ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Skysona 2-30 × 10^6 cells/mL dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Skysona (elivaldogene autotemcel) is a genetically modified autologous $CD34^+$ cell-enriched population that contains haematopoietic stem cells (HSCs) transduced *ex vivo* with lentiviral vector (LVV) encoding *ABCD1* complementary deoxyribonucleic acid (cDNA) for human adrenoleukodystrophy protein (ALDP).

2.2 Qualitative and quantitative composition

Each patient-specific infusion bag of Skysona contains elivaldogene autotemcel at a batch-dependent concentration of genetically modified autologous $CD34^+$ cell enriched population. The finished product is packaged in one or more infusion bags, containing a dispersion of 2-30 × 10^6 cells/mL of $CD34^+$ enriched cell population suspended in cryopreservative solution. Each infusion bag contains approximately 20 mL of dispersion for infusion.

The quantitative information of medicinal product regarding strength, $CD34^+$ cells, and dose for the specific patient is provided in the Lot Information Sheet. The Lot Information Sheet is included inside the lid of the cryoshipper used to transport Skysona.

Excipient(s) with known effect

Each dose contains 391-1564 mg sodium (included in Cryostor CS5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion.

A colourless to white to red, including shades of white or pink, light yellow, and orange dispersion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Skysona is indicated for the treatment of early cerebral adrenoleukodystrophy in patients less than 18 years of age, with an *ABCD1* genetic mutation, and for whom a human leukocyte antigen (HLA)-matched sibling haematopoietic stem cell (HSC) donor is not available (see section 5.1).

4.2 Posology and method of administration

Skysona must be administered in a qualified treatment centre by a physician(s) with experience in HSC transplantation and in the treatment of patients with neurological disorders.

Posology

Treatment consists of a single dose for infusion containing a dispersion of $CD34^+$ cells in one or more infusion bags.

The minimum recommended dose of Skysona is 5×10^6 $CD34^+$ cells/kg. In clinical studies doses up to 38.2×10^6 $CD34^+$ cells/kg have been administered.

Mobilisation and apheresis

Patients are required to undergo HSC mobilisation followed by apheresis to obtain $CD34^+$ stem cells which will be used for medicinal product manufacturing (see section 5.1 for description of the mobilisation regimen used in clinical studies).

The patient's weight at first apheresis collection should be used to calculate the final dose.

The minimum target number of $CD34^+$ cells to be collected is 12×10^6 $CD34^+$ cells/kg. If the minimum dose of Skysona 5×10^6 $CD34^+$ cells/kg is not met after initial medicinal product manufacturing, the patient may undergo one or more additional cycles of mobilisation and apheresis, separated by at least 14 days, in order to obtain more cells for additional manufacture.

A back-up collection of $CD34^+$ stem cells of $\geq 1.5 \times 10^6$ $CD34^+$ cells/kg is required. These cells must be collected from the patient and be cryopreserved prior to initiating conditioning and infusion with Skysona. The back-up collection may be needed for rescue treatment if there is: 1) compromise of Skysona after initiation of conditioning and before Skysona infusion, 2) primary engraftment failure, or 3) loss of engraftment after infusion with Skysona (see section 4.4).

Pre-treatment conditioning

The treating physician should confirm that Skysona therapy is appropriate for the patient before conditioning is initiated (see section 4.4).

Myeloablative conditioning must be administered before infusion of Skysona (see section 5.1 for a description of the conditioning regimens used in clinical studies).

Conditioning should not begin until the complete set of infusion bag(s) constituting the dose of Skysona has been received at the administration site, and the availability of the back-up collection is confirmed.

Skysona administration

See Method of Administration below and section 6.6 for details on Skysona administration and handling.

After Skysona administration

Any blood products required within the first 3 months after Skysona infusion should be irradiated.

Special populations

Previous gene therapy administration
Skysona has not been studied in patients previously treated with a gene therapy medicinal product. There is no experience treating a patient more than once with Skysona.

Renal impairment
Skysona has not been studied in patients with renal impairment. Patients should be assessed for renal impairment to ensure Skysona therapy is appropriate. No dose adjustment is required.

Hepatic impairment
Skysona has not been studied in patients with hepatic impairment. Patients should be assessed for hepatic impairment to ensure Skysona therapy is appropriate. No dose adjustment is required.

Female patients
The safety and efficacy of Skysona in female patients have not been established. No data are available.

Paediatric population
The safety and efficacy of Skysona in children aged up to 3 years have not been established. No data are available.

Patients seropositive for human immunodeficiency virus (HIV)
Skysona has not been studied in patients with HIV-1, HIV-2, HTLV-1, and HTLV-2. A negative serology test for HIV is necessary to ensure acceptance of apheresis material for Skysona manufacturing. Apheresis material from patients with a positive test for HIV will not be accepted for Skysona manufacturing.

Method of administration

Skysona is for intravenous use only.
For detailed instructions on preparation, administration, accidental exposure and disposal of Skysona, see section 6.6.

After completion of the conditioning, there must be a minimum of 48 hours of washout before Skysona infusion.

Before infusion, it must be confirmed that the patient's identity matches the unique patient information on the Skysona infusion bag(s). The total number of infusion bags to be administered should also be confirmed with the Lot Information Sheet (see section 4.4).

Skysona infusion should be completed as soon as possible and no more than 4 hours after thawing. Each infusion bag should be administered in less than 60 minutes. In the event that more than one infusion bag

is provided, all infusion bags must be administered consecutively. The entire volume of each infusion bag should be infused.

Standard procedures for patient management in line with HSC transplantation should be followed after Skysona infusion.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

Contraindications to the mobilisation agents and the conditioning agents must be considered.

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient should be kept for a period of 30 years after expiry date of the product.

