergency number was changed to general contact number and a fax number was included. For serious adverse event reporting: the office phone number and e-mail were updated. For appropriate sponsor contact personnel: the project physician's phone number was deleted and fax number was updated. The project manager's name and contact details were updated.	Updated appropriate details to reflect the current contact information
PROTOCOL VERSION INFORMATION	Sections of this protocol have been revised. Sections marked "Φ" were revised as Amendment 1, 23 June 2006. Sections marked "#" were revised as Amendment 2, 28 August 2007. Sections marked "∞" were revised as Amendment 3; 15 October 2008. Please refer to Appendix 3 – Protocol Amendment History for a detailed description of the specific changes.	Sections of this protocol have been revised. Amendment 1 was issued on 23 June 2006. Amendment 2 was issued on 28 August 2007. Amendment 3 was issued on 15 October 2008. Sections marked "†" have been revised as Amendment 4; 07 June 2017. Please refer to Appendix 3 – Protocol Amendment History for a detailed description of the specific changes.	The identifiers "Φ", "#", and "∞" for the first three protocol amendments were removed throughout the text of the protocol amendment for improving readability.
SYNOPSIS Objective	The objective of this study is to evaluate the long-term safety of a cell-delivered ribozyme gene transfer product (OZ1) in patients infected with HIV-1. OZ1 comprises a Moloney Murine Leukemia Virus based retroviral vector (LNL6) containing a gene that encodes an anti-HIV ribozyme. It is currently a requirement of the United States Food and Drug Administration (FDA) that all individuals receiving retroviral gene transfer products are followed for life.	The objective of this study is to evaluate the long-term safety of a cell-delivered ribozyme gene transfer product (OZ1) in patients infected with HIV-1. OZ1 comprises a Moloney Murine Leukemia Virus based retroviral vector (LNL6) containing a gene that encodes an anti-HIV ribozyme. It is currently a recommendation of the United States Food and Drug Administration (FDA) and Australian Therapeutic Goods Administration (TGA) that all individuals receiving retroviral gene transfer products are followed to collect data on delayed adverse events.	This follow up protocol is to monitor the long-term safety of OZ1/LNL6 gene transfer product in patients who were enrolled in the OTH/OZ1-INT-1 study. Based on the integrated safety analysis of observations of up to 10 years in this LTFU study, up to 15 years with the same OZ1/LNL6 gene transfer product in 2 Phase 1 LTFU studies (OZ1-HV1-101 and OZ1-HV1-102), and published reports of adverse events observed with gene therapeutic products using the same type of retroviral vector, the sponsor has determined that the risk of OZ1/LNL6 gene transfer product to patients beyond 10 years post-infusion is minimal. Accordingly, this long term follow up study will conclude by 30 November 2017.

<p>SYNOPSIS Overview of Study Design</p>	<p>This will be a follow-up study of patients previously enrolled in the OTH/OZ1-INT-1 trial. All patients in this protocol will be reviewed at six monthly intervals until year 5 post infusion. Thereafter all patients will be reviewed annually, on the anniversary of the infusion. Patients who were enrolled in the placebo arm will be discontinued after OTH/OZ1-INT-1 has been unblinded.</p>	<p>This will be a follow-up study of patients previously enrolled in the OTH/OZ1-INT-1 trial. All patients in this protocol will be reviewed at six monthly intervals until year 5 post infusion. Thereafter all patients will be reviewed annually, on the anniversary of the infusion until withdrawal or study completion. Patients who were enrolled in the placebo arm will be discontinued after OTH/OZ1-INT-1 has been unblinded.</p>	<p>Reference to study completion and withdrawal added</p>
<p>SYNOPSIS Safety Evaluations</p>	<p>Follow-up will be conducted as per FDA/Center for Biologics Evaluation and Research (CBER) recommendations. Evaluations will include monitoring for related adverse events such as the development of replication competent retrovirus (RCR), predominant integration sites and insertional oncogenesis. Blood samples will be collected for archival storage for assessment of replication competent retrovirus (RCR) and other safety testing as necessary.</p>	<p>Follow-up will be conducted as per current FDA/Center for Biologics Evaluation and Research (CBER) recommendations. Evaluations will include monitoring for related adverse events such as the development of replication competent retrovirus (RCR), predominant integration sites and insertional oncogenesis. Blood samples will be collected for archival storage for assessment of replication competent retrovirus (RCR) and other safety testing as necessary.</p>	<p>Specifically mentioned the use of ‘current’ FDA recommendations.</p>
<p>TIME & EVENTS SCHEDULE</p>	<p>Column Heading “Annual Visit Yr 5-15”</p>	<p>Removed the column “Annual Visit Yr 15+” as it is no longer applicable.</p> <p>Changed to “Annual Yr 5+/End-of-Study Added footnote 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.</p>	<p>Amended to be consistent with modified rationale for study section.</p>

