TITLE PAGE

Division: Worldwide Development
Information Type: Worldwide Epidemiology Study Protocol

Title:	Evaluation of referring HCPs' and parents'/carers' understanding of specific risks associated with Strimvelis™ treatment

Compound Number:	GSK2696273
Development Phase	IV
Effective Date:	24-MAR-2017
Subject:	Rare Diseases; Strimvelis; Adenosine Deaminase Severe Combined Immunodeficiency; (ADA-SCID); Safety and Effectiveness of Risk Minimisation Activities; Post Authorisation Safety Study (PASS) Category 3
Author(s):	PPD

PASS Information *

Title	Evaluation of referring HCPs' and parents'/carers' understanding of specific risks associated with Strimvelis™ treatment
Protocol version identifier	Draft 1
Date of last version of protocol	6th December 2016
EU PAS (ENCEPP) register number	[Registration number in the EU PAS register; indicate "Study not registered" if the study has not been registered in the EU PAS (ENCEPP) register. Note: all non-interventional PASS should be entered in the EU-PAS register before study start as per SOP_72635.] <*will be entered once the protocol is finalized*>
Active substance	Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence. (ACT Code available after marketing authorisation)
Medicinal product	Strimvelis™
Product reference	Not yet available
Procedure number	EMEA/H/C/003854
Marketing authorization holder(s)	GlaxoSmithKline Trading Services Limited Currabinny, Carrigaline, County Cork Ireland
Joint PASS	No
Research question and objectives	To evaluate the effectiveness of routine and additional risk minimization measures by assessing the understanding of parents/carers and referring HCPs with regard to specific risks associated with Strimvelis.

Country(-ies) of study	Italy and other European Union (EU) member states, and other non EU countries to be determined as patients are treated.
Author	Dr. PPD GSK Medicine Research Center, Gunnels Wood Road, Stevenage, Herts, SG1 2NY.

MARKETING AUTHORISATION HOLDER(S) *

Marketing authorisation holder(s)	GlaxoSmithKline Trading Services Ltd
MAH contact person	Dr. PPD Director, Gene Therapy Therapeutic Group UK Therapeutic Groups R&D Chief Regulatory Office GSK Stockley Park West, 1-3 Ironbridge Road, Uxbridge, Middlesex, UB11 1BT, United Kingdom Email: PPD

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SPONSOR SIGNATORY:

PPD

Heide [redacted]-Farrant
Primary Author/ Project officer

24/3/17
Date

PPD

Monika Stender
Therapy Area Leader

24. March 2017
Date

PPD

SPONSOR INFORMATION PAGE

WWEpi Project Identifier: PRJ2678/205881

Sponsor

The Marketing Authorisation Holder (MAH) will serve as the sponsor of this study. It is the responsibility of the MAH to ensure proper monitoring of the study and compliance with all applicable regulatory guidelines and laws.

Study Coordination

The MAH has contracted with PPD, a contract research organization (CRO) with expertise in registries and observational post marketing studies, to provide scientific leadership and to conduct the study. The CRO will conduct the study with review and input from the MAH.

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Sponsor Contact Address

GlaxoSmithKline Research & Development Limited
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: PPD

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Sponsor Medical Monitor Contact Information:

Dr PPD
GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Mobile: PPD
Tel: PPD

CRO Serious Adverse Events (SAE) Contact Information:

PPD MEng
PPD Italy S.r.l.
Via San Bovio, 3
San Felice
20090 Segrate (MI)
Italy

Mobile: PPD
Tel: PPD

Regulatory Agency Identifying Number(s): tbd

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

Investigator Signature	Date

1. LIST OF ABBREVIATIONS

ADA	Adenosine deaminase
ADA-SCID	Adenosine deaminase severe combined immunodeficiency
AE	Adverse event
BMT	Bone marrow translpant
CD34+	Hematopoetic progenitor stem cells
CRO	Contract research organization
dAXP	Deoxyadenosine nucleotides
DNA	Deoxyribonucleic acid
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERT	Enzyme replacement therapy
EU	European Union
EU RMP	European Risk Management Plan
GTRC	Gene Therapy Registry Centre
GSK	GlaxoSmithKline
HCP	Healthcare provider
HLA	Human leukocyte antigen
HSCT	Hematopoetic stem cell transplant
HSR	Hospital San Raffaele, Italy
KRM	Key Risk Message
MUD	Matched unrelated donor
NK	Natural killer cells
PASS	Post-Authorization Safety Study
PEG-ADA	Polyethylene glycol modified bovine adenosine deaminase
PVP	Pharmacovigilance Plan
RBC	Red blood cell
SAE	Serious adverse event
SCID	Severe combined immunodeficiency
SmPC/PIL	Summary of Product Characteristics/Patient Information Leaflet
US	United States
WBC	White blood cell

Trademark Information

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Trademarks not owned by the GlaxoSmithKline group of companies
None

2. RESPONSIBLE PARTIES

Dr PPD
GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Mobile: PPD
Tel: PPD

PPD PhD
Director Epidemiology
GlaxoSmithKline
R&D Projects Clinical Platforms and Sciences
RWE Epidemiology
GSK Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK

PPD Development, L.P
929 North Front Street
Wilmington, NC 28401
United States

3. ABSTRACT

Title: Evaluation of referring HCPs' and parent/carers' understanding of specific risks associated with Strimvelis™ treatment

Rationale and background: Adenosine deaminase (ADA) deficiency results in severe combined immunodeficiency (SCID), a fatal autosomal recessive inherited immune disorder. Strimvelis is a medicinal product developed by GlaxoSmithKline (GSK) that restores ADA function in hematopoietic cell lineages, thereby preventing the pathology caused by purine metabolites (i.e., impaired immune function). Strimvelis is indicated for the treatment of patients with ADA-SCID, for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

Research question and Objective(s): The objective of this study is to evaluate the effectiveness of routine and additional risk minimization measures (*e.g.* Summary of Product Characteristics/Patient Information Leaflet (SmPC/PIL), educational materials) by assessing the understanding of referring HCPs and parents/carers with regard to the specific risks associated with Strimvelis.

Study Design: In this cross-sectional study, surveys will be provided to referring HCPs and parents/carers of children approximately six months after treatment with Strimvelis. Both surveys were developed to assess the understanding of the risks associated with Strimvelis treatment. The outcome of the surveys is the proportion of referring HCPs and parents/carers' that provide correct responses to a series of questions concerning the specific risks associated with Strimvelis. Additional analyses will assess implementation metrics (e.g., proportion of respondents who received the educational materials).

Population: A non-interventional registry is being implemented to prospectively monitor the long-term safety and effectiveness of Strimvelis. Referring HCPs and parents/carers of patients enrolled within the registry will be contacted and asked to participate in this study.

Variables: Two survey instruments with approximately 20 questions are included in this study, a HCP survey and a parent/carer survey. Survey questions are based on the Strimvelis prescribing information and educational materials, and will evaluate HCPs' and parent/carers' understanding of the key risk messages (KRMs). The questions will also assess HCPs' and parent/carers' awareness, receipt, and reading of the educational materials. Demographic information, including geographic region and HCP specialty, will be collected.

Data sources: Referring HCPs and parents/carers of patients enrolled within the registry will be asked to complete the survey. Surveys will be developed in English and translated in the parent/carers' and HCPs' local language. Survey's will be conducted via telephone interview.