Autologous use

Skysona is intended solely for autologous use and should under no circumstances be administered to other patients. Skysona must not be infused if the information on the patient-specific label on the infusion bag(s), Lot Information Sheet and metal cassette(s) do not match the intended patient.

Mobilisation and myeloablative conditioning medicinal products

Warnings and precautions of the mobilisation agents and the conditioning agents must be considered.

Hypersensitivity reactions

The dimethyl sulfoxide (DMSO) in Skysona may cause severe hypersensitivity reactions, including anaphylaxis.

Engraftment failure as measured by neutrophil engraftment

Treatment with Skysona involves the infusion and engraftment of $CD34^+$ HSCs that have been genetically modified *ex vivo* with a Lentiviral vector (LVV). Failure of neutrophil engraftment is a short-term but potentially severe risk, defined as failure to achieve 3 consecutive absolute neutrophil counts (ANC) $\geq$ 500 cells/µL obtained on different days by Day 43 after infusion of Skysona (see section 5.1). Patients who experience neutrophil engraftment failure should receive rescue treatment with the back-up collection (see section 4.2).

Prolonged cytopenias

Patients may exhibit cytopenias for several months following conditioning and Skysona infusion and cases of pancytopenia have been reported. In clinical studies with Skysona, Grade 3 or higher cytopenias after Day 60 following infusion occurred in 26% of patients and included decreased platelet count (13%), decreased neutrophil count (17%), and decreased hemoglobin (2%). After 100 days following infusion, 16% of patients had any Grade 3 or higher cytopenia, including decreased platelet count (9%), decreased

neutrophil count (11%); no patient had Grade 3 or higher decreased haemoglobin (0%). Blood counts should be monitored after Skysona infusion and patients should be evaluated for signs and symptoms of bleeding and infection.

Risk of insertional oncogenesis

There are no reports of LVV-mediated insertional mutagenesis resulting in oncogenesis, including myelodysplasia, leukaemia, or lymphoma, associated with Skysona. Nevertheless, there is a theoretical risk after treatment with Skysona. Clonal expansion resulting in clonal predominance without clinical evidence of malignancy has been detected in some patients treated with Skysona.

Patients should be monitored at least annually for myelodysplasia, leukaemia, or lymphoma (including with a complete blood count) for 15 years post treatment with Skysona. If myelodysplasia, leukaemia, or lymphoma is detected in a patient who received Skysona, blood samples should be collected for integration site analysis.

Serological testing

All patients should be tested for HIV-1/-2 prior to mobilisation and apheresis to ensure acceptance of the apheresis material for Skysona manufacturing (see section 4.2).

Anti-retroviral use

Patients should not take anti-retroviral medicinal products from at least one month prior to mobilisation (see section 4.5). If a patient requires anti-retrovirals for HIV prophylaxis, Skysona treatment, including mobilisation and apheresis of $CD34^+$ cells through Skysona infusion, should be delayed until an HIV infection could be adequately ruled out according to local guidance for HIV testing.

Interference with serology testing

It is important to note that patients who have received Skysona are likely to test positive by polymerase chain reaction (PCR) assays for HIV due to LVV provirus insertion, resulting in a false positive test for HIV. Therefore, patients who have received Skysona should not be screened for HIV infection using a PCR-based assay.

Blood, organ, tissue and cell donation

Patients treated with Skysona should not donate blood, organs, tissues, or cells for transplantation at any time in the future. This information is provided in the Patient Information Leaflet and also in the Patient Alert Card which must be given to the patient.

After Skysona administration

There are no data showing an effect of Skysona treatment on the adrenal insufficiency related to ALD. Replacement therapy should be continued.

Patients are expected to enrol in a registry-based study and will be followed in the registry in order to better understand the long-term safety and efficacy of Skysona.

Sodium content

This medicinal product contains 391-1564 mg sodium per dose, equivalent to 20-78% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Patients should not take anti-retroviral medicinal products from at least one month prior to mobilisation until at least apheresis is completed (see section 4.4).

No formal drug interaction studies have been performed. Skysona is not expected to interact with the hepatic cytochrome P-450 family of enzymes or drug transporters.

Live vaccines

The safety of immunisation with live viral vaccines during or following Skysona treatment has not been studied. Vaccination with live virus vaccines is not recommended during the 6 weeks preceding the start of myeloablative conditioning, and until haematological recovery following treatment with Skysona.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

There are insufficient exposure data to provide a precise recommendation on duration of contraception following treatment with Skysona. Women of childbearing potential and men capable of fathering a child and their female partners must use an effective method of contraception (intrauterine device or combination of hormonal and barrier contraception) from start of mobilisation through at least 6 months after administration of Skysona. The SmPC of the conditioning agents should be consulted for information on the need for effective contraception in patients who undergo conditioning.

A negative serum pregnancy test in women of childbearing potential must be confirmed prior to the start of mobilisation and re-confirmed prior to conditioning procedures and before medicinal product administration.

Pregnancy
No clinical data on exposed pregnancies are available.

Reproductive and developmental toxicity studies with Skysona were not performed. Skysona must not be used during pregnancy because of conditioning (see section 4.3). It is unknown whether Skysona transduced cells have the potential to be transferred in utero to a foetus. Pregnancy after treatment with Skysona should be discussed with the treating physician.

There is no opportunity for germline transmission of the LVV that encodes an *ABCD1* cDNA for human ALDP after treatment with Skysona, therefore the likelihood that an offspring would have general somatic expression of the lentiviral vector that encodes an *ABCD1* cDNA for human ALDP is considered negligible.

Breast-feeding

It is unknown whether Skysona is excreted in human milk. The effect of administration of Skysona to mothers on their breast-fed children has not been studied.

