Strimvelis

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0039	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	14/12/2023	n/a		
T/0038	Transfer of Marketing Authorisation	02/06/2023	17/07/2023	SmPC, Labelling and	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

				PL	
PSUSA/10505 /202211	Periodic Safety Update EU Single assessment - autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	06/07/2023	n/a		PRAC Recommendation - maintenance
IA/0037	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	27/03/2023	n/a		
II/0033	Submission of the final report from study STRIM-001 "Evaluation of referring healthcare providers' and parents'/carers' understanding of specific risks associated with Strimvelis treatment" listed as a category 3 study in the RMP. The RMP version 6.1 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/07/2022	n/a		This variation discusses the final study results of the post-authorisation study: "Evaluation of referring Healthcare Providers' and parents'/carers' understanding of specific risks associated with Strimvelis treatment" (STRIM-001). The study demonstrated that the routine and additional RMMs were effective in informing the HCPs and parents/carers about most of the risks associated with Strimvelis treatment and that the outcome of study STRIM-001 does not change the current risk-benefit conclusions for Strimvelis. The RMP was updated to reflect the completion of this study.
IAIN/0035	A.1 - Administrative change - Change in the name and/or address of the MAH	08/07/2022	17/07/2023	SmPC, Labelling and PL	
PSUSA/10505 /202111	Periodic Safety Update EU Single assessment - autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA	10/06/2022	n/a		PRAC Recommendation - maintenance

	sequence				
IB/0032	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	01/12/2021	n/a		
PSUSA/10505 /202011	Periodic Safety Update EU Single assessment - autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	10/06/2021	n/a		PRAC Recommendation - maintenance
R/0029	Renewal of the marketing authorisation.	25/02/2021	30/04/2021	SmPC, Annex II, Labelling and PL	Patients treated with Strimvelis gene therapy continued to demonstrate stable efficacy, as evidenced by sustained engraftment of gene modified cells, the maintenance of purine metabolite levels at non-pathological levels, robust immune reconstitution, and significantly fewer severe infections over time. However, a case of Lymphoid T cell leukemia has been reported in a patient with ADA-SCID 4.7 years after treatment with Strimvelis. This first case of a hematological malignancy following treatment with Strimvelis is considered to be due to insertional oncogenesis. Patients should therefore be monitored long term, with at least annual visits for the first 11 years and then at 13- and 15-years post treatment with Strimvelis and include a complete blood count with differential, biochemistry and thyroid stimulating hormone. Despite this event, the Committee agreed that the overall 100 % survival and high rate of intervention free survival

					encompasses significant and clinically relevant benefit for patients with ADA-SCID for whom no suitable matched related stem cell donor is available. Based on the review of data on quality, safety and efficacy, the Committee considered that the benefit-risk balance of Strimvelis in the approved indication remains favourable but considered that this recent safety signal should be closely monitored and, therefore, an additional renewal is recommended to further evaluate the benefit risk balance of this product.
IAIN/0030/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	16/12/2020	30/04/2021	Annex II and PL	
IB/0028	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	08/07/2020	n/a		
PSUSA/10505 /201911	Periodic Safety Update EU Single assessment - autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA	11/06/2020	n/a		PRAC Recommendation - maintenance

	sequence				
II/0026	Update of sections 4.8 and 5.1 of the SmPC in order to update the safety information following the completion of the STRIM-004 study, which is a non-interventional long term follow up of the subjects who received Strimvelis gene therapy. This study included paediatric patients and is listed as a category 3 study in the RMP. The Package Leaflet is updated accordingly. The RMP version 3.0 has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor administrative changes in the PI. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	28/05/2020	n/a		This variation provides the final results of the STRIM-004 study, the long-term follow up of subjects who received Strimvelis gene therapy in four studies previously assessed in the MAA. The study contributes an additional 5 years follow-up data in 16 patients previously treated with Strimvelis. Overall survival remains at 100%. Subjects treated with Strimvelis gene therapy continued to demonstrate stable efficacy. The overall safety profile for Strimvelis is in line with that expected in an ADA-SCID population which has undergone busulfan conditioning and is undergoing immune reconstitution. No new safety findings have been identified. As a result of this variation, the frequency of smooth muscle antibody (ASMA) positive AEs has been amended from Common to Very common and updated information based on results from LTFU study has been included.
II/0024	Update of sections 4.8 and 5.1 of the SmPC in order to update the safety information following the completion of the STRIM-004 study, which is a non-interventional long term follow up of the subjects who received Strimvelis gene therapy. This study included paediatric patients and is listed as a category 3 study in the RMP. The Package Leaflet is updated accordingly. The RMP version 3.0 has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to	30/04/2020	30/04/2021	SmPC and PL	This variation provides the final results of the STRIM-004 study, the long-term follow up of subjects who received Strimvelis gene therapy in four studies previously assessed in the MAA. The study contributes an additional 5 years follow-up data in 16 patients previously treated with Strimvelis. Overall survival remains at 100%. Subjects treated with Strimvelis gene therapy continued to demonstrate stable efficacy and overall survival remains at 100%. The overall safety profile for Strimvelis is in line with that expected in an ADA-SCID population which has

