PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Strimvelis (autologous $CD34^+$ enriched cell fraction that contains $CD34^+$ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence)

This is a summary of the risk management plan (RMP) for Strimvelis. The RMP details important risks of Strimvelis, how these risks can be minimised, and how more information will be obtained about Strimvelis' risks and uncertainties (missing information).

Strimvelis' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Strimvelis should be used.

This summary of the RMP for Strimvelis should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Strimvelis' RMP.

I. The medicine and what it is used for

Strimvelis is indicated for the treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available (see SmPC for the full indication). It contains autologous $CD34^+$ enriched cell fraction that contains $CD34^+$ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence as the active substance and it is given by infusion.

Further information about the evaluation of Strimvelis' benefits can be found in Strimvelis' EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/strimvelis

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Strimvelis, together with measures to minimise such risks and the proposed studies for learning more about Strimvelis's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Strimvelis, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Strimvelis is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Strimvelis are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Strimvelis. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Autoimmunity Unsuccessful response to gene therapy Risks related to medical or surgical procedures (e.g. central venous catheter) Risks related to short shelf-life of product Malignancy due to insertional oncogenesis (e.g. leukaemia, myelodysplasia)
Important potential risks	Non-immunologic manifestations of ADA-SCID (e.g. hepatic steatosis cognitive defects, behavioural abnormalities, hearing impairment) Risks related to residuals present in the drug product administered to the patient Hypersensitivity to the product Replication competent retrovirus
Missing information	Lack of data in neonates Lack of data in adolescents Lack of immunogenicity data No reproductive toxicity studies or embryofetal development studies Lack of data in delayed onset or late onset ADA-SCID

II.B Summary of important risks

Important identified risk: Autoimmunity	
Evidence for linking the risk to the medicine	In clinical trials, the adverse event (AE) category with the highest incidence of reported AEs following treatment with Strimvelis was autoimmunity (caused by the immune system becoming over-active and attacking the body's own tissues) ranging from transient appearance of antibodies to serious events requiring treatment. Serious adverse