Study size: The study will recruit for approximately two years until 10 referring HCPs and 10 parents/carers have completed their respective surveys (length of study may vary contingent upon product uptake). Results of surveys are distinct for each of the groups and will be reported separately.

Data analysis: Data from all survey respondents will be analysed and reported as descriptive statistics. A frequency distribution of responses to each question will be presented. Summary statistics will be prepared describing the proportion of referring HCPs and parents/carers for whom questionnaires were returned relative to the total number of referring HCPs and parents/carers of patients eligible for enrolment into the study.

4. AMENDMENTS AND UPDATES

None

5. MILESTONES

Milestone	Planned date
Start of data collection	Q2 2017
End of data collection	Q3 2020
Final report of study results	Q1 2021

6. RATIONALE AND BACKGROUND

6.1. Background

ADA deficiency results in severe combined immunodeficiency (SCID), a fatal autosomal recessive inherited immune disorder. ADA deficiency is extremely rare, with an overall prevalence ranging from 0.22 to 0.68 per 100,000 live births, or fewer than 50 children per year in the United States (US) and European Union (EU) combined.

ADA is a ubiquitous enzyme of purine metabolism, and mutations in the ADA gene lead to accumulation of deoxyadenosine nucleotides (dAXP) in plasma, white blood cells, (WBCs), red blood cells (RBCs), and tissues. The main features of ADA-SCID are profound lymphopenia; impaired differentiation and function of T cells, B cells, and natural killer (NK) cells; recurrent infections; and failure to thrive [Hirschorn, 1999; Chapel, 2003]. Non-immunological abnormalities may also occur as a consequence of the systemic metabolic defect and include hepatic, lung, and skeletal alterations, as well as neurological deficits affecting motor function, hearing, and cognitive/behavioral deficits [Hirschorn, 1999; Gaspar, 2010; Sauer, 2009]. Moreover, it is now apparent that the clinical spectrum extends into a late-onset ADA deficiency diagnosed between 3 and 15 years of age, in which there is significant immunodeficiency as well as other associated findings, including elevated IgE, eosinophilia, immune dysregulation manifested by autoimmunity including autoimmune hypothyroidism, diabetes mellitus, hemolytic anemia, and idiopathic thrombocytopenia [Hirschorn, 2014]. As a result of recurrent infections, patients with ADA-SCID often present initially to a family physician or general pediatrician before care is eventually transferred to a pediatric immunologist, who may ultimately make the diagnosis and consider treatment options.

Patients with ADA-SCID can be effectively treated with conventional bone marrow transplant (BMT) (also referred to as hematopoietic stem cell transplant [HSCT]) from allogeneic donors, but the better outcomes for this intervention are only achieved when an HLA-matched family donor is available. Unfortunately, such a donor is a viable

option for fewer than 25% of patients with ADA-SCID [Hirschorn, 2014]. Stem cells from HLA-matched siblings or family members are usually given without chemotherapeutic conditioning to reduce the risk of chemotherapy-associated toxicity.

In those ADA-SCID patients for whom related matched donors are not available, alternative sources of stem cells are used for transplantation. These procedures may require chemotherapeutic preconditioning and are associated with increased morbidity and mortality primarily related to inadequate immune reconstitution and graft versus host disease. Decreased long-term survival (compared with matched sibling or matched family donor) has been observed with less well-matched donor sources of stem cells. Specifically, long-term survival rates (after a median follow-up of 6.5 years) were significantly better with matched sibling and family donors at 86% and 81%, in comparison with 67%, 43%, and 29% after HCT from matched unrelated donors (MUDs), haplo-identical donors, and mismatched unrelated donors, respectively [Gaspar, 2010; Hassan, 2012]. Survival data by decade has also been studied, to evaluate whether transplantation outcome had improved over time as a result of increased awareness of SCID, greater experience of transplantation in these children, and improvement in transplant-related processes/medications. Overall survival improved by decade for all donor types, from 51.7% pre-1991 to 72.5% from 2000-2009. In the subgroup of haploidentical transplant recipients, overall survival improved from 40% (8/20) pre-1991 to 71.4% (5/7) from 2000-2009. In this latter period, haploidentical transplant was successful in 42.3% of patients (3/7), as two transplants did not engraft [Hassan, 2012].

Strimvelis (or GSK2696273, its investigational name) is a gene therapy that aims to restore ADA function in hematopoietic cell lineages and prevent the immunological manifestations caused by purine metabolites (i.e., impaired immune function). Strimvelisis a CD34+ cell enriched dispersion of human autologous bone marrow-derived hematopoietic stem/progenitor cells for infusion that have been transduced with a retroviral vector containing the human adenosine deaminase (ADA) gene. The cell populations that constitute the active substance are genetically modified CD34+ cells and unmodified CD34+ cells. Cells that have been genetically modified will contain one or more copies of the human ADA transgene. The treatment regimen consists of autologous bone marrow harvested for gene transduction, non-myeloablative pre-conditioning with the chemotherapy agent busulfan, followed by gene therapy with Strimvelis (infusion of gene modified CD34+ cells).

Strimvelis is currently administered at Hospital San Raffaele (HSR) in Italy by physicians with previous experience in the treatment and management of patients with ADA-SCID and the use of autologous CD34+ *ex vivo* gene therapy products. Prior to treatment with Strimvelis, patients must be tested and shown to be negative for the presence of infectious agents as listed in the current EU Cell and Tissue Directive. The patient must be able to donate adequate CD34+ cells in order to deliver the minimum of 4 million purified CD34+ cells/kg required for the manufacture of Strimvelis. The recommended dose range of Strimvelis is between 2 and 20 million CD34+ cells/kg and is intended to be administered as an intravenous infusion once only.

6.2. Rationale

Strimvelis is only to be used in the ultra-rare disorder ADA-SCID and in patients for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available. Routine risk minimization activities to mitigate risks are communicated via labelling (*e.g.* SmPC/PIL). GSK also provides additional risk minimization measures that take into account guidelines on safety and efficacy follow-up of advanced therapy medicinal products (ATMPs), the product risk profile, and the very restricted scope of the administration procedure (e.g. treatment for patients who do not have an adequeate HLA matched related donor for HSCT) to facilitate informed decision making and to support risk minimization when initiating treatment. These additional risk minimization measures, including educational materials, will be distributed to parents/carers and referring HCPs. The educational materials specifically address the following safety concerns: autoimmunity, unsuccessful response to gene therapy, malignancy due to insertional oncogenesis (e.g. leukaemia, myelodysplasia) and pregnancy.

7. RESEARCH QUESTION AND OBJECTIVE(S)

The objective of this study is to evaluate the effectiveness of routine and additional risk minimization measures (*e.g.* SmPC/PIL, educational materials) by assessing the understanding of parents/carers and referring HCPs with regard to the following:

Safety concerns:

- Malignancy due to insertional oncogenesis (*e.g.* leukaemia, myelodysplasia)
- Autoimmunity
- Unsuccessful response to gene therapy
- Pregnancy

Other areas of interest:

- Requirement for long-term monitoring
- Patient alert card

This study will help determine whether the current routine and additional risk minimisation measures have been successfully implemented. The study will assess the proportion of parents/carers and referring HCPs providing correct responses to a series of questions concerning specific risks associated with Strimvelis. Additional analyses will assess implementation metrics (e.g. proportion of respondents who received the educational materials).