INVESTIGATOR AGREEMENT		Replaced the old investigator agreement page with a new one.	
1. INTRODUCTION 1.1 Background		Updated reference citations	
1. INTRODUCTION 1.2 Rationale for Study	Currently FDA/CBER requires lifetime follow-up of participants in gene therapy/transfer studies. The safety of patients who were enrolled in the OTH/OZ1-INT-1 study will continue to be assessed under this long term follow-up protocol.	Food and Drug Administration (FDA)/Center for Biologics Evaluation and Research (CBER) recommends a 15-year time-period for follow-up observations. However, CBER also recognizes that assessment of risk is a continuous process, and the nature and duration of follow up observations may be revised accordingly. ⁴ This follow up protocol is to assess the long-term safety of OZ1/LNL6 gene transfer product in patients who were enrolled in the OTH/OZ1-INT-1 study. Based on the integrated safety analysis of observations up to 10 years in this LFTU study, up to 15 years with the same OZ1/LNL6 gene transfer product in 2 Phase 1 LTFU studies (OZ1-HV1-101 and OZ1-HV1-102), and published reports of adverse events observed with gene therapeutic products using the same type of retroviral vector, ^{2,3,5,6,7,8,10,11,12} the sponsor has determined that the risk to OZ1/LNL6 gene transfer product to recipients beyond 10 years post-infusion is minimal. Accordingly, this long term follow up study will conclude by 30 November 2017. This completion date represents a minimum of 10 years follow up following the receipt of OZ1/LNL6-modified CD34+ cells.	Amended the duration of follow-up in individuals receiving O1/LNL6 gene modified products with current FDA Guidance dated Nov 2006. "Guidance for Industry: Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events". Current recommendation is for a 15-year time period for follow-up observations. However, shorter periods of observation may be appropriate in individual trials based on supporting evidence. The complete rationale for the shortened follow up period is provided by FDA in a separate document (Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events; November 2006)
4. COMPLIANCE	1. The semi-annual visit interval is 6 months \pm 6 weeks (for years 2.5-5). The annual visit interval is 12 months \pm 12 weeks (year 6+). 2. Complete Blood Count/Differential data will be obtained specifically as part of the follow up procedures for a total of fifteen (15) years following the time of the infusion in the original phase II study. After this	1. The semi-annual visit interval is 6 months \pm 6 weeks (for years 2.5-5). The annual visit interval is 12 months \pm 12 weeks (year 5+) except the End-of-Study visit. 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 recipient cannot attend a site visit, a	Point #1 and Point #2 were amended to reflect that the study will complete up to fifteen (15) years post-infusion, or 30 November 2017, whichever occurs first.