	reactions related to autoimmunity include autoimmune haemolytic anaemia and autoimmune aplastic anaemia (reduced numbers of blood cells), autoimmune hepatitis (inflamed liver), autoimmune thrombocytopenia (reduced numbers of blood platelets), and Guillain-Barré syndrome (weakness and pain in the feet and hands). Autoimmunity is a concern for patients with severe combined immunodeficiency (SCID) who achieve partial or poor immune reconstitution after bone marrow transplant or with polyethylene glycol-ADA (PEG-ADA) treatment [Sauer, 2012], and in late onset ADA deficiency [Santisteban, 1993; Shovlin, 1994]. In addition, autoimmunity can be caused by the underlying disease, as reported in late onset ADA-SCID. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice. The published medical literature can support the evidence of a causal association based on what has been observed with other medications in patients with the same or similar condition.
Risk factors and risk groups	Family history of autoimmunity and medical history of autoimmunity (the customised search of Medical Dictionary for Regulatory Activities [MedDRA] preferred terms [PTs] revealed four AEs potentially related to autoimmunity, positive antinuclear antibody (ANA) test, autoimmune haemolytic anaemia).
Risk minimisation measures	Routine risk minimisation measures: • *Warning in SmPC section 4.4 that treated patients can develop autoimmunity including autoimmune antibodies and other manifestations and that regular monitoring for clinical autoimmunity is recommended.* • *Autoimmune adverse reactions listed in SmPC section 4.8* • *Warning that some patients can develop autoimmunity in PL section 2* • *Autoimmune side effects listed in PL section 4* • *Restricted medical prescription* Additional risk minimisation measures: • *Educational materials for parents/carers and HCPs*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *STRIM-003 (Patient registry): ADA-SCID registry for patients treated with Strimvelis gene therapy: long-term prospective, non-interventional follow-up of safety and efficacy* See Section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Unsuccessful response to gene therapy	
Evidence for linking the risk to the medicine	Similar to most medicines, not all patients treated with Strimvelis will respond to gene therapy. In the clinical trial three patients did not respond to Strimvelis treatment and required long-term reintroduction of PEG-ADA with two of the patients having a successful sibling matched haematopoietic stem cell transplant (HSCT). Additionally, two patients treated in the Named Patient Program (NPP) did not respond to Strimvelis treatment. For these two patients, no additional information about the treatment failure is currently available. Clinical trials can provide an estimation of the lack of response to treatment that is expected to occur in clinical practice.
Risk factors and risk groups	Insufficient bone marrow harvest (resulting in final product dose less than $2x10^6$ $CD34^+$ cells/kg). Medical history of autoimmunity.
Risk minimisation measures	Routine risk minimisation measures: • *Information in SmPC section 4.2 that treatment failure was observed in a clinical trial patient* • *Guidance in SmPC section 4.2 that the recommended dose range is 2 to 20 million $CD34^+$ cells/kg and that if the product contains <2 million $CD34^+$ cells/kg to conduct an individual patient benefit risk assessment* • *Warning in SmPC section 4.4 that in case of lack of response, the introduction of other ADA-SCID treatments should be under the supervision of a physician* • *Guidance in SmPC sections 4.4 and 5.1 about unsuccessful treatment and that some patients had to resume long-term enzyme replacement therapy and/or receive a stem cell transplant* • *Restricted medical prescription* Additional risk minimisation measures: • *Restricted prescription* • *Controlled access – product consent form* • *Educational materials for parents/carers and HCPs*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *STRIM-003 (Patient registry): ADA-SCID registry for patients treated with Strimvelis gene therapy: long-term prospective, non-interventional follow-up of safety and efficacy* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Risks related to medical or surgical procedures (e.g. central venous catheter)	
Evidence for linking the risk to the medicine	A central venous catheter (CVC) is necessary for harvesting of bone marrow and administration of other medicines including busulfan for making the bone marrow ready for Strimvelis, intravenous immunoglobulin (IVIG); and other medicines such as pentamidine. CVCs may have to be kept in for up to 2 years post-treatment. Seven patients treated with Strimvelis have reported CVC infections and three patients reported thrombosis (blot clot) in device, device occlusion (blockage), jugular vein thrombosis or pneumothorax following CVC positioning. Infections are common when a CVC is in place [WHO, 2014]. Patients with SCID may be at increased risk due to their immune-compromised state. Catheter occlusions and catheter-related thrombosis are common complications of catheters and catheter-related thrombosis occurs in up to 50% of children with a long-term CVC [Baskin, 2009]. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice. The published medical literature can support the evidence of a causal association based on what has been observed with other medications in patients with CVCs.
Risk factors and risk groups	Indwelling CVCs are a known risk factor for infection in all patients, not just those with SCID. CVC-related complications, including infections and thrombosis, are common in children with oncological or haematological diseases and have been reported in up to 40% of patients; the most significant risk factors are haematological disease, age (age <6 years) and type and duration of catheter insertion [Fratino, 2005].
Risk minimisation measures	Routine risk minimisation measures: • *Warning in SmPC section 4.4 to closely monitor patients for potential CVCs related adverse events as serious CVC infections and thrombosis in the device have been reported* • *Restricted medical prescription* Additional risk minimisation measures: • *None*

Important identified risk: Risks related to short shelf-life of product	
Evidence for linking the risk to the medicine	Strimvelis has a short shelf-life of six hours that does not allow for completion of the full range of specification tests. Two stages of testing of Strimvelis for quality issues are used. The first stage provides information on safety, efficacy and genetic modification before Strimvelis is administered. Some quality control results (namely the confirmation of absence of microbiological contamination) are only available after infusion of Strimvelis. Overall two product sterility failures have been reported but neither of these was associated with adverse events. Chemistry, Manufacturing, and Controls (CMC) identified the need for two stages of testing of Strimvelis to allow use of Strimvelis even though not all the quality control results (especially the microbiological status) are available until after infusion of Strimvelis. The product sterility failures reported to date provide an estimate of the frequency of quality control failures that are expected to occur in clinical practice.
Risk factors and risk groups	Not applicable.
Risk minimisation measures	Routine risk minimisation measures: • *Guidance in SmPC section 4.4 that stage two quality control results will only be available after product infusion and if clinically relevant quality issues are identified the treating physician may need to modify the treatment program of the patient.* • *Guidance in PL section 2 that Strimvelis is given soon after it is made and that if tests show anything that may affect the patient then other treatment may be needed.* • *Information in SmPC section 6.3 on the shelf-life* • *Restricted medical prescription* Additional risk minimisation measures: • *None*