8. RESEARCH METHODS

8.1. Study Design

This is a cross-sectional study in which surveys will be conducted in EU and non-EU countries and provided to both parents/carers and referring HCPs of children approximately six months after treatment with Strimvelis. The two surveys will be developed to evaluate the effectiveness of routine and additional risk minimization measures (*e.g.* SmPC/PIL, educational materials) by assessing the understanding of referring HCPs and parents/carers with regard to the specific risks associated with Strimvelis. All data collected during the surveys will be confidential and anonymzed to protect the identity and privacy of the survey participants.

8.2. Study Population and Setting

Strimvelis is indicated for the treatment of patients with ADA-SCID, for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available. A registry study (PRJ2684/200195) will be implemented with long-term prospective, non-interventional follow-up of the safety and effectiveness of Strimvelis. Patients in the registry will be monitored for at least 15 years post-treatment with Strimvelis.

Parents/carers and referring HCPs of patients enrolled within this registry will be contacted separately and asked to participate in their respective surveys evaluating the effectiveness of risk minimisation measures. The survey will be conducted via telephone interviews in the local languages for parents/carers and for referring HCPs. Parent/Carers and referring HCPs survey are distinct and results will not be linked for confidentiality reasons.

In order to be considered eligible to participate in the study, HCPs will be required to meet the following criteria:

- HCPs or HCPs' close family members may not have been employees of GlaxoSmithKline, Pharmaceutical Product Development, LLC (PPD), the Food and Drug Administration (FDA), or the European Medicines Agency (EMA).
- HCPs must be licensed.
- An HCP must not have previously completed a survey regarding Strimvelis educational materials.
- An HCP must have previously referred a patient for Strimvelis treatment.

In order to be considered eligible to participate in the Parent/Carer survey, parents or carers will be required to meet the following criteria:

- Parents/carers or parents'/carers' close family members may not have been employees of GlaxoSmithKline, Pharmaceutical Product Development, LLC (PPD), the Food and Drug Administration (FDA), or the European Medicines Agency (EMA).

- A parent/carer must not have previously completed a survey regarding Strimvelis educational materials.

- A parent's or carer's child must have previously received treatment with Strimvelis.

The study will recruit for approximately two years until 10 referring HCPs and 10 parents/carers have completed their respective surveys (length of study may vary contingent upon product uptake).

8.3. Survey design

8.3.1. Survey Instruments

There are two survey instruments included in this study, (1) a HCP survey and (2) a parent/carer survey.

Following agreement to participate, the understanding of the potential risks associated with Strimvelis will be evaluated via telephone interview. The telephone interviews will be conducted in the local countries language. The survey will start with screening questions to ensure eligibility and willingness to participate in the survey. Participation in the study can be terminated during screening. The survey will include multiple choice and close-ended questions. There will be no open-ended questions included.

Survey questions are based on the Strimvelis prescribing information and educational materials including those that address risks of autoimmunity, unsuccessful response, oncogenesis and pregnancy. There will be approximately 20 questions per survey.

For HCPs, the survey refers to the following risk minimisation measures:

- Educational materials:

    - Important risk minimisation information for healthcare professionals who provide long-term follow-up of ADA-SCID patients post-treatment with Strimvelis

- Strimvelis Summary of Product Characteristics

For parents/carers, the survey refers to the following risk minimisation measures:

- Educational materials:

    - "Important follow-up risk minimisation information for children who have received gene therapy with Strimvelis (autologous CD34+ cells transduced to express ADA) – an educational leaflet for parents/carers"

    - Patient Treatment Alert Card

- Strimvelis Patient Information Leaflet

The questions will evaluate HCPs' and patients'/carers' understanding of the key risk messages (KRMs) of the routine and additional risk minimisation measures. The questions will also assess HCPs' and patients'/carers' awareness, receipt, and reading of the educational materials. Demographic information such as geographic region and HCP specialty will also be captured (see Annexes 4 and 5). This information is required to further characterise the respondent population, including the number of patients.

The KRM topics for both the HCP and parent/carer surveys are listed in Section 8.3.3:

8.3.2. Question design

The survey will start with screening questions. The surveys will be composed of multiple choice and close-ended questions. There will be no open-ended questions included.

8.3.3. Outcome definitions

This study will assess the proportion of parents/carers and referring HCPs at six months post treatment with Strimvelis that understood the possible risks relating to:

Safety concerns (KRM topics):

1. Malignancy due to insertional oncogenesis (*e.g.* leukaemia, myelodysplasia)
2. Autoimmunity
3. Unsuccessful response to gene therapy
4. Pregnancy

Other areas of interest:

- Requirement for long-term monitoring
- Receipt of the patient treatment alert card

The proportion of parents/carers and referring HCPs who acknowledge receipt of routine and additional risk minimization measures (e.g., SmPC/PIL, educational materials, Patient Alert Card) will be assessed as a measure of implementation.

The type of medical specialty and experience of referring HCPs will be summarized.

The primary outcome of these surveys is the proportion of parents/caregivers and referring HCPs that provide correct responses to a series of questions concerning the specific risks associated with Strimvelis.

Sufficient understanding of a key risk message can be assumed if at least 80% or more respondents correctly answer all questions that are included within that particular key risk message [ISPE White Paper 2016].

8.3.4. Measures to Minimise Bias in the Surveys

The following are measures to minimise bias in the surveys:

All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a

question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. This is important because subsequent questions could provide answers to previous questions, and because all subjects should have the same chance of answering the questions correctly. Other biases are described in the limitation section, however, cannot be minimized by survey design alone.

8.4. Data sources

Parents/carers and referring HCPs of patients enrolled within the registry will be contacted and asked to participate in this study evaluating the effectiveness of risk minimisation measures.

Parent/carers surveys and HCPs surveys will be developed in English and available in translations in the parent/carers' and HCPs' local languages for provision via telephone interviews.

8.5. Study size

All parents/carers and referring HCPs from patients enrolled in the Strimvelis product registry will be invited to complete the surveys. The study will recruit for approximately two years until 10 referring HCPs and 10 parents/carers have completed their respective surveys (length of study may vary contingent upon product uptake).

8.6. Data management

A user-friendly Internet-based survey tool with an intuitive interface will be employed to manage data in this survey. Parents/carers, who have agreed that they may be contacted about such future studies, will be contacted by the Gene Therapy Registry Centre (GTRC). Questions will be asked to the parents/carers and HCPs and responses to the survey entered by the GTRC. Surveys for both parents/carers and HCPs will be entered via an electronic data collection system by the local interviewer.

In order to minimize bias, the survey instruments will include the following design features:

- Response options for multiple-choice questions will be randomized, where appropriate.

- Participants will be asked by the interviewer to answer all questions.

8.6.1. Data handling conventions

Management of survey data will be performed by a CRO in accordance with applicable GSK standards. Personally identifiable information will not be transmitted to GSK, in accordance with GSK policies.

8.6.2. Resourcing needs

This study is overseen by a senior PhD level epidemiologist, MD level physician and GSK Study Accountable Person (SAP). Study management, the reporting analysis plan, data collection, data analysis and reporting will be provided by a CRO.