Skysona must not be administered to women who are breast-feeding.

Fertility

There are no data on the effects of Skysona on human fertility. Effects on male and female fertility have not been evaluated in animal studies.

Data are available on the risk of infertility with conditioning. It is therefore advised to consider cryopreservation of semen or ova before treatment.

4.7 Effects on ability to drive and use machines

Skysona has no influence on the ability to drive or use machines.

The effect of the mobilisation agents and the conditioning agents on the ability to drive or use machines, or engage in activities such as cycling or skateboarding, must be considered.

4.8 Undesirable effects

Summary of the safety profile

The safety of Skysona was evaluated in 51 patients with CALD in Studies ALD-102, ALD-104, and LTF-304 (see section 5.1). The most serious adverse reaction attributed to Skysona was pancytopenia (3.9%). Given the small patient population and size of cohorts, adverse reactions in the table below do not provide a complete perspective on the nature and frequency of these events. Information related to safety endpoints used in the studies is provided in section 5.1.

Tabulated list of adverse reactions

Adverse reactions are listed by MedDRA body system organ class and by frequency. Frequencies are defined as: very common (≥1/10) and common (≥1/100 and <1/10). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Tables 1, 2, and 3 are lists of adverse reactions attributed to mobilisation/apheresis, conditioning, and Skysona, respectively, experienced by patients with CALD in clinical studies with Skysona.

Table 1 Adverse reactions attributed to mobilisation/apheresis

System Organ Class (SOC)	Very common	Common
Blood and lymphatic system disorders		Thrombocytopenia, Anaemia
Metabolism and nutrition disorders	Hypokalaemia	Hypomagnesaemia
Nervous system disorders		Headache
Vascular disorders		Hypertension
Gastrointestinal disorders		Vomiting, Nausea, Paraesthesia oral
Skin and subcutaneous tissue disorders		Pruritus

Musculoskeletal and connective tissue disorders		Bone pain, Pain in extremity,
Investigations		Haemoglobin decreased

Table 2 Adverse reactions attributed to conditioning

System Organ Class (SOC)	Very common	Common
Infections and infestations		Pseudomonal bacteraemia, Bacteraemia, Streptococcal bacteraemia, Pneumonia, Bacterial infection, Device related infection, Enterocolitis infectious, Gastroenteritis viral, Oral candidiasis, Otitis media, Pharyngitis streptococcal, Respiratory syncytial virus infection, Rhinovirus infection, Sinusitis, Skin infection, Upper respiratory tract infection bacterial, Viral upper respiratory tract infection, Folliculitis, Anal candidiasis
Blood and lymphatic system disorders	Febrile neutropenia, Neutropenia, Thrombocytopenia, Anaemia, Leukopenia, Lymphopenia	Lymph node pain
Endocrine disorders		Adrenal insufficiency, Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	Hypokalaemia, Hypomagnesaemia, Decreased appetite, Hypophosphataemia	Hypoglycaemia, Fluid retention, Hyponatraemia
Psychiatric disorders		Aversion, Insomnia
Nervous system disorders	Headache	Sensory loss, Tremor, Hyporeflexia
Eye disorders		Conjunctival haemorrhage
Cardiac disorders		Bradycardia, Sinus tachycardia, Tachycardia
Vascular disorders	Hypertension	Petechiae
Respiratory, thoracic and mediastinal disorders	Epistaxis	Hypoxia, Tachypnoea, Cough, Oropharyngeal pain, Rhinorrhoea
Gastrointestinal disorders	Stomatitis, Vomiting, Diarrhoea, Abdominal pain, Constipation, Nausea	Gastritis, Gastrointestinal inflammation, Anal fissure, Proctitis, Anal pruritis, Dyspepsia, Oral pain, Proctalgia
Skin and subcutaneous tissue disorders	Alopecia, Skin hyperpigmentation	Rash pustular, Skin exfoliation, Dermatitis diaper, Drug eruption, Dry skin,

		Hyperhidrosis, Pruritis, Rash, Rash maculo-papular
Renal and urinary disorders		Haematuria, Incontinence, Urinary incontinence, Dysuria, Urinary tract pain
Reproductive system and breast disorders		Penile pain, Scrotal ulcer
General disorders and administration site conditions	Pyrexia	Face oedema, Mucosal inflammation, Fatigue
Investigations	Alanine aminotransferase increased, Aspartate aminotransferase increased	Occult blood positive, Adenovirus test positive, International normalised ratio increased, Blood alkaline phosphatase increased, Blood immunoglobulin G decreased, Blood lactate dehydrogenase increased, C-reactive protein increased, Weight decreased, Weight increased
Injury, poisoning and procedural complications		Allergic transfusion reaction,

Table 3 Adverse reactions attributed to Skysona

System Organ Class (SOC)	Very common	Common
Infections and infestations		Cystitis viral
Blood and lymphatic system disorders		Pancytopenia
Gastrointestinal disorders		Vomiting

Description of selected adverse reactions

Haematopoietic reconstitution
Two serious reactions of pancytopenia occurred in two patients, with onset following neutrophil engraftment. Both patients had delayed hematopoietic reconstitution requiring prolonged support with blood and platelet transfusions as well as growth factors (G-CSF and eltrombopag). One patient had intercurrent parvovirus. Both events were ongoing at least 18 months after Skysona infusion.