Important identified risk: Malignancy due to insertional oncogenesis (e.g. leukaemia, myelodysplasia)	
Evidence for linking the risk to the medicine	Oncogenesis is a safety concern for gene therapy medicinal products and, in particular, with therapies using a gamma-retroviral vector such as Strimvelis. The incidence of leukaemia is calculated to be 2.6% for the 38 patients who have received Strimvelis, 2.5% for the 40 patients who have received the Strimvelis gamma-retroviral vector (gRV) (data cut of 25 November 2020) and 1.4% for ADA-SCID patients who have received gRV-GT from any source (including Strimvelis). In comparison, the incidence of malignancy in ADA-SCID patients following allogenic HSCT is estimated at 1.5%; however, as the degree of donor matching is a strong predictor of the development of post-HSCT malignancy it is likely that ADA-SCID patients without access to

	a suitable HLA-matched donor (i.e. those eligible for Strimvelis) will have an incidence of post-HSCT malignancy higher than 1.5%. In two gene therapy clinical trials evaluating a different form of primary immunodeficiency (SCID-X1), using a similar retroviral vector, but encoding a different gene, six of the approximately 20 treated subjects developed T-cell leukaemia at 2.5 to 15 years after gene therapy [Cavazzanna, 2019, Hacein Bey-Abina, 2003; Fischer, 2010a]. There is also evidence of neoplasms in ADA-SCID patients treated with either enzyme replacement therapy (ERT) or conventional HSCT [Kesserwan, 2012; Gaspar, 2009; Husain, 2007; Kaufman, 2005; Monforte-Muñoz, 2003]. Clinical trials and post-marketing data can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice. The published medical literature can support the evidence of a possible causal association based on what has been observed with other similar medications in patients with the same condition.
Risk factors and risk groups	Factors thought to be important in contributing to the risk of oncogenesis (EMA/CAT/190186/2012): a) Vector design (including backbone and regulatory elements) b) Insertion profile c) Vector dose d) Transgene product e) Target cell population/organ f) Risk of malignancy for the underlying disease
Risk minimisation measures	Routine risk minimisation measures: • *Contraindication in SmPC section 4.3 and PL section 2 for patients with a current or previous history of leukaemia or myelodysplasia* • *Warning in SmPC section 4.4 that one case of Lymphoid T cell leukaemia (PT 'T-cell type acute leukaemia') has been reported with Strimvelis.* • *Inclusion of 'T-cell type acute leukaemia' under SOC 'Neoplasms, benign, malignant and unspecified' in section 4.8 of the SmPC.* • *Warning in PL section 2 that a new gene into the DNA could cause leukaemia* • *Leukaemia added to the list of common side effects in PL section 4* • *Guidance in SmPC section 4.4 that long term monitoring of patients, including a complete blood count with differential biochemistry and thyroid stimulating hormone, should occur at least annually for eleven years and then at 13 and 15 years post treatment with Strimvelis* • *Guidance in PL section 2 that the patient's doctor has been advised to monitor the patient for any signs of leukaemia during long-term follow-up* • *Restricted medical prescription*