	introduce minor administrative changes in the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				undergone busulfan conditioning and is undergoing immune reconstitution. No new safety findings have been identified. As a result of this variation, the frequency of smooth muscle antibody (ASMA) positive adverse event has been amended from Common to Very common and updated information based on results from the long-term follow up study has been included.
IB/0027/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	17/04/2020	n/a		
IB/0023	B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	20/12/2019	n/a		
II/0022	Submission of an updated RMP version 2.0 in order to introduce changes to the design of the post-authorisation study STRIM-002, from a prospective to a retrospective study. Following additional minor changes to the RMP are also included: Update of the RMP in line with EMA Rev.2.0.1 template; update of the RMP to make the	17/10/2019	n/a		Through this variation application, the MAH is proposing the revise the design of the study STRIM-002 from prospective to a retrospective analysis of samples previously collected from Strimvelis-treated patients. This proposal to change the retroviral insertion sites analysis is considered acceptable, as the quality of the data obtained should be similar by using a retrospective analysis

	necessary amendments to the name of the MAH following the MAH transfer; update of the data in the RMP in line with the updated data lock point; update of timelines for the STRIM-001 study. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				instead of a prospective one, assuming that enough stored samples are suitable for testing. In addition, as the MAH states, with the retrospective analysis the data will be available in a short time from now, as compared to the prospective study, which will allow earlier conclusions on the suitability of the SLiM-PCR method for the RIS analysis. Following additional minor changes to the updated RMP are also included: Update of the RMP in line with EMA Rev.2.0.1 template; update of the RMP to make the necessary amendments to the name of the MAH following the MAH transfer; update of the data in the RMP in line with the updated data lock point; update of timelines for the STRIM-001 study.
IB/0021	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	02/08/2019	n/a		
IB/0020/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	31/07/2019	n/a		
PSUSA/10505 /201811	Periodic Safety Update EU Single assessment - autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	14/06/2019	n/a		PRAC Recommendation - maintenance

IB/0019	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	29/03/2019	n/a		
II/0016	B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products	31/01/2019	n/a		
PSUSA/10505 /201805	Periodic Safety Update EU Single assessment - autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	17/01/2019	n/a		PRAC Recommendation - maintenance
IB/0017	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	09/01/2019	n/a		
T/0014	Transfer of Marketing Authorisation	27/07/2018	23/08/2018	SmPC, Labelling and PL	
IA/0013/G	This was an application for a group of variations. B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	15/06/2018	n/a		

	B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol				
PSUSA/10505 /201711	Periodic Safety Update EU Single assessment - autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	14/06/2018	n/a		PRAC Recommendation - maintenance
IB/0012	B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	22/05/2018	n/a		
IB/0010	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	01/02/2018	n/a		
PSUSA/10505 /201705	Periodic Safety Update EU Single assessment - autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	11/01/2018	n/a		PRAC Recommendation - maintenance
IB/0009	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	04/12/2017	n/a		

IB/0007	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	02/08/2017	n/a		
II/0006	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	20/07/2017	30/07/2018	SmPC, Annex II and PL	To introduce changes in section 4.3 and 4.4 of the product information following changes in the analytical control of bone marrow samples of patients to allow prospective patients who have previously tested positive for hepatitis C can be treated with Strimvelis, provided they demonstrate absence of ongoing infection using a nucleic acid test with a limit of quantification of □15 international units/ml.
PSUSA/10505 /201611	Periodic Safety Update EU Single assessment - autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	09/06/2017	n/a		PRAC Recommendation - maintenance
IB/0005	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	28/03/2017	n/a		
IB/0003/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	30/01/2017	n/a		

	or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
II/0001/G	This was an application for a group of variations. B.I.b.1 z) To change the acceptance criteria for the	13/10/2016	n/a		

	transduction efficiency test for the drug substance from "Transduction detected" to "≥ 29%". B.I.b.2 d) To replace the method for the measurement of transduction efficiency of the drug substance with an improved transduction efficiency method (the qPCR method). B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS				
IB/0002	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	06/09/2016	n/a		