Summary of risk management plan for Skysona (elivaldogene autotemcel)

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

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

This summary of the RMP for Skysona 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 Skysona's RMP.

I. The medicine and what it is used for

Skysona is authorised for treatment of early cerebral adrenoleukodystrophy in patients less than 18 years of age with an *ABCD1* genetic mutation) (see SmPC for the full indication). It contains elivaldogene autotemcel (eli-cel) as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Skysona's benefits can be found in Skysona's 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/skysona

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

Important risks of Skysona, together with measures to minimise such risks and the proposed studies for learning more about Skysona'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 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 Skysona, 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 Skysona is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Skysona 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 Skysona. 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	Prolonged cytopenias/pancytopenia
Important potential risks	Insertional oncogenesis (e.g. myelodysplasia, leukaemia, lymphoma) Lack or loss of response to gene therapy Neutrophil engraftment failure Platelet engraftment failure
Missing information	Long-term safety and efficacy

II.B Summary of important risks

Identified risk: Prolonged cytopenias/pancytopenia	
Evidence for linking the risk to the medicine	This risk is based on the safety analysis of data collected within the eli-cel clinical development programme which showed prolonged cytopenias/pancytopenia in certain subjects with CALD treated with eli-cel. These findings of prolonged cytopenia/pancytopenia were not correlated with increased incidence of serious infections or bleeding in affected subjects. However, prolonged cytopenia can lead to clinically significant outcomes of serious and potentially life-threatening infections and/or bleeding episodes.
Risk factors and risk groups	Not yet established for eli-cel.
Risk minimisation measures	**Routine risk minimisation measures** SmPC sections 4.4 and 4.8 PL sections 2 and 4 Monitoring of blood counts and evaluation of patients for signs and symptoms of bleeding and infection in SmPC section 4.4. Restricted prescription medicine **Additional risk minimisation measures** Educational materials for healthcare professionals Educational materials for patients/parents/carers Patient alert card
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: REG-502 LTF-304 ALD-102 ALD-104 See section II.C of this summary for an overview of the post-authorisation development plan.

Potential risk: Insertional oncogenesis (e.g. myelodysplasia, leukaemia, lymphoma)	
Evidence for linking the risk to the medicine	Lentiviral vectors (LVVs) integrate into host genomic deoxyribonucleic acid and have a potential for insertional oncogenesis. Gene transfer with γ-retroviral vectors led to development of lymphoma or leukaemia in some of the treated patients within 2-6 years post therapy (Hacein-Bey-Abina et al. 2008; Howe et al. 2008; Boztug et al. 2010; Stein et al. 2010; Paruzynski et al. 2012). Lentiviruses represent a class of retroviruses distinct from γ-retroviruses. Unlike the γ-retroviral vectors that led to leukaemia, self-inactivating-LVVs lack the strong enhancer/promoter long-terminal repeat sequences of γ-retroviral vectors and, unlike γ-retroviral vectors, do not preferentially integrate near gene promoter regions (Riviere et al. 2012). Lenti-D LVV bears a significantly reduced risk of insertional oncogenesis which, however, cannot be fully excluded at this point. Clonal expansion resulting in persistent clonal predominance without clinical evidence of malignancy has been detected in some patients treated with eli-cel. Persistent Clonal predominance is defined as clonal contribution of >50% (integration site specific VCN >0.5 c/dg) at two or more timepoints, and applies to individual lineage evaluations (myeloid, lymphoid, etc.) when performed. These persistent predominant clones had multiple vector insertions and exhibited higher clonal contributions in the $CD15^+$ cells, suggesting a preference for clonal expansion in the myeloid lineage. To date, these clonal expansions have not been associated with a haematologic malignancy. To date, no case of insertional oncogenesis (e.g. myelodysplasia, leukaemia, lymphoma) has been observed within the clinical development programme for eli-cel.
Risk factors and risk groups	No Skysona or Lenti-D LVV-related risks groups or factors have been established.
Risk minimisation measures	**Routine risk minimisation measures** SmPC sections 4.4 and 5.3 PL section 2 At least annual monitoring for myelodysplasia, leukaemia, or lymphoma (including a complete blood count) for 15 years post treatment with Skysona is recommended in SmPC section 4.4 and PL section 2. If myelodysplasia, leukaemia, or lymphoma is detected, collection of blood samples for integration site analysis is recommended in SmPC section 4.4. Restricted prescription medicine **Additional risk minimisation measures** Educational materials for healthcare professionals Educational materials for patients/parents/carers Patient alert card
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: REG-502 LTF-304 ALD-102 ALD-104

	See section II.C of this summary for an overview of the post-authorisation development plan.

Boztug K, Schmidt M, Schwarzer A, Banerjee PP, Diez IA et al. (2010). "Stem-cell gene therapy for the Wiskott-Aldrich syndrome." N Engl J Med 363(20): 1918-1927.

Hacein-Bey-Abina S, Garrigue A, Wang GP, Soulier J, Lim A et al. (2008). "Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1." The Journal of Clinical Investigation 118(9): 3132-3142.

Howe SJ, Mansour MR, Schwarzwaelder K, Bartholomae C, Hubank M et al. (2008). "Insertional mutagenesis combined with acquired somatic mutations causes leukemogenesis following gene therapy of SCID-X1 patients." J Clin Invest 118(9): 3143-3150.