	Additional risk minimisation measures: • *Restricted prescription* • *Controlled access – product consent form* • *Educational materials for parents/carers and HCPs*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *STRIM-005 Methodology study to investigate retroviral insertion site analysis in samples from subjects treated with Strimvelis gene therapy* • *STRIM-003 (Patient registry): ADA-SCID registry for patients treated with Strimvelis gene therapy: long-term prospective, non-interventional follow-up of safety and efficacy* See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Non-immunologic manifestations of ADA-SCID (e.g. hepatic steatosis cognitive defects, behavioural abnormalities, hearing impairment)	
Evidence for linking the risk to the medicine	Hepatic steatosis In the clinical trial, Compassionate Use Program (CUP) and Named Patient Programme (NPP) eight subjects reported events of hepatic steatosis (accumulation of fat in the liver), and an additional patient had hyperecogenous liver lesions (lesions in the liver), for a total of twelve events. Three of the twelve events resolved and of the unresolved events, no progression was reported. All cases were Grade 1 in severity and were identified as findings on abdominal ultrasound, without any reported clinical symptoms. There have been several published reports of hepatic steatosis in ADA-SCID patients suggesting that some ADA deficient patients may have specific hepatic sensitivity [Candotti, 2012; Bollinger, 1996; Sokolic, 2013; Lingala, 2015]. Cognitive defects, behavioural abnormalities, hearing impairment The majority of patients treated with Strimvelis in the clinical trial had cognitive defects, behavioural abnormalities or hearing impairments with many of the events reported pre-treatment. Many of the pre-treatment events remain unresolved after long-term follow-up and most events were mild to moderate in severity and non-serious.CNS abnormalities frequently occur in ADA-SCID patients, even in patients treated with BMT [Rogers, 2001; Booth, 2007]. Neurologic deficits in ADA-SCID involve motor dysfunction, deafness, and defects in cognitive and behavioural function and mental retardation [Gaspar, 2009; Hönig, 2007]. Patients with ADA deficiency are known to have increased neurologic deficits when compared with other forms of SCID [Rogers, 2001].

	Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice. The published medical literature can support the evidence of a causal association based on what has been observed with other medications in patients with the same or similar condition.
Risk factors and risk groups	Hepatic steatosis Adenosine A1, A2A, A2B, and A3 receptors are expressed on hepatocytes. Adenosine and extracellular nucleotides are recognised by a variety of P1-adenosine and P2-receptors on hepatocytes, hepatic stellate cells and immune cells. Accumulation of the purine metabolite adenosine has been linked to the development of hepatic steatosis. It has been suggested that adenosine participates in a final common pathway leading to the development of hepatic steatosis, hepatic fibrosis and cirrhosis [Robson, 2010]. Underlying hepatotoxicity due to adenosine deaminase substrates may be additive with the effects of cytotoxic agents used in HSCTs. Metabolic abnormalities associated with insulin resistance, such as steatohepatitis and diabetes, are commonly found in ADA-SCID patients, in whom immunodeficiency is well-controlled with ERT or gene therapy [Bollinger, 1996; Sokolic, 2013]. Cognitive defects, behavioural abnormalities, hearing impairment There are several specific considerations that may affect neurocognitive function in ADA-SCID patients: a) Disease-specific characteristics, such as deoxyadenosine-X-phosphate (dAXP) level at baseline, the molecular defect, or systemic toxicity with build-up of dAXP b) Psychosocial factors, such as socioeconomic status c) Impact of chronic illness d) Effects of CNS infection and treatment with certain antibiotics e) Treatment-related complications i.e. ERT, HSCT, or gene therapy, with or without chemotherapy conditioning. f) Co-morbidities (e.g. Arnold Chiari malformation) g) Familial predisposition and increased risk due to consanguineous parents h) Neurologic medical history
Risk minimisation measures	Routine risk minimisation measures: • *Warning in SmPC section 4.4 that non-immunological manifestations of ADA-SCID may not respond to Strimvelis* • *Restricted medical prescription* Additional risk minimisation measures: • *None*