Infusion-related reactions
Vomiting occurred in two patients on the day of infusion, potentially related to the cryopreservation agent. Premedication may be utilized at physician discretion.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No data from clinical studies are available regarding overdose of Skysona.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, ATC code: not yet assigned

Mechanism of action

Skysona adds functional copies of the *ABCD1* cDNA into patients' HSCs through transduction of autologous $CD34^+$ cells with Lenti-D LVV. After Skysona infusion, transduced $CD34^+$ HSCs engraft in the bone marrow and differentiate into various cell types, including monocytes ($CD14^+$) that migrate to the brain where they are believed to further differentiate into macrophages and cerebral microglia that can produce functional ALDP. The functional ALDP can then enable the local degradation of very long chain fatty acids (VLCFAs) in the brain, which in turn can stabilise the disease by preventing further inflammation and demyelination. However, it is not anticipated that Skysona treatment will affect other manifestations of ALD including adrenal insufficiency. Impact of Skysona treatment on adrenomyeloneuropathy has not been studied. Following successful engraftment with genetically modified cells, the expression of ALDP is expected to be life-long.

Pharmacodynamic effects

One month after Skysona treatment, all evaluable patients in Study ALD-102 (N = 25) produced ALDP in $CD14^+$ peripheral blood cells with a median (min, max) $CD14^+$ ALDP+ of 29.50% (8.20%, 49.65%) demonstrating early expression of the transgene. For patients with at least 6 months of follow-up, $CD14^+$ ALDP+ cells generally declined slightly after Skysona infusion and stabilized by approximately Month 6. Patients had a Month 6 median (min, max) $CD14^+$ %ALDP+ of 22.20% (2.00%, 71.40%) in Study ALD-102 (N = 27).

The percentage of ALDP+ cells remained generally stable in $CD14^+$ peripheral blood cells through Month 24 with a median (min, max) of 16.90% (5.80%, 44.60%) in Study ALD-102 (N = 26). The percentage of $CD14^+$ ALDP+ cells continued to be stable at last follow-up through Month 60, demonstrating long-term expression of transgenic ALDP in the progeny of haematopoietic stem cells.

Clinical efficacy and safety

The safety and efficacy of Skysona were assessed in an open-label, single-arm study in patients with CALD (ALD-102; N = 32) and compared to the efficacy and safety of allo-HSCT in patients with CALD in a contemporaneous comparator study (ALD-103; N = 59). All patients who completed or discontinued Study ALD-102 were asked to participate in a long-term follow-up study, LTF-304.

Enrolment in Study ALD-102 is complete with 32 patients enrolled and treated; 30 patients are evaluable for the Month 24 primary efficacy endpoint.

In addition, a second open-label, single-arm study (ALD-104; N = 19) is ongoing; no patients have reached the Month 24 evaluation timepoint and thus are not included in any efficacy analyses.

Mobilisation and apheresis

All patients were administered a median dose of 10 µg/kg of G-CSF for a minimum of 4 days to mobilise stem cells prior to the apheresis procedure.

In Study ALD-102, patients were assessed on the morning after the 4th G-CSF dose. If the peripheral blood $CD34^+$ count on that morning was <50 cells/µL, a 5th dose of G-CSF was administered and plerixafor was administered at a dose of 0.24 mg/kg of body weight approximately 10 hours prior to the next day's apheresis collection. Plerixafor could be given daily for up to 4 days. Eleven of the 32 (34.4%) patients in Study ALD-102 received plerixafor.

For all patients, 1 cycle of mobilisation and apheresis was sufficient to collect the minimum number of $CD34^+$ cells to manufacture Skysona.

Pre-treatment conditioning

In Study ALD-102, 32 patients received pharmacokinetically-dosed busulfan in conjunction with cyclophosphamide prior to treatment with Skysona. Busulfan was administered with a recommended cumulative AUC of 17,000 to 21,000 µmol*min/L over four days of conditioning. For patients ≤ 12 kg, busulfan was dosed at 1.1 mg/kg/dose IV every 6 hours and for patients > 12 kg busulfan was dosed at 0.8 mg/kg/dose IV every 6 hours for 4 days. Busulfan dose adjustments were made as needed based on pharmacokinetic monitoring. Patients received anti-seizure, anti-fungal, and antibiotic prophylaxis in accordance with institutional guidelines. The recommended dose of cyclophosphamide was 50 mg/kg/day. The median (min, max) daily average busulfan dose was 3.5 (2.8, 4.2) mg/kg/day (N = 31) and the median (min, max) estimated average daily AUC was 4729 (4039, 5041) µmol*min/L/day (N = 31).

In Study ALD-104, 19 patients received pharmacokinetically-dosed busulfan in conjunction with fludarabine prior to treatment with Skysona.

Skysona administration

All patients were administered Skysona as an intravenous infusion with a median (min, max) dose of 11.78 (5.0, 38.2) × 10^6 $CD34^+$ cells/kg (N = 51).

After Skysona administration

In Study ALD-102, patients received G-CSF at the investigator's discretion per institutional practice following treatment with Skysona. Of the 32 treated patients, 24 received G-CSF following treatment with Skysona.

In Study ALD-104, patients were to receive G-CSF beginning on Day 5 following treatment with Skysona.

<u>Study ALD-102</u>

Study ALD-102 was an open-label, single-arm, 24-month study that included a total of 32 patients with CALD treated with Skysona. In study ALD-102, early CALD was defined as: a Loes score between 0.5 and 9 (inclusive), gadolinium enhancement on MRI of demyelinating lesions and a neurologic function score (NFS) of ≤ 1, indicating limited changes in neurologic function. Patients were excluded from Study ALD-102 if they had a willing and available HLA-matched sibling HSC donor. The median (min, max) age at Skysona infusion was 6.0 (4, 14) years, 100% of patients were males, and 46.9% were White/Caucasian. The median (min, max) Loes score at baseline was 2.00 (1.0, 9.0). Of the 32 patients, 31 had an NFS of 0 and one had an NFS of 1 at baseline. All patients that completed ALD-102 enrolled

for long-term follow-up in the LTF-304 study. The median (min, max) duration of follow-up was 38.59 (13.4, 82.7) months.