8.6.3. Timings of Assessment during follow-up

This is a cross-sectional study assessing the proportion of parents/carers and referring HCPs at six months post-treatment with Strimvelis. There will be no follow up.

8.7. Data analysis

There are two distinct analysis populations comprising all (1) Parents/Carers and (2) referring HCPs recruited in the study. Information on response rate will be summarized. For each analysis population, all data from all survey respondents will be analysed and reported as descriptive statistics. Each survey will be analysed for all countries combined.

8.7.1. Essential analysis

A frequency distribution of responses to each question (the number of respondents who give an answer to each question) will be presented. Summary statistics will be prepared describing the proportion of parents/carers and referring HCPs for whom questionnaires were returned relative to the total number of parents/carers and referring HCPs of patients eligible for enrolment into the study.

For the analysis population, the proportion of participants answering each question correctly and incorrectly will be summarized. In case of multiple choice questions, the number and proportion of participants reporting each response will be provided.

For the analysis population, the proportion of correct answers to survey questions overall and by risk category will be summarized.

Table shells are presented in Annex 2.

8.8. Quality control and Quality Assurance

The following measures will be taken to ensure data quality and integrity:

- All procedures will be performed according to the protocol and will be documented appropriately.

- The electronic data capture system will be built to include drop-down lists and select buttons to minimize typing errors by the telephone interviewer as much as possible. The system allows data entry checks to be implemented, as well as complex skip patterns, and other functionalities.

Survey questions will be reviewed by an internal physician (not involved in this project) and by a patient group representative, prior to starting the survey, to ensure readability and understanding of the questions.

8.9. Limitations of the research methods

This study has the following limitations:

- Small sample size: given the rarity of the disease a high response rate is important. The response rate will most likely be dependent on who is willing to participate in the registry. The actual time of survey participation coincides with the follow up regime of the registry and is thus not seen as a major challenge.
- Recall bias: there may be a potential recall bias when answering more complex questions as the educational materials were distributed at least 6 months prior to the telephone interviews (at the time of entering the registry and consenting to both the registry and this survey). Therefore medical terms are often explained before asking a specific question, to ensure understanding of the topic.
- Possible bias due to telephone interviewer led questioning and their delivery style.
- Possible misunderstanding on the part of participants or questionnaire fatigue could lead to inaccurate answers. Therefore, questions have been limited to approximately 20 only and some of the medical terms or themes are introduced before a particular question is asked.
- The participants' educational attainment is unknown; and we assume that participants are representative of the entire Strimvelis HCPs/parents/carers spectrum and that the questions can be understood across the entire educational range.
- Parents/Carers of patients who did not respond to treatment may understandably be under extreme stress with potentially many medical interactions happening unrelated to Strimvelis which may impact their recall of educational materials. Stratification of the survey results by response to treatment may help in discarding this imbalance.

8.10. Study closure/uninterpretability of results

The study will be closed when 10 parents/care givers and 10 HCPs have completed the surveys. The survey will begin with a question indicating the agreement to participate in the survey. If the individual does not agree, the survey will be ended.

Ethics approval will be sought as required by individual countries.

8.11. Other aspects

None

9. PROTECTION OF HUMAN SUBJECTS

To ensure the quality and integrity of research, this study will be conducted under the Guidelines for Good Pharmacovigilance Practices (GVPs) and Good Pharmacoepidemiology Practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE) (ISPE, 2008), the Declaration of Helsinki (Declaration of Helsinki, 2008) and its amendments, and any applicable national guidelines.

9.1. Ethical approval and subject consent

The survey participation is voluntary.

Parents/carers being followed within the long-term registry, who have specifically agreed to be contacted for such studies, will be asked to consider and give informed consent for this study of their understanding of educational materials.

HCPs involved in the long term registry will also be asked to provide informed consent for their participation in this survey.

9.2. Subject confidentiality

Each participant's identity will be known only to GTRC, who will help facilitate completion of the surveys. Identification numbers will be assigned and used to identify participants. The dataset used in the analysis of data will contain coded participant identifiers only.

All parties will ensure protection of patients' and participants' personal data and will not include patient or participant names on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations in each of the countries in which the study is implemented, participants will be informed about data handling procedures and asked for their consent. The registry will be conducted in accordance with all applicable patient and participant privacy and data storage requirements. Regulatory authorities or GSK-approved auditors may inspect the data files, which may include personally identifiable information of participants. In all cases, personally identifiable information will not be transmitted to GSK.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The reporting of Adverse Events (AE) is not expected or requested during the survey given that answers are closed ended (i.e., there are no free text fields into which the telephone interviewer could enter AE information on the interviewee's behalf). However, as reporting suspected adverse reactions after authorisation of the medicinal product is important to allow continued monitoring of the benefit/risk balance of the medicinal product, physicians will be asked to report any suspected AEs via the national reporting system.

All serious and non-serious adverse events (AEs), pregnancy exposures, or incidents related to any GSK product will be collected and reported as described in the study-specific pharmacovigilance plan (sPVP). This plan will include the following elements to ensure a comprehensive approach to safety event collection and reporting:

- Supplier pharmacovigilance training
- Investigator and site staff pharmacovigilance training
- Safety-specific roles
- AEs, pregnancy exposures, and incidents collection and reporting processes
- AE, pregnancy exposure, and incident collection forms
- Frequency of data review
- Reporting process and timelines
- Interim reports
- Reconciliation process
- Study-specific PVP monitoring process
- Provision of final study report

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

The information generated by this study will be transmitted to Regulatory Authorities, primarily the EMA, as required, and will contribute to the published literature. The results may be disseminated externally via manuscripts or presentations.

11.2. Study reporting and publications

Whenever 10 parents/carers and 10 HCPs have completed the surveys, a final report will be submitted to the EMA within six months of the end of data collection. See Section 7 for milestones related to this study, which are contingent upon uptake of Strimvelis.

The final report will encompass all planned analyses, including a description of the complete study population, as described above.

In accordance with the 2010 EU pharmacovigilance legislation, information about this Post-authorisation Safety Study will be entered into the publically available European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Register of Studies. The study protocol will be entered into the register before the start of data collection and will also be entered into clinicaltrials.gov. Updates to the study protocol in case of substantial amendments, progress reports where applicable, and the final study report will also be entered in the register.

Any publication of the results from this study will be consistent with GSK's publication policy and guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated April 2010 (ICMJE, 2010). To comply with the requirements of the EU Pharmacovigilance Regulation, the final manuscript of the article will be submitted to the Agency and competent authorities, within two weeks of the first acceptance for publication.

12. REFERENCES

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13. ANNEX 1: LIST OF STAND-ALONE-DOCUMENTS

No.	Document Reference No	Date	Title
1.		<Date>	GSK Epidemiology and Health Outcome PVP approval form >
2.	<No>	<Date>	<Text>
N	<No>	<Date>	<text>

14. ANNEX 2: LIST OF TABLE AND FIGURE SHELLS

14.1. Tables

Table 1. Survey participant summary

	HCP survey		Parent/Carer survey	
Number of participants screened				
Number of participants terminated				
Number of participants completed the survey				
Total				

Table 2: HCP survey - availability and review of Educational Materials

	Yes (N, %)	No (N, %)	Total (N, 100%)	
1. Have you received copies of the following Educational Materials on Strimvelis for healthcare practitioners? • Important risk minimization information for healthcare professionals who provide long-term follow-up of ADA-SCID patients post-treatment with Stimvelis. • Summary of Product Characteristics (SmPC).				
If you answered "No" to all of the above materials, prior to this survey, were you aware of these educational materials about Strimvelis?				
	Yes	No	Some	N total (% Yes)
Did you read the provided Educational Materials about Strimvelis?				
If Some, which ones did you read? • Important risk minimization information for healthcare professionals who provide long-term follow-up of ADA-SCID patients post-treatment with Strimvelis. • Summary of Product Characteristics (SPC).				