	<p>date, complete blood count/differential data obtained as part of routine clinic assessments will be collected in the study CRF on an unscheduled basis. Failure to obtain these data will not be considered protocol non-compliance.</p>	<p>telephonic follow-up will be an acceptable alternative. 2. Complete Blood Count/Differential data will be obtained specifically as part of the follow up procedures.</p>	
<p>7. STUDY EVALUATIONS 7.1 Study Procedures by Visit</p>	<p>Table 3: Long term follow-up allowed visit intervals.</p> <p>In the event that a subject is unable to attend the clinic within the allowed visit window, a telephone interview can be conducted to collect information on important medical events since the last study visit (or telephone interview). Refer to Appendix 2 for the interview questionnaire. If the clinical trial site is unable to contact the patient directly a nominated secondary contact will be contacted. A lost or withdrawn patient may re-enter this long term follow-up protocol at any stage in the future.</p>	<p>The following footnote was added: Except the End-of-Study visit, which will be scheduled at a date no later than 30 November 2017.</p> <p>In the event that a subject is unable to attend the clinic within the allowed visit window, a telephone interview can be conducted to collect information on important medical events since the last study visit (or telephone interview). Refer to Appendix 2 for the interview questionnaire. If the clinical trial site is unable to contact the patient directly a nominated secondary contact will be contacted. A patient will be considered to be lost-to-follow-up, at any stage of the clinical trial, after three failed documented attempts (telephone calls, certified letters, e-mail requests) to contact either the patient or a nominated secondary contact. A lost or withdrawn patient may re-enter this long term follow-up protocol at any stage up until 30 November 2017.</p>	<p>To keep consistency within the protocol.</p> <p>Text included to explain when a patient would be considered to be lost-to-follow-up.</p>
	<p>2 to 5 years post-Infusion Visits will be at six monthly intervals from year 2 to year 5 post-infusion</p> <p>Annual Visits Year 5+ post infusion and End-of-Study visit</p> <ul style="list-style-type: none"> • Clinical History and Physical Examination including a detailed record of: <ul style="list-style-type: none"> ○ exposure to possible mutagenic agents e.g. radiotherapy or chemotherapeutic agents 	<p>2.5 to 5.0 years post-infusion Visits will be at six monthly intervals from year 2.5 to year 5.0 post-infusion.</p> <p>Annual Visits Year 5+ post infusion and End-of-Study visit</p> <ul style="list-style-type: none"> • Clinical History and Physical Examination including a detailed record of: <ul style="list-style-type: none"> ○ exposure to possible mutagenic agents e.g. radiotherapy or chemotherapeutic agents ○ new malignancies ○ new or exacerbated preexisting neurologic, 	<p>LTFU visit headings corrected within the subsection-‘Study procedures by visit’. Addition of a telephonic follow-up as an acceptable End-of study criterion.</p>

	<ul style="list-style-type: none"> ○ new malignancies ○ new or exacerbated preexisting neurologic, rheumatologic, autoimmune and hematologic disorders • Complete Blood Count (CBC), differential and platelet count. • Archival storage of plasma and PBMC samples for safety testing including Replication-Competent Retrovirus (RCR) as required. • Testing for clonality of OZ1/LNL6 integration in PBMC samples (PCR) if the percentage of cells marked by the vector (quantitative OZ1/LNL6 DNA-PCR) is greater than or equal to 1% of the test cell population. • Analysis of quantitative marking of the gene transfer product (OZ1 and LNL6) in peripheral blood mononuclear cells (PBMC) will be performed as part of the testing of predominant integration sites. These marking data will also be analyzed independently of the integration analysis to detect changes in the number of cells carrying the gene transfer product. • Recording of AEs. • Contact details updated for subject and nominated secondary contact. 	<p>rheumatologic, autoimmune and hematologic disorders</p> <ul style="list-style-type: none"> • Complete Blood Count (CBC), differential and platelet count. • Archival storage of plasma and PBMC samples for safety testing including Replication-Competent Retrovirus (RCR) as required. • Testing for clonality of OZ1/LNL6 integration in PBMC samples (PCR) if the percentage of cells marked by the vector (quantitative OZ1/LNL6 DNA-PCR) is greater than or equal to 1% of the test cell population. • Analysis of quantitative marking of the gene transfer product (OZ1 and LNL6) in peripheral blood mononuclear cells (PBMC) will be performed as part of the testing of predominant integration sites. These marking data will also be analyzed independently of the integration analysis to detect changes in the number of cells carrying the gene transfer product. • Recording of AEs. • Contact details updated for subject and nominated secondary contact. <p>In the event that a recipient does not report for an in-person End-of-Study visit, a telephonic follow-up will be an acceptable alternative.</p>	
	<p>Annual Visits Year 5-15 post infusion</p> <p>Annual Visits Year 15+ post infusion</p>	<p>Annual Visits Year 5+ post infusion and End-of Study visit</p> <p>Deleted</p>	<p>Removed the heading ‘Annual Visits Year 15+ post infusion’ within the subsection- ‘Study procedures by visit’ as it is not applicable.</p>