The primary efficacy endpoint was the proportion of patients who had none of the 6 Major Functional Disabilities (MFDs), were alive, did not receive a second allo-HSCT or rescue cell administration, and had not withdrawn or been lost to follow-up at Month 24 (i.e., Month 24 MFD-free survival). The 6 MFDs are: loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement.

An analysis was conducted after 30 patients were evaluable for the primary efficacy endpoint, Month 24 MFD-free survival. Twenty-seven out of 30 patients (90%, 95% CI: 73.5, 97.9) achieved Month 24 MFD-free survival, with the lower bound of 95% CI above the clinically meaningful benchmark (Month 24 MFD-free survival rate of 50%) indicating that treatment with Skysona provides clinically meaningful benefits by preserving motor function and communication ability and improves survival when compared to untreated patients at an early stage of cerebral disease.

A contemporaneous comparator study was conducted in 59 patients with CALD treated with allo-HSCT (ALD-103 Safety Population). A subset of 27 patients (ALD-103 Efficacy Population) was matched to the ALD-102 population for baseline Loes score, presence of contrast enhancement and NFS score. This population was further divided into those who received an allo-HSCT from a matched sibling donor (N = 10; ALD-103 Efficacy Population with MSD) and those who received an allo-HSCT from an alternative donor source, i.e., not a matched sibling donor (N = 17; ALD-103 Efficacy Population without MSD).

MFD-free survival over time and overall survival were analysed in 32 patients in ALD-102 and compared to 17 patients treated with allo-HSCT in the ALD-103 Efficacy Population (without MSD), which are presented in Table 4 and Figure 1.

Skysona showed a durable effect on MFD-free survival, with most patients (26/27, 96.3%) that enrolled in LTF-304 remaining alive and maintaining their MFD-free status through their last follow-up on study, including 14 patients with 5 or more years of follow-up. One patient refused further follow-up.

Table 4: Efficacy Endpoints

	ALD-102 Skysona Treated[a] (N=32)	ALD-103 Allo-HSCT Efficacy Population[b] (N=27)	ALD-103 Allo-HSCT Efficacy Population[c] without MSD (N=17)	ALD-103 Allo-HSCT Efficacy Population[d] with MSD (N=10)
Proportion of MFD-Free Survival[e] at Month 24				
Evaluable Patients[f]	30	18	9	9
n	27	14	6	8
%	90.0%	77.8%	66.7%	88.9%
[95% CI]	[73.5, 97.9]	[52.4, 93.6]	[29.9, 92.5]	[51.8, 99.7]
Number of Patients with Events by Month 24[g]				
n	3	8	6	2
%	9.4%	29.6%	35.3%	20.0%
Number of Surviving Patients by Month 24[h]				
n	31	22	14	8
%	96.6%	86.2%	86.3%	88.9%
[95% CI]	[77.9, 99.5]	[62.6, 95.4]	[54.7, 96.5]	[43.3, 98.4]

[a] entry criteria included elevated VLCFA values, a Loes score between 0.5 and 9 (inclusive), gadolinium enhancement on MRI of demyelinating lesions, NFS of ≤ 1 and no willing and available HLA-matched sibling HSC donor

[b] matched to the ALD-102 population for baseline Loes score, presence of contrast enhancement, and NFS score

[c] matched to the ALD-102 population for baseline Loes score, presence of contrast enhancement, and NFS score and no willing and available HLA-matched sibling HSC donor

[d] matched to the ALD-102 population for baseline Loes score, presence of contrast enhancement, and NFS score and had an HLA-matched sibling HSC donor

[e] Primary efficacy endpoint; proportion of patients with no event by Month 24; includes death, MFD, rescue cell administration, or subsequent allo-HSCT

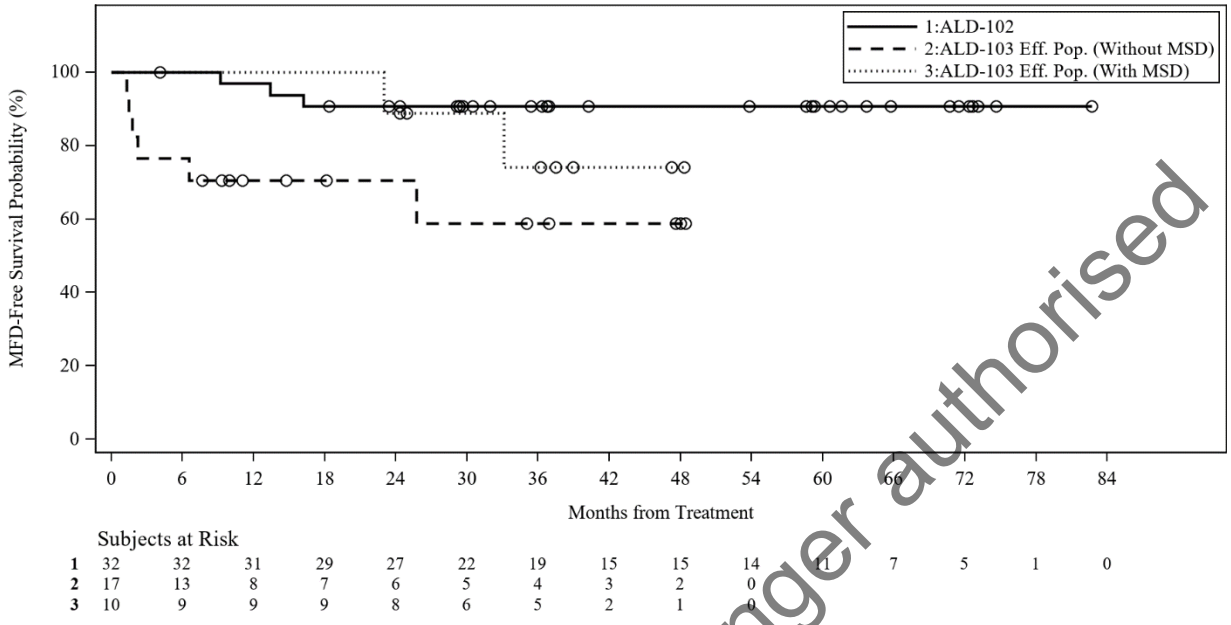
[f] ALD-102 and ALD-103 Month 24 Evaluable Subjects for MFD-free Survival are defined as treated subjects who had been followed for 24 months, or had completed the Month 24 Visit, or had discontinued from the studies (for any reason, including death) but would have been followed for 24 months if still in the study, at the time of the data cut for these analyses