Paruzynski A, Glimm H, Schmidt M, Kalle C (2012). "Analysis of the clonal repertoire of gene-corrected cells in gene therapy." Methods Enzymol 507: 59-87.

Riviere I, Dunbar CE, Sadelain M (2012). "Hematopoietic stem cell engineering at a crossroads." Blood 119(5): 1107-1116.

Stein S, Ott MG, Schultze-Strasser S, Jauch A, Burwinkel B et al. (2010). "Genomic instability and myelodysplasia with monosomy 7 consequent to EVI1 activation after gene therapy for chronic granulomatous disease." Nat Med 16(2): 198-204.

Potential risk: Lack or loss of response to gene therapy	
Evidence for linking the risk to the medicine	Lack or loss of response to gene therapy is a potential risk of Skysona.
Risk factors and risk groups	Not yet established.
Risk minimisation measures	**Routine risk minimisation measures** Restricted prescription medicine **Additional risk minimisation measures** Educational materials for healthcare professionals Educational materials for patients/parents/carers
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: REG-502 LTF-304 ALD-102 ALD-104 See section II.C of this summary for an overview of the post-authorisation development plan.

Potential risk: Neutrophil engraftment failure	
Evidence for linking the risk to the medicine	Data available to date do not indicate that administration of Skysona is associated with neutrophil engraftment failure. However, any transplant procedure is associated with a potential risk of such failure, which is more common for allogeneic haematopoietic stem cell transplantations than for autologous. Considering the potential implications for patients, this risk represents a safety concern of Skysona.
Risk factors and risk groups	Not yet established.
Risk minimisation measures	**Routine risk minimisation measures**: SmPC sections 4.2 and 4.4 PL section 2 Restricted prescription medicine **Additional risk minimisation measures**: Educational materials for healthcare professionals
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: REG-502 ALD-102 ALD-104 See section II.C of this summary for an overview of the post-authorisation development plan.

Potential risk: Platelet engraftment failure	
Evidence for linking the risk to the medicine	Data available to date do not indicate that administration of Skysona is associated with platelet engraftment failure. However, any transplant procedure is associated with a potential risk of such failure. Considering the potential implications for patients, this risk represents a safety concern of Skysona.
Risk factors and risk groups	Not yet established.
Risk minimisation measures	**Routine risk minimisation measures**: Restricted prescription medicine **Additional risk minimisation measures**: Educational materials for healthcare professionals Educational materials for patients/parents/carers
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: REG-502 ALD-102 ALD-104 See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term safety and efficacy	
Risk minimisation measures	**Routine risk minimisation measures**: SmPC section 5.1 Restricted prescription medicine **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: REG-502 LTF-304 ALD-102 ALD-104 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

Post-Approval Registry Study (Stargazer; REG-502)

Purpose of the study:

The purpose purpose ofis to assess the long-term safety and effectiveness of Skysona contextualized against CALD patients concurrently treated with allo-HSCT.

Primary Objectives

- To describe the safety outcomes of patients with CALD treated with Skysona or allogeneic haematopoietic stem cell transplant
- To describe the effectiveness outcomes of patients treated with Skysona or allogeneic haematopoietic stem cell transplant

List of Addressed Safety Concerns:

- Prolonged cytopenias/pancytopenia
- Insertional oncogenesis (e.g. myelodysplasia, leukaemia, lymphoma)
- Lack or loss of response to gene therapy
- Neutrophil engraftment failure
- Platelet engraftment failure
- Long-term safety and efficacy

Ongoing Long-Term Follow-Up Study (LTF-304)

Purpose of the study:

Long-term follow-up of safety and efficacy

Primary Objectives:

- To monitor for long-term safety of eli-cel administered in parent clinical studies.
- To monitor for long-term efficacy of eli-cel administered in parent clinical studies.

List of Addressed Safety Concerns:

- Prolonged cytopenias/pancytopenia
- Insertional oncogenesis (e.g. myelodysplasia, leukaemia, lymphoma)
- Lack or loss of response to gene therapy
- Long-term safety and efficacy

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

Study ALD-102

Purpose of the study:

The objective of the current study is to demonstrate that treatment with eli-cel is able to stabilise the disease at a level of neurological function that preserves the capacity for independent living for subjects with CALD. Furthermore, the second objective of this study is to evaluate the safety of eli-cel in subjects with CALD.

Primary Objectives:

- To evaluate the efficacy of eli-cel in subjects with CALD
- To evaluate the safety of eli-cel in subjects with CALD

List of Addressed Safety Concerns:

- Prolonged cytopenias/pancytopenia
- Insertional oncogenesis (e.g. myelodysplasia, leukaemia, lymphoma)

- Lack or loss of response to gene therapy
- Neutrophil engraftment failure
- Platelet engraftment failure
- Long-term safety and efficacy

Study ALD-104

Purpose of the study:

The objective of the current study is to evaluate the efficacy and safety of eli-cel after myeloablative conditioning with busulfan and fludarabine in subjects with CALD.

Primary Objectives:

- To evaluate the efficacy and safety of eli-cel after myeloablative conditioning with busulfan and fludarabine in subjects with CALD

List of Addressed Safety Concerns:

- Prolonged cytopenias/pancytopenia
- Insertional oncogenesis (e.g. myelodysplasia, leukaemia, lymphoma)
- Lack or loss of response to gene therapy
- Neutrophil engraftment failure
- Platelet engraftment failure
- Long-term safety and efficacy