<p>7. STUDY EVALUATIONS 7.2 Safety Evaluations Autopsy</p>	<p>As per the FDA/CBER guidelines or gene transfer studies, when a patient dies during the long-term follow up, an autopsy will be requested to determine the extent of gene transfer into bone marrow, spleen, lymph nodes and gonadal tissue, as well as any potentially transformed tissues (e.g. lymphomas, leukemia). A separate informed consent for autopsy will be requested. Patients may sign the consent for autopsy at the time of enrollment. Autopsy will not be required for patients randomized to placebo (after unblinding of the OTH/OZ1-INT-1 trial).</p>	<p>If a patient dies during the long-term follow up, an autopsy will be requested to determine the extent of gene transfer into bone marrow, spleen, lymph nodes and gonadal tissue, as well as any potentially transformed tissues (e.g. lymphomas, leukemia). A separate informed consent for autopsy will be requested. Patients may sign the consent for autopsy at the time of enrollment. Autopsy will not be required for patients randomized to placebo (after unblinding of the OTH/OZ1-INT-1 trial).</p>	<p>Request for autopsy will remain, but current FDA guidance (Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products; June 2015) does not specify this.</p>
<p>8. PATIENT COMPLETION</p>	<p>It is an FDA requirement that individuals receiving retroviral gene transfer products are followed for life.</p> <p>Patients must be withdrawn from the study if:</p> <ul style="list-style-type: none"> • They received placebo in the OTH/OZ1-INT-1 trial. This will only become known when the OTH/OZ1-INT-1 study has been unblinded. • They withdraw their consent. <p>If a patient withdraws, the reason for withdrawal is to be documented on the CRF and in the source document. A withdrawn patient or a patient who was lost to follow-up can re-enter this long term follow-up protocol at any time.</p>	<p>Patients will complete long term follow up with an End-of-Study visit to be completed by 30 November 2017.</p> <p>Patients must be withdrawn from the study if:</p> <ul style="list-style-type: none"> • They received placebo in the OTH/OZ1-INT-1 trial. This will only become known when the OTH/OZ1-INT-1 study has been unblinded. • They withdraw their consent. <p>If a patient withdraws, the reason for withdrawal is to be documented on the CRF and in the source document. A withdrawn patient or a patient who was lost to follow-up can re-enter this long term follow-up protocol at any time up until 30 November 2017.</p>	<p>Amended the description of patient completion possibilities in accordance with the modified Rationale for Study section</p>
<p>9. STATISTICAL METHODS</p>	<p>Statistical analysis of data collected during the long term follow-up study will be performed every 5 years. The primary focus of analysis will be descriptive summarizing changes over time. Patterns over time will be analysed using appropriate techniques.</p>	<p>Statistical analysis of data collected during the long term follow-up study will be performed every 5 years. After patients complete an End-of Study visit, the final analysis of data will be done. The primary focus of analysis will be descriptive summarizing changes over time.</p>	<p>Text highlighting the timing of final analysis included.</p>

	Factors associated with quantitative changes may be assessed.	Patterns over time will be analysed using appropriate techniques. Factors associated with quantitative changes may be assessed.	
9. STATISTICAL METHODS 9.1 Efficacy Evaluation	Ongoing analysis of quantitative marking of the gene transfer product (OZ1 and LNL6) in peripheral blood mononuclear cells will be performed as part of the testing of OZ1 or LNL6 vector integration sites until year 15 post infusion. These data will be used to independently assess changes in the number of peripheral blood mononuclear cells that carry the gene transfer product over time.	Ongoing analysis of quantitative marking of the gene transfer product (OZ1 and LNL6) in peripheral blood mononuclear cells will be performed as part of the testing of OZ1 or LNL6 vector integration sites. These data will be used to independently assess changes in the number of peripheral blood mononuclear cells that carry the gene transfer product over time.	Amended to be consistent with modified rationale for study section.
10. ADVERSE EVENT REPORTING 10.1 Adverse Event Definitions and Classifications	<p>Adverse Event An adverse event is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (Definition per International Conference on Harmonisation [ICH]). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.</p> <p>Note: The sponsor collects adverse events starting with the signing of the informed consent</p>	<p>Adverse Event An adverse event is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (Definition per International Conference on Harmonisation [ICH]). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.</p> <p>Note: The sponsor collects adverse events starting with the signing of the informed consent until completion of the subject's last study related procedure.</p>	The note was amended to be consistent with modified rationale for study section.
13. REFERENCES		Updated reference list.	Deleted references that are no longer cited. Added references: # 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12

			References are alphabetically ordered and renumbered
Appendix 2 Telephone follow-up questionnaire	For semi-annual or annual review of clinical history	For semi-annual, annual, or end-of-study review of clinical history	Added end-of-study to the telephone follow-up questionnaire title to be consistent.