[g] Time-to-event Kaplan-Meier analysis; includes death, MFD, rescue cell administration, or subsequent allo-HSCT

[h] Time-to-event Kaplan-Meier analysis; includes death only

MSD = matched sibling donor.

Figure 1 **Kaplan-Meier Curve of MFD-free Survival Between ALD-102 (Skysona Treated) and ALD-103 Efficacy Population (without MSD and with MSD)**



The neurologic function score (NFS) was used as a secondary endpoint to evaluate 15 domains of neurological function; it has a total maximum score of 25. A score of 0 denotes no abnormality in the assessed areas of neurological function. At baseline, patients were required to have an NFS ≤ 1. In ALD-102, 26 of 28 evaluable patients maintained an NFS less than or equal to 1 through Month 24 and 24 of those patients had no change in their NFS, which showed maintenance of neurological function in the majority of patients. The majority of patients in ALD-102 maintained cognitive function (IQ, including performance IQ sub-measures) within the normal range (100 ± 15 points), with minimal decline and with stabilization by Month 24. A small subgroup of patients who had higher Loes scores at baseline tended to have a less favourable outcome.

The primary safety endpoint, the proportion of evaluable patients who experienced either acute (≥ Grade II) or chronic graft versus host disease (GVHD) in ALD-102 vs. ALD-103 by Month 24, was 0 vs. 52%.

The proportion of all patients who experienced either acute (≥ Grade II) or chronic GVHD in ALD-102/ALD-104 vs. ALD-103 is summarized in Table 5.

Table 5: Graft Versus Host Disease

	Skysona treated		Allo-HSCT
	ALD-102 (N = 32)	**ALD-102/104** (N = 51)	**ALD-103 Safety Population[a]** (N = 59)
Acute (≥ Grade II) GVHD or Chronic GVHD			
n	0	0	26
%	0%	0%	44.1%
[95% CI]	[0.0, 10.9]	[0.0, 7.0]	[31.2, 57.6]
Acute (≥ Grade II) GVHD			
n	0	0	15
%	0%	0%	25.4%
[95% CI]	[0, 10.9]	[0.0, 7.0]	[15.0, 38.4]
Chronic GVHD			
n	0	0	14
%	0%	0%	23.7%
[95% CI]	[0, 10.9]	[0.0, 7.0]	[13.6, 36.6]

[a] For censored observations in the ALD-103 Safety Population, it was assumed that no GVHD was observed in any category

Neutrophil engraftment was monitored as a secondary endpoint and was defined as achieving 3 consecutive absolute neutrophil counts (ANC) ≥ 500 cells/µL obtained on different days by Day 43 after Skysona infusion. In clinical studies neutrophil engraftment occurred on median (min, max) Day 13 (11, 41) after Skysona infusion (see section 4.4) (N = 32, ALD-102; N = 17, ALD-104) compared to Day 17 (12, 36) in ALD-103 (N = 53).

No primary or secondary neutrophil engraftment failure was observed in subjects in ALD-102/ALD-104 (N=51), compared to 10/59 (16.9%) subjects in ALD-103.

Platelet engraftment was monitored as a secondary endpoint and was defined as achieving 3 consecutive unsupported platelet counts of $\geq 20 \times 10^9$ cells/L obtained on different days after Skysona infusion, with no platelet transfusions administered for 7 days immediately preceding and during the evaluation period. In clinical studies, platelet engraftment occurred on median (min, max) Day 32 (14, 108) after Skysona infusion (N = 32, ALD-102; N = 15, ALD-104) compared to Day 26 (13, 67) in ALD-103 (N = 47).

No patients experienced transplant-related mortality (TRM), a secondary endpoint, at 100 days or 365 days after transplant in ALD-102 and ALD-104. In contrast, 2/59 (3.4%) patients experienced TRM at 100 days and 8/59 (13.6%) patients experienced TRM at 365 days after transplant in the ALD-103 Safety Population.

5.2 Pharmacokinetic properties

Skysona is an autologous gene therapy medicinal product consisting of autologous cells that have been genetically modified *ex vivo*. The nature of Skysona is such that conventional studies on pharmacokinetics, absorption, distribution, metabolism, and elimination are not applicable.

5.3 Preclinical safety data

Conventional mutagenicity, carcinogenicity and reproductive and developmental toxicity studies have not been conducted.

The pharmacology, toxicology and genotoxicity of the Lenti-D LVV used for transduction were evaluated *in vitro* and *in vivo*. In an *in vitro* immortalization assay, Lenti-D LVV-transduced mouse bone marrow cells showed strongly reduced mutagenic potential as compared to positive control vectors. Integration site analysis of pre-transplantation Lenti-D LVV-transduced human $CD34^+$ HSCs demonstrated the expected self-inactivating LVV integration profile, with no enrichment for insertion in or near cancer-related genes.