Table 3. Listing of HCP Survey Responses for each survey question

Survey Question	**Answer**	**N**	**% (total)**
Demography Q1. How many patients have you referred to for treatment			

Survey Question	**Answer**	**N**	**% (total)**
with Strimvelis?			
Demography Q2. How would you classify your **primary** medical speciality?	a. Paediatrician		
	b. Immunologist		
	c. Haematologist		
	d. Other (please specify): _____.		
Demography Q3. In what country is your **primary** medical practice?			
Demography Q4. What is the length of your experience in your **primary** medical speciality?	a. Less than 3 years		
	b. More than 3 and up to 5 years		
	c. More than 5 and up to 10 years		
	d. More than 10 and up to 15 years		
	e. More than 15 years		
	f. Prefer not to answer		
Demography Q5. How many patients with ADA-SCID are you currently treating?			
1. Have you received copies of the following educational materials about Strimvelis for healthcare providers?	a. Important risk minimization information for healthcare professionals who provide long-term follow-up of ADA-SCID patients post-treatment with Strimvelis. b. Summary of Product Characteristics (SPC).		

Survey Question	Answer	N	% (total)
If you answered "No" to all of the above materials, prior to this survey, were you aware of these educational materials about Strimvelis?	a. Yes		
	b. No		
	c. I don't know (I cannot remember)		
2. Did you read the provided educational materials about Strimvelis?	a. Yes		
	b. No		
	c. Some		
	d. I don't know		
3. Strimvelis is recommended as first-line therapy for **any** patient affected by ADA-SCID.	a. True		
	b. False		
	c. I don't know		
4. Strimvelis is indicated for the treatment of patients with severe combined immunodeficiency due to ADA deficiency, for whom no suitable HLA matched related stem cell donor is available.	a. True		
	b. False		
	c. I don't know		
5. Strimvelis is contraindicated in patients with a history of previous gene therapy.	a. True		
	b. False		
	c. I don't know		
6. Patients eligible to receive treatment with Strimvelis should have a bone marrow harvest for stem cell back-up at least 3 weeks prior to treatment with Strimvelis.	a. True		
	b. False		
	c. I don't know		

Survey Question	Answer	N	% (total)
7. Parents and carers of patients receiving treatment with Strimvelis should be educated on the fact that the patient should not be able to donate blood, organs, tissues, or cells for transplantation.	a. True		
	b. False		
	c. I don't know		
8. It is recommended that patients treated with Strimvelis are regularly followed up clinically (at least annually).	a. True		
	b. False		
	c. I don't know		
KRM 1: Gene therapy for ADA-SCID and malignancy risk (e.g. leukaemia)			
9. Strimvelis is contraindicated in patients with a current or previous history of leukaemia or myelodysplasia.	a. True		
	b. False		
	c. I don't know		
10. Have you given advice to parents/carers/patients regarding monitoring for signs and symptoms of leukaemia?	a. Yes		
	b. No		
	c. I don't know		
11. Have you performed blood tests (including red blood cell indices, white blood cell count differential, platelet count, and a routine biochemistry screen) within the first year of a patient's returning from treatment with Strimvelis?	a. Yes		
	b. No		
	c. I don't know		

Survey Question	Answer	N	% (total)
KRM 2: Autoimmunity			
12. Regular monitoring for clinical autoimmunity (possibly including tests for auto-antibodies) is recommended.	a. True		
	b. False		
	c. I don't know		
13. Autoimmunity may be observed during immune reconstitution after gene therapy.	a. True		
	b. False		
	c. I don't know		
KRM 3: Unsuccessful response to gene therapy			
14. Strimvelis is not proven, nor likely to be effective for the non-immunological aspects of the disease (e.g. hepatic steatosis, CNS manifestations, and hearing and neurobehavioural disorders).	a. True		
	b. False		
	c. I don't know		
15. Patients should be followed up indefinitely using routine haematological tests.	a. True		
	b. False		
	c. I don't know		
16. Which tests can be used during follow-up if loss of immunity is suspected?	a. Lymphocyte counts, including T-cell differential counts.		
	b. T-cell function [as measured by T-cell proliferative capacity to mitogen challenge (TCA/PHA)].		
	c. ADA metabolite levels (e.g. dAXP levels).		

Survey Question	Answer	N	% (total)
17. In patients treated with Strimvelis, elevated red blood cell dAxP levels may indicate loss of ADA enzyme activity and failure of gene therapy.	a. Yes		
	b. No		
	c. I don't know		
18. In patients treated with Strimvelis, if you suspect a loss of efficacy or inadequate efficacy for the immunological manifestations of ADA-SCID, can patients still be considered for treatment with enzyme replacement therapy (ERT) or subsequent bone marrow transplant (BMT)?	a. Yes		
	b. No		
	c. I don't know		
KRM 4: Pregnancy			
19. Strimvelis is intended to correct the ADA gene defect in patient gametes (e.g. ovum, sperm).	a. True		
	b. False		
	c. I don't know		
20. Family planning advice should be given to patients when it is appropriate for their ages and circumstances.	a. True		
	b. False		
	c. I don't know		

Table 4. Summary of HCP survey results

		Correct answer		
No.	Question	Yes	No	N total; %Yes
1	Have you received copies of the following educational materials about Strimvelis for healthcare providers?			
2	Did you read the provided educational materials about Strimvelis?			

		Correct answer		
No.	Question	Yes	No	N total; %Yes
3	Strimvelis is recommended as first-line therapy for **any** patient affected by ADA-SCID.			
4	Strimvelis is indicated for the treatment of patients with severe combined immunodeficiency due to ADA deficiency, for whom no suitable HLA matched related stem cell donor is available.			
5	Strimvelis is contraindicated in patients with a history of previous gene therapy.			
Total (Q1-5)				
Gene therapy for ADA-SCID and malignancy risk (e.g. leukaemia)				
6	Patients eligible to receive treatment with Strimvelis should have a bone marrow harvest for stem cell back-up at least 3 weeks prior to treatment with Strimvelis.			
7	Parents and carers of patients receiving treatment with Strimvelis should be educated on the fact that the patient should not be able to donate blood, organs, tissues, or cells for transplantation.			
8	It is recommended that patients treated with Strimvelis are regularly followed up clinically (at least annually).			
9	Strimvelis is contraindicated in patients with a current or previous history of leukaemia or myelodysplasia.			
10	Have you given advice to parents/carers/patients regarding monitoring for signs and symptoms of leukaemia?			
11	Have you performed blood tests (including red blood cell indices, white blood cell count differential, platelet count, and a routine biochemistry screen) within the first year of a patient's returning from			