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *STRIM-003 (Patient registry): ADA-SCID registry for patients treated with Strimvelis gene therapy: long-term prospective, non-interventional follow-up of safety and efficacy* See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Risks related to residuals present in the drug product administered to the patient	
Evidence for linking the risk to the medicine	Safety risk assessments of residual impurities present (or potentially present) in Strimvelis have been conducted at the time of administration to patients. The outcome of the risk assessments was that they are unlikely to present a hazard to humans based on the low doses of the residual impurities. No adverse events have been reported to date as related to residual impurities from the manufacturing process. CMC identified that the low doses of the residual impurities in Strimvelis are unlikely to present a hazard to humans. The lack of adverse events reported as related to residual impurities from the manufacturing process supports that the risk is likely to be minimal.
Risk factors and risk groups	Not applicable.
Risk minimisation measures	Routine risk minimisation measures: • *Contraindication in SmPC section 4.3 and PL section 2 for patients who have hypersensitivity to Strimvelis or to any of the excipients* • *Warning in SmPC section 4.4 and PL section 2 that Strimvelis contains 42 to 137 mg sodium per dose for consideration for patients on a controlled sodium diet.* • *Warning in SmPC section 4.4 that Strimvelis should be used with caution in patients with hypersensitivity to aminoglycosides or bovine serum albumin.* • *SmPC sections 2.2 and 6.1 and PL section 6 where sodium chloride is listed as an excipient.* • *Restricted medical prescription* Additional risk minimisation measures: • *None*

Important potential risk: Hypersensitivity to the product	
Evidence for linking the risk to the medicine	Biological medicines have the potential to cause an immune response when administered to patients. However, Strimvelis is considered to have a low risk for immunogenicity in ADA-SCID patients due to nature of the disease and the attributes of the therapy. No cases of hypersensitivity to Strimvelis have been reported to date.

	Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice.
Risk factors and risk groups	Clinical risk factors Due to the nature of this disease, ADA-SCID patients are immune deficient and have minimal ability for an immunogenic response to Strimvelis at the time of infusion. Patients are preconditioned with busulfan, which additionally suppresses the immune system and further reduces the risk of an acute immune response to Strimvelis. This may be particularly relevant for patients that have some restored immune function due to prior treatment with ERT with PEG-ADA. Most subjects that receive Strimvelis are also likely to receive ongoing treatments of IVIG, an immunomodulatory agent. This therapy is known to reduce the levels of pathologic antibodies in humans through multiple mechanisms, including potentially causing accelerated clearance of these antibodies [Simon, 2003]. Treatment with IVIG is likely to further reduce the immunogenicity risk of Strimvelis. Product related risk factors The incidence and magnitude of anti-therapeutic antibody formation depends on the level of foreignness and tolerance to a protein. Strimvelis is comprised predominately of autologous-derived cells, which poses essentially no immunogenicity risk to the patient. The risk of an acute immune response against components of the retroviral vector used to transduce the autologous cells or process-related impurities is relatively low due to the patient's suppressed immune status at the time of treatment. Reconstitution of a functional immune system is relatively slow allowing degradation and clearance of potentially immunogenic components in the drug product.
Risk minimisation measures	Routine risk minimisation measures: • *Contraindication in SmPC section 4.3 and PL section 2 for patients who have hypersensitivity to Strimvelis or to any of the excipients* • *Warning in SmPC section 4.4 that Strimvelis should be used with caution in patients with hypersensitivity to aminoglycosides or bovine serum albumin* • *Restricted medical prescription* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *STRIM-003 (Patient registry): ADA-SCID registry for patients treated with Strimvelis gene therapy: long-term prospective, non-interventional follow-up of safety and efficacy* See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Replication competent retrovirus	
Evidence for linking the risk to the medicine	Retroviral vectors are designed to be replication defective but replication competent retrovirus (RCR) may be generated during manufacturing [FDA, 2010]. However, RCR has never been detected in any clinical grade vector or in any patient despite long-term follow-up [FDA, 2010]. In the clinical trial all tests for RCR from bone marrow aspirate and peripheral venous blood yielded negative results. Clinical trials can provide an estimation of the frequency of RCR that is expected to occur in clinical practice. The published medical literature can support the evidence of a possible causal association based on what has been observed with other similar medications.
Risk factors and risk groups	Not applicable.
Risk minimisation measures	Routine risk minimisation measures: • *Restricted medical prescription* Additional risk minimisation measures: • *None*