A pivotal GLP-compliant combined toxicity, genotoxicity and biodistribution study of Lenti-D LVV-transduced mobilized peripheral blood $CD34^+$ HSCs was conducted in myeloablated immunodeficient mice. There was no evidence of toxicity, genotoxicity (insertional mutagenesis resulting in oncogenic mutations) or oncogenesis (tumorigenicity) related to Lenti-D LVV integration. Integration site analysis of post-transplantation bone marrow cells demonstrated no preferred integration in the proximity of or within cancer-related genes. An additional study with Lenti-D LVV-transduced human $CD34^+$ HSCs administered to myeloablated, immunodeficient mice demonstrated engraftment of human-origin microglial cells within brain tissues with no toxicity or tumorigenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cryostor CS5

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

6 months
Once thawed: maximum 4 hours at room temperature (20 ºC – 25 ºC)

6.4 Special precautions for storage

Store in the vapour phase of liquid nitrogen at ≤ -140 °C until ready for thaw and administration.

Keep infusion bag(s) in the metal cassette(s).

Do not re-freeze after thawing.

For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Approximately 20 mL in a fluoro ethylenepropylene infusion bag(s), each packed in a transparent pouch inside a metal cassette.

Skysona is shipped from the manufacturing facility to the infusion centre storage facility in a cryoshipper, which may contain multiple metal cassettes intended for a single patient. Each metal cassette contains one infusion bag with Skysona. One lot of drug product may be packaged in either one or two 20 mL bags, depending on the total number of cells present. Multiple lots may be administered to the patient as a single dose.

6.6 Special precautions for disposal and other handling

Irradiation could lead to inactivation of the product.

Precautions to be taken before handling or administering the medicinal product

- This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Skysona should take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.
- Keep the infusion bag(s) in the metal cassette(s) and store in the vapor phase of liquid nitrogen at ≤ -140 °C until ready for thaw and administration.

Preparation for the infusion

- Remove each metal cassette from liquid nitrogen storage and remove each infusion bag from the metal cassette.
- Confirm that Skysona is printed on the infusion bag(s).
- Confirm that patient identity matches the unique patient identification information located on the Skysona infusion bag(s) and on the Lot Information Sheet. Skysona is intended solely for autologous use. Do not infuse Skysona if the information on the patient-specific label on the infusion bag does not match the intended patient.
- Ensure that you have the correct number of infusion bags and confirm each infusion bag is within the expiry date using the accompanying Lot Information Sheet.
- Each infusion bag should be inspected for any breaches of integrity before thawing and infusion. If an infusion bag is compromised, follow the local guidelines for handling of waste of human-derived material and contact bluebird bio immediately.

Thawing

- If more than one infusion bag is provided, thaw and administer each infusion bag completely before proceeding to thaw the next infusion bag.
- Do not sample, alter, irradiate, or refreeze the medicinal product.
- Thaw Skysona at 37 °C in a water bath or dry bath. Thawing of each infusion bag takes approximately 2 to 4 minutes. Do not over thaw the medicinal product. Do not leave the medicinal product unattended and do not submerge the infusion ports in a water bath.
- After thaw, mix the medicinal product gently by massaging the infusion bag until all of the contents are uniform.

Administration

- Expose the sterile port on the infusion bag by tearing off the protective wrap covering the port.
- Access the medicinal product infusion bag and infuse per the administration site's standard procedures for administration of cell therapy products. Do not use an in-line blood filter or an infusion pump.
- Infuse Skysona as soon as possible and store for no more than 4 hours at room temperature (20 ºC – 25 ºC) after thawing.

- Administer each infusion bag of Skysona via intravenous infusion over a period of less than 60 minutes.
- Flush all Skysona remaining in the infusion bag and any associated tubing with at least 50 mL of sodium chloride 9 mg/mL (0.9%) solution for injection to ensure as many cells as possible are infused into the patient.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and all material that has been in contact with Skysona (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.

Accidental exposure

In case of accidental exposure, local guidelines on handling of human derived materials should be followed, which may include washing of the contaminated skin and removal of contaminated clothes. Work surfaces and materials which have potentially been in contact with Skysona must be decontaminated with appropriate disinfectant.

7. MARKETING AUTHORISATION HOLDER

bluebird bio (Netherlands) B.V.
Stadsplateau 7
WTC Utrecht
3521AZ Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1563/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Minaris Regenerative Medicine GmbH
Haidgraben 5
85521 Ottobrunn
GERMANY

Name and address of the manufacturer(s) responsible for batch release

Minaris Regenerative Medicine GmbH
Haidgraben 5
85521 Ottobrunn
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Skysona in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational material and its implementation plan, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational material is aimed at providing additional information on the use of Skysona.

The MAH shall ensure that in each Member State where Skysona is marketed, all healthcare professionals (HPCs) and patients/parents/carers who are expected to prescribe, dispense or use Skysona have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

The physician educational material should contain:
  - The Summary of Product Characteristics
  - Guide for healthcare professionals
  - Guide for handling and method of administration.