		Correct answer		
No.	Question	Yes	No	N total; %Yes
	treatment with Strimvelis?			
	Total (Q6-11)			
Autoimmunity				
12	Regular monitoring for clinical autoimmunity (possibly including tests for auto-antibodies) is recommended.			
13	Autoimmunity may be observed during immune reconstitution after gene therapy.			
	Total (Q12,13)			
Unsuccessful response to gene therapy				
14	Strimvelis is not proven, nor likely to be effective for the non-immunological aspects of the disease (e.g. hepatic steatosis, CNS manifestations, and hearing and neurobehavioural disorders).			
15	Patients should be followed up indefinitely using routine haematological tests.			
16	Which tests can be used during follow-up if loss of immunity is suspected?			
17	In patients treated with Strimvelis, elevated red blood cell dAxP levels may indicate loss of ADA enzyme activity and failure of gene therapy.			
18	In patients treated with Strimvelis, if you suspect a loss of efficacy or inadequate efficacy for the immunological manifestations of ADA-SCID, can patients still be considered for treatment with enzyme replacement therapy (ERT) or subsequent bone marrrow transplant (BMT)?			
	Total (Q14-18)			
Pregnancy				
19	Strimvelis is intended to correct the ADA gene defect in patient gametes (e.g. ovum, sperm).			
20	Family planning advice should be given to patients when it is			

		Correct answer		
No.	Question	Yes	No	N total; %Yes
	appropriate for their ages and circumstances.			
Total (Q19,20)				
Total (Q1-20)				

Table 5. HCP demographics

Survey Question	**Answer**	**N**	**%**
Demography Q1. How many patients have you referred to for treatment with Strimvelis?			
Demography Q2. How would you classify your **primary** medical speciality?	a. Paediatrician		
	b. Immunologist		
	c. Haematologist		
	d. Other (please specify): _____.		
Demography Q3. In what country is your **primary** medical practice?		*<LISTING>*	
Demography Q4. What is the length of your experience in your **primary** medical speciality?	a. Less than 3 years		
	b. More than 3 and up to 5 years		
	c. More than 5 and up to 10 years		
	d. More than 10 and up to 15 years		
	e. More than 15 years		
	f. Prefer not to answer		
Demography Q5. How many patients with ADA-SCID are you currently treating?		*<N>*	

Table 6. Parent/Carer survey - availability and review of Educational Materials

	Yes	No	N; % YES	
1. Have you received copies of the following educational materials related to Strimvelis? • "Important follow-up risk minimization information for children who have received gene therapy with Strimvelis (autologous CD34+ cells transduced to express ADA) – an educational leaflet for parents/carers" • Patient information leaflet • Patient Treatment Alert Card				
	Yes	No	Some	N; %
If you answered "No" to all of the above materials, prior to today, were you aware of any of these educational materials about Strimvelis?				
2. Did you read these educational materials about Strimvelis?				
If Some, which ones did you read? • "Important follow-up risk minimization information for children who have received gene therapy with Strimvelis (autologous CD34+ cells transduced to express ADA) – an educational leaflet for parents/carers" • Patient information leaflet • Patient Treatment Alert Card				

Table 7. Listing of Parent/Carer survey response for each survey question

Survey Question	**Answer**	**N**	**%**
1. Have you received copies of the following educational materials	a. "Important follow-up risk minimization information for children who have		

Survey Question	Answer	N	%
related to Strimvelis?	received gene therapy with Strimvelis (autologous CD34+ cells transduced to express ADA) – an educational leaflet for parents/carers"		
	b. Patient information leaflet		
	c. Patient Treatment Alert Card		
If you answered “No” to all of the above materials, prior to today, were you aware of any of these educational materials about Strimvelis?	a. Yes		
	b. No		
	c. I don’t know		
2. Did you read these educational materials about Strimvelis?	a. Yes		
	b. No		
	c. Some		
	d. I don’t know		
3. Your child’s specialist doctor will follow your child's progress regularly over time to check for symptoms related to key risks after treatment with Strimvelis.	a. True		
	b. False		
	c. I don’t know		
4. There are NO risks associated with Strimvelis treatment.	a. True		
	b. False		
	c. I don’t know		
5. You should report any concerning signs or symptoms that you	a. True		
	b. False		

Survey Question	Answer	N	%
notice after your child is treated with Strimvelis to your child's specialist doctor.	c. I don't know		
KRM 1: Gene therapy for ADA-SCID and risk of blood cancer (e.g. leukaemia)			
6. Your child's specialist doctor will check your child's blood for any signs of leukaemia during check-ups.	a. True		
	b. False		
	c. I don't know		
7. Within the last last 6 months, has your child been seen by their specialist doctor for follow-up after receiving Strimvelis?	a. Yes		
	b. No		
	c. I don't know		
If you answered "Yes," approximately how many times have you seen your child's specialist doctor?			
If you answered "Yes,"has your child given blood samples at least once within the last 6 months?	a. Yes		
	b. No		
	c. I don't know		
8. How often should your child be followed up by his or her specialist doctor?	**a. At least once a year**		
	b. Every 5 years		
	c. Every 10 years		
KRM 2: Autoimmunity			
9. Autoimmunity occurs when the body's immune system sees its own tissues and cells as foreign and attacks these healthy cells. Symptoms may include a high temperature,	a. True		
	b. False		
	c. I don't know		

Survey Question	Answer	N	%
rash, joint pain, painful or weak muscles, or feeling tired or unwell most of the time. If you are concerned about autoimmunity, you should contact your specialist doctor.			
10. Autoimmunity can occur (select all that apply):	a. Before treatment because of the disease		
	b. After treatment as the immune system is restored		
	c. Both		
KRM 3: Unsuccessful response to gene therapy			
11. Gene therapy is designed to treat the immune issues of ADA-SCID, including frequent severe infections.	a. True		
	b. False		
	c. I don't know		
12. Gene therapy is designed to treat non-immune issues such as fatty liver, reduced hearing, or behavioural problems.	a. True		
	b. False		
	c. I don't know		
13. Immune and non-immune issues will be followed up during routine visits by your child's specialist doctor.	a. True		
	b. False		
	c. I don't know		
14. Symptoms such as fever, cough, loose stools, pain on passing urine may suggest infection and should be reported to your specialist doctor	a. True		
	b. False		
	c. I don't know		

Survey Question	**Answer**	**N**	**%**
KRM 4: Pregnancy			
15. Strimvelis is not designed to correct the genetic defect in your child's reproductive cells.	a. True		
	b. False		
	c. I don't know		
16. When your child has reached a suitable age, seeking family planning advice is recommended.	a. True		
	b. False		
	c. I don't know		

Table 8. Summary of Patient/Carer survey results

		Correct answer		
No.	Question	Yes	No	%
1	Have you received copies of the following educational materials related to Strimvelis?			
2	Did you read these educational materials about Strimvelis?			
3	Your child's specialist doctor will follow your child's progress regularly over time to check for symptoms related to key risks after treatment with Strimvelis.			
4	There are NO risks associated with Strimvelis treatment.			
5	You should report any concerning signs or symptoms that you notice after your child is treated with Strimvelis to your child's specialist doctor.			
Total (Q1-5)				
Gene therapy for ADA-SCID and malignancy risk (e.g. leukaemia)				
6	Your child's specialist doctor will check your child's blood for any signs of leukaemia during check-ups.			
7	Within the last 6 months, has			