Missing information: Lack of data in neonates	
Risk minimisation measures	Routine risk minimisation measures: • *Guidance in SmPC section 4.2 that the safety and efficacy of Strimvelis in children less than six months of age has not been established and that no data are available* • *Warning in SmPC section 4.4 that Strimvelis should be used with caution in patients younger than 6 months as there are no data from clinical trials* • *Information in SmPC section 5.1 on the age range of patients studied in the clinical trials* • *Restricted medical prescription* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *STRIM-003 (Patient registry): ADA-SCID registry for patients treated with Strimvelis gene therapy: long-term prospective, non-interventional follow-up of safety and efficacy* See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Lack of data in adolescents	
Risk minimisation measures	Routine risk minimisation measures: • *Guidance in SmPC section 4.2 that the safety and efficacy of Strimvelis in children over 6 years and 7 months of age has not been established and that no data are available* • *Warning in SmPC section 4.4 that Strimvelis should be used with caution in patients older than 6 years and 7 months and reserved for occasions where all other reasonable treatment options have been exhausted.* • *Information in SmPC section 5.1 on the age range of patients studied in the clinical trials* • *Restricted medical prescription.* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *STRIM-003 (Patient registry): ADA-SCID registry for patients treated with Strimvelis gene therapy: long-term prospective, non-interventional follow-up of safety and efficacy* See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Lack of immunogenicity data	
Risk minimisation measures	Routine risk minimisation measures: • *Information in SmPC section 4.4 that no immunogenicity testing has been conducted with Strimvelis* • *Restricted medical prescription* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *STRIM-003 (Patient registry): ADA-SCID registry for patients treated with Strimvelis gene therapy: long-term prospective, non-interventional follow-up of safety and efficacy* See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: No reproductive toxicity studies or embryofetal development studies	
Risk minimisation measures	Routine risk minimisation measures: • *Guidance in SmPC section 5.3 that reproductive and developmental studies have not been conducted.* • *Guidance in SmPC section 4.6 that human data on use during pregnancy or lactation and animal reproduction studies are not available* • *Warning in SmPC section 4.6 that Strimvelis is not intended for use in adults, human data on use during pregnancy or lactation and animal reproduction studies are not available and that the treating physician should inform the patient's parents/carers about options for cryopreservation of spermatogonial stem cells or ovarian tissue.* • *Restricted medical prescription* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *STRIM-003 (Patient registry): ADA-SCID registry for patients treated with Strimvelis gene therapy: long-term prospective, non-interventional follow-up of safety and efficacy* See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Lack of data in delayed onset or late onset ADA-SCID	
Risk minimisation measures	Routine risk minimisation measures: • *Guidance in SmPC section 4.2 that the safety and efficacy of Strimvelis in children over 6 years 1 month of age has not been established and that no data are available* • *Warning in SmPC section 4.4 that Strimvelis should be used with caution in patients older than 6 years and 1 month and reserved for occasions where all other reasonable treatment options have been exhausted* • *Restricted medical prescription* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *STRIM-003 (Patient registry): ADA-SCID registry for patients treated with Strimvelis gene therapy: long-term prospective, non-interventional follow-up of safety and efficacy* See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following study is a condition of the marketing authorisation:

STRIM-003 (Patient registry): ADA-SCID registry for patients treated with Strimvelis gene therapy: long-term prospective, non-interventional follow-up of safety and efficacy

Purpose of the study: To collect long-term safety and effectiveness outcomes for patients treated with Strimvelis

II.C.2 Other studies in post-authorisation development plan

STRIM-005: Methodology study to investigate retroviral insertion site analysis in samples from subjects treated with Strimvelis gene therapy

Purpose of the study: The objective of this study is to evaluate insertion site analysis to predict leukaemia or myelodysplasia in patients treated with Strimvelis