		Correct answer		
No.	Question	Yes	No	%
	your child been seen by their specialist doctor for follow-up after receiving Strimvelis?			
8	How often should your child be followed up by his or her specialist doctor?			
Total (Q6-8)				
Autoimmunity				
9	If you are concerned about autoimmunity, you should contact your specialist doctor.			
10	Autoimmunity can occur (select all apply)?			
Total (Q9,10)				
Unsuccessful response to gene therapy				
11	Gene therapy is designed to treat the immune features of ADA-SCID, such as frequent severe infections.			
12	Gene therapy is designed to treat non-immune characteristics such as fatty liver, reduced hearing, or behavioural problems.			
13	Immune and non-immune features or characteristics will be followed up during routine visits by your child's specialist doctor.			
14	Symptoms such as fever, cough, loose stools, pain on passing urine may suggest infection and should be reported to your specialist doctor.			
Total (Q15-16)				
Pregnancy				
15	Strimvelis is not designed to correct the genetic defect in your child's reproductive cells.			
16	When your child has reached a suitable age, seeking family planning advice is recommended.			

Table 9. Summary of patients yearly follow up and number of blood samples taken during this time (Q7)

Sub-question	Answer	N (%)
If you answered "Yes," approximately how many times have you seen your child's specialist doctor?		
If you answered "Yes," within the last 6 months, has your child given blood samples at least once within the last 6 months?	Yes	
	No	
	I don't know	

14.2. Figures

None

15. ANNEX 3: ENCEPP CHECKLIST FOR STUDY PROTOCOLS (REVISION 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Evaluation of referring HCPs' and parents'/carers' understanding of specific risks associated with Strimvelis™ treatment

Study reference number:
GSK2696273

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	7
1.1.2 End of data collection[2]	☒	☐	☐	7
1.1.3 Study progress report(s)	☐	☐	☐	
1.1.4 Interim progress report(s)	☐	☐	☐	
1.1.5 Registration in the EU PAS register	☐	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	7

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8.2
2.1.2 The objective(s) of the study?	☒	☐	☐	9
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	10.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	9
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	10.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	10.3.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	10.3.3
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	12

Comments:

This is a descriptive study only

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	10.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2 Is the planned study population defined in terms of:	☒	☐	☐	10.2
4.2.1 Study time period?	☒	☐	☐	10.2
4.2.2 Age and sex?	☒	☐	☐	10.2
4.2.3 Country of origin?	☒	☐	☐	10.2
4.2.4 Disease/indication?	☒	☐	☐	10.2
4.2.5 Duration of follow-up?				
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	10.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	10.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	10.3.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	10.3.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value,	☐	☐	☒	

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
prospective or retrospective ascertainment, use of validation sub-study)				
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	10.3.4
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	10.3.4
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	10.3.4
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

This is a descriptive survey

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	10.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	10.4
9.1.3 Covariates?	☐	☐	☒	
9.2 Does the protocol describe the information				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	10.4
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	10.4
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	10.7
10.2 Are descriptive analyses included?	☒	☐	☐	10.7.1
10.3 Are stratified analyses included?	☐	☐	☒	
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	10.7.1
10.6 Is sample size and/or statistical power estimated?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection,	☒	☐	☐	10.6

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
archiving)				
11.2 Are methods of quality assurance described?	☒	☐	☐	10.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	10.6.1

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	10.9
12.1.2 Information bias?	☒	☐	☐	10.9
12.1.3 Residual/unmeasured confounding?	☒	☐	☐	10.9
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	10.10

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	11
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	11
13.3 Have data protection requirements been described?	☒	☐	☐	11

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	6

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	13
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13

Comments:

Name of the main author of the protocol: PPD

Date: / /
Signature: _____

16. ANNEX 4: HEALTHCARE PROVIDER SURVEY

The purpose of this survey is to assess your understanding of the risks associated with Strimvelis gene therapy.

SCREENING QUESTIONS	**Yes**	**No**	**I don't know**
Are you or any of your close family members an employee of GlaxoSmithKline, Pharmaceutical Product Development, LLC (PPD), the Food and Drug Administration (FDA), or the European Medicines Agency (EMA)?	[Terminate]		[Terminate]
This survey is voluntary. Do you agree to take part in this survey?		[Terminate]	[Terminate]
We appreciate your participation, no payment for completion of the survey can be provided. Do you wish to continue with the survey?		[Terminate]	[Terminate]
Have you previously taken part in a survey of your knowledge of educational materials about Strimvelis?	[Terminate]		
Are you a licensed medical healthcare provider?		[Terminate]	[Terminate]
Have you previously referred one of your patients to an Italian Strimvelis treatment centre?		[Terminate]	[Terminate]

DEMOGRAPHY QUESTIONS:

Demography Q1: How many patients have you referred to for treatment with Strimvelis?

Demography Q2: How would you classify your **primary** medical speciality?

Please select one response.

a. Paediatrician

b. Immunologist

c. Haematologist

d. Other (please specify): _____.

Demography Q3: In what country is your **primary** medical practice?

Demography Q4: What is the length of your experience in your **primary** medical speciality?

Please select one response.

a. Less than 3 years

b. More than 3 and up to 5 years

c. More than 5 and up to 10 years

d. More than 10 and up to 15 years

e. More than 15 years

f. Prefer not to answer

Demography Q5: How many patients with ADA-SCID are you currently treating?

<#>

MAIN SURVEY QUESTIONS:

1. Have you received copies of the following educational materials about Strimvelis for healthcare providers?

Select all that apply.

a. Important risk minimization information for healthcare professionals who provide long-term follow-up of ADA-SCID patients post-treatment with Strimvelis.

b. Summary of Product Characteristics (SmPC).

If you answered "No" to all of the above materials, prior to this survey, were you aware of these educational materials about Strimvelis?

Please select one response.

a. Yes

b. No

c. I don't know (I cannot remember)

2. Did you read the provided educational materials about Strimvelis?

Please select one response.

a. Yes

b. No

c. Some

d. I don't know

If Some, which ones did you read?

Please answer based on your knowledge of Strimvelis as informed by the Strimvelis Educational Materials, including the product Summary of Product Characteristics (Product Label).

3. Strimvelis is recommended as first-line therapy for **any** patient affected by ADA-SCID.

Please select one response.

a. True

b. False

c. I don't know

4. Strimvelis is indicated for the treatment of patients with severe combined immunodeficiency due to ADA deficiency, for whom no suitable HLA matched related stem cell donor is available.

Please select one response.

a. True

b. False

c. I don't know

5. Strimvelis is contraindicated in patients with a history of previous gene therapy.

Please select one response.

a. True

b. False

c. I don't know

6. Patients eligible to receive treatment with Strimvelis should have a bone marrow harvest for stem cell back-up at least 3 weeks prior to treatment with Strimvelis.

Please select one response.

a. True

b. False

c. I don't know

7. Parents and carers of patients receiving treatment with Strimvelis should be educated on the fact that the patient should not be able to donate blood, organs, tissues, or cells for transplantation.

Please select one response.

a. True

b. False

c. I don't know

8. It is recommended that patients treated with Strimvelis are regularly followed up clinically (at least annually).

Please select one response.

a. True

b. False

c. I don't know

9. Strimvelis is contraindicated in patients with a current or previous history of leukaemia or myelodysplasia. [KRM 1]

Please select one response.

a. True

b. False

c. I don't know

10. Have you given advice to parents/carers/patients regarding monitoring for signs and symptoms of leukaemia? [KRM1]

Please select one response.

a. Yes

b. No

c. I don't know

11. Have you performed blood tests (including red blood cell indices, white blood cell count differential, platelet count, and a routine biochemistry screen) within the first year of a patient's returning from treatment with Strimvelis? [KRM1]

Please select one response.

a. Yes

b. No

c. I don't know

12. Regular monitoring for clinical autoimmunity (possibly including tests for auto-antibodies) is recommended. [KRM2]

Please select one response.

a. True

b. False

c. I don't know

13. Autoimmunity may be observed during immune reconstitution after gene therapy. [KRM2]

Please select one response.

a. True

b. False

c. I don't know

14. Strimvelis is not proven, nor likely to be effective for the non-immunological aspects of the disease (e.g. hepatic steatosis, CNS manifestations, and hearing and neuro-behavioural disorders). [KRM3]

Please select one response.

a. True

b. False

c. I don't know

15. Patients should be followed up indefinitely using routine haematological tests. [KRM3]
Please select one response.

a. True

b. False

c. I don't know

16. Which tests can be used during follow-up if loss of immunity is suspected? [KRM3]

Select all that apply.

a. Lymphocyte counts, including T-cell differential counts.

b. T-cell function [as measured by T-cell proliferative capacity to mitogen challenges (TCA/PHA)]

c. ADA metabolite levels (e.g. dAXP levels).

17. In patients treated with Strimvelis, elevated red blood cell dAxP levels may indicate loss of ADA enzyme activity and failure of gene therapy. [KRM3]

Please select one response.

a. Yes

b. No

c. I don't know

18. In patients treated with Strimvelis, if you suspect a loss of efficacy or inadequate efficacy for the immunological manifestations of ADA-SCID, can patients still be considered for treatment with enzyme replacement therapy (ERT) or subsequent bone marrrow transplant (BMT)? [KRM3]

Please select one response.

a. Yes

b. No

c. I don't know

19. Strimvelis is intended to correct the ADA gene defect in patient gametes (e.g. ovum, sperm). [KRM4]

Please select one response.

a. True

b. False

c. I don't know

20. Family planning advice should be given to patients when it is appropriate for their age and circumstances. [KRM4]

Please select one response.

a. True

b. False

c. I don't know

17. ANNEX 5: PARENT/CARER SURVEY

The purpose of this survey is to assess your understanding of the risks associated with Strimvelis gene therapy. This survey consists of questions and statements.

SCREENING QUESTIONS	**Yes**	**No**	**I don't know**
Are you or any of your close family members an employee of GlaxoSmithKline (GSK), Pharmaceutical Product Development, LLC (PPD), the Food and Drug Administration (FDA), or the European Medicines Agency (EMA)?	[Terminate]		[Terminate]
This survey is voluntary. Do you agree to take part in this survey?		[Terminate]	[Terminate]
Have you previously taken part in a survey of your knowledge of educational materials about Strimvelis?	[Terminate]		[Terminate]
Are you a parent/carer of a child who has been treated with Strimvelis gene therapy?		[Terminate]	[Terminate]

SCREENING QUESTIONS:

Screening Q1: What is your country of residence?

MAIN SURVEY QUESTIONS:

1. Have you received copies of the following educational materials related to Strimvelis?

Select all that apply.

a. "Important follow-up risk minimization information for children who have received gene therapy with Strimvelis (autologous CD34+ cells transduced to express ADA) – an educational leaflet for parents/carers"

b. Patient information leaflet

c. Patient Treatment Alert Card

If you answered "No" to all of the above materials, prior to today, were you aware of any of these educational materials about Strimvelis?

Please select one response.

a. Yes

b. No

c. I don’t know

2. Did you read these educational materials about Strimvelis?

Please select one response.

a. Yes

b. No

c. Some

d. I don’t know

If Some, which ones did you read?

Please answer based on your knowledge of Strimvelis provided through the Strimvelis Educational Materials.

3. Your child’s specialist doctor will follow your child's progress regularly over time to check for symptoms related to key risks after treatment with Strimvelis. Is this statement True or False?

Please select one response.

a. True

b. False

c. I don’t know

4. There are NO risks associated with Strimvelis treatment. Is this statement True or False?

Please select one response.

a. True

b. False

c. I don’t know

5. You should report any concerning signs or symptoms that you notice after your child is treated with Strimvelis to your child's specialist doctor. Is this statement True or False?

Please select one response.

a. True

b. False

c. I don't know

6. Your child's specialist doctor will check your child's blood for any signs of leukaemia during check-ups. [KRM1] Is this statement True or False?

Please select one response.

a. True

b. False

c. I don't know

7. Within the last 6 months, has your child been seen by their specialist doctor for follow-up after receiving Strimvelis? [KRM1]

Please select one response.

a. Yes

b. No

c. I don't know

If you answered "Yes," approximately how many times have you seen your child's specialist doctor? [KRM1]

Please capture number of times here.

If you answered "Yes," within the last 6 months, has your child given blood samples at least once within the last 6 months? [KRM1]

Please select one response.

a. Yes

b. No

c. I don't know

8. How often should your child be followed up by his or her specialist doctor? [KRM1]

Please read out responses to parent/carer and select one response.

a. At least once a year

b. Every 5 years

c. Every 10 years

Autoimmunity occurs when the body's immune system sees its own tissues and cells as foreign and attacks these healthy cells. Symptoms may include a high temperature, rash, joint pain, painful or weak muscles, or feeling tired or unwell most of the time.

9. If you are concerned about autoimmunity, you should contact your specialist doctor. Is this statement True or False? [KRM2]

Please select one response.

a. True

b. False

c. I don't know

10. Autoimmunity can occur (select all apply)?. [KRM2]

Please read responses to parent/carer to select one response.

a. Before treatment because of the disease

b. After treatment as the immune system is restored

c. Both

11. Gene therapy is designed to treat the immune issues of ADA-SCID, such as frequent severe infections. Is this statement True or False? [KRM3]

Please select one response.

a. True

b. False

c. I don’t know

12. Gene therapy is designed to treat non-immune issues such as fatty liver, reduced hearing, or behavioural problems. Is this statement True or False? [KRM3]

Please select one response.

a. True

b. False

c. I don’t know

13. Immune and non-immune issues will be followed up during routine visits by your child’s specialist doctor. Is this statement True or False? [KRM3]

Please select one response.

a. True

b. False

c. I don’t know

14. Symptoms such as fever, cough, loose stools, pain on passing urine may suggest infection and should be reported to your specialist doctor. Is this statement True or False? [KRM3]

Please select one response.

a. **True**

b. False

c. I don’t know

15. Strimvelis is not designed to correct the genetic defect in your child's reproductive cells. Is this statement True or False? [KRM4]

Please select one response.

a. True

b. False

c. I don’t know

16. When your child has reached a suitable age, seeking family planning advice is recommended. Is this statement True or False? [KRM4]

Please select one response.

a. True

b. False

c. I don’t know