- **The guide for healthcare professionals** shall contain the following key elements:
  - Warnings and precautions of the mobilisation agents and the conditioning agents must be considered.
  - Treatment with Skysona was associated in clinical studies with prolonged cytopenias/pancytopenia. No correlation was observed between prolonged cytopenias/pancytopenia and incidence of serious adverse events of bleeding or infection. Blood counts should be checked after Skysona infusion and patients should be monitored for bleeding events and infections.
  - Treatment with Skysona is associated with the potential risk of insertional oncogenesis (e.g. myelodysplasia, leukaemia, lymphoma). All patients must be advised on signs of myelodysplasia, leukaemia, or lymphoma and instructed to seek immediate medical attention if these signs are present. All patients should receive at least annual monitoring including with complete blood counts for myelodysplasia, leukaemia, or lymphoma.
  - A negative serology test for HIV is necessary to ensure acceptance of apheresis material for Skysona manufacturing.
  - The potential risk of lack or loss of response to gene therapy may lead to the return of signs and symptoms of the disease.
  - Treatment with Skysona is associated with a short-term potential risk of neutrophil engraftment failure, which shall be managed by administration of rescue cells.
  - Treatment with Skysona is associated with a potential risk of platelet engraftment failure which may require supportive treatment.
  - The need to explain and to ensure that patients understand:
    - potential risks of treatment with Skysona
    - signs and symptoms of bleeding and infection and what action to take

        - signs of myelodysplasia, leukaemia, and lymphoma and what action to take
        - the importance of annual check-ups, including at least annual complete blood counts
        - content of patient/parent/carer guide
        - the need to carry the patient alert card and show it to every HCP
        - enrolment in the Registry Study REG-502.
    - Scope of the Registry Study REG-502 and how to enrol patients.

- **The guide to handling and method of administration for healthcare professionals** shall contain the following key elements:
    - Information on receiving and storing of Skysona and how to check Skysona prior to administration.
    - Information on thawing and administration of Skysona.
    - Information on protective equipment and treatment of spills.

The patient information pack should contain:

- Package leaflet
- A patient/parent/carer guide
- A patient alert card

- **The patient/parent/carer guide** shall contain the following key messages:
    - Treatment with Skysona is associated with the risk of prolonged cytopenias/pancytopenia that could lead to an increased chance of infection and/or bleeding. Signs and symptoms of bleeding and infections and the need to contact the physician.
    - Treatment with Skysona is associated with a possible risk of malignancy (e.g. myelodysplasia, leukaemia, lymphoma). Signs of myelodysplasia, leukaemia, or lymphoma and the need to obtain urgent medical care if these signs are present.
    - The importance of annual check-ups and at least annual complete blood counts.
    - Patient alert card and the need to carry it on their person and tell any treating HCP that they were treated with Skysona.
    - Treatment with Skysona is associated with a possible risk of platelet engraftment failure which may require treatment.
    - The potential risk of lack or loss of response to gene therapy may lead to the return of signs and symptoms of cerebral adrenoleukodystrophy.
    - Enrolment in the Registry Study REG-502.

- **The patient alert card** shall contain the following key messages:
    - Information on the risk of prolonged cytopenias/pancytopenia and the potential for infection and/or bleeding events.
    - Statement that the patient was treated with gene therapy and should not donate blood, organs, tissues, or cells.
    - Statement that the patient was treated with Skysona, including Lot number and treatment date(s).
    - Details on reporting of adverse events.
    - Information on the possibility of false positivity of certain commercial HIV tests because of Skysona.
    - Statement on importance of annual check-ups and at least annual complete blood counts.
    - Contact details where the patient or an HCP can receive further information.

The MAH shall ensure that in each Member State where Skysona is marketed, a system aimed to control distribution to Skysona is ensured as a routine risk minimisation measure. The following requirements need to be fulfilled before the product is prescribed, manufactured, dispensed and used:

- Skysona will only be available through bluebird bio-qualified treatment centres (QTCs) that have demonstrable procedures and a quality agreement to ensure traceability of the patient`s cells and manufactured drug product between the treating hospital and manufacturing site. The traceability system, i.e. the Service Portal, will be initiated prior to apheresis collection of donor cells with a set of identifier numbers specific for the individual patient. These numbers will be documented by the QTC in the site records and patient medical records. All identifier numbers will additionally be documented and tracked by bluebird bio and the drug product manufacturer in records that accompany the autologous cells and the systems used to track the workflow.
- The treatment centre qualification process includes mandatory training of the healthcare professionals of the hospital, including on ordering, management and handling of Skysona as well as on its Summary of Product Characteristics (SmPC). The process of enrolling patients for treatment with Skysona will be supported by the Service Portal and includes a selection of the indication in accordance with the SmPC or "other use", which will alert of intended off-label use. In case "other use" has been selected in the system Service Portal, the ordering process will be stopped and consultation with bluebird bio's medical affairs team initiated, therefore, minimising the risk for off-label use.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Non-interventional post-authorisation safety study (PASS): In order to further characterise and contextualise the long-term safety and efficacy of Skysona in patients with cerebral adrenoleukodystrophy (CALD), the MAH should conduct, and submit the results of a prospective observational Registry Study (REC-502) of patients with CALD treated with Skysona or allogeneic haematopoietic stem cell transplantation (allo-HSCT) according to an agreed protocol (Stargazer).	Interim reports to be submitted in accordance with the RMP. Final report: 2042
In order to evaluate the long-term efficacy and safety of Skysona in patients with cerebral adrenoleukodystrophy (CALD), the MAH should submit final results of Study LTF-304.	Interim reports to be submitted in accordance with the RMP. Final report: 2037

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING - METAL CASSETTE

1. NAME OF THE MEDICINAL PRODUCT

Skysona 2-30 × 10^6 cells/mL dispersion for infusion
elivaldogene autotemcel ($CD34^+$ cells encoding *ABCD1* gene)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

An autologous $CD34^+$ cell-enriched population that contains haematopoietic stem cells transduced with lentiviral vector encoding *ABCD1* complementary deoxyribonucleic acid for human adrenoleukodystrophy protein (ALDP).

3. LIST OF EXCIPIENTS

Also contains Cryostor CS5 (contains sodium).

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion

Approximately 20 mL
See Lot Information Sheet for number of infusion bags and $CD34^+$ cells per kg for this patient.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in the vapour phase of liquid nitrogen at ≤ -140 °C until ready for thaw and administration. Keep infusion bag(s) in the metal cassette(s). Once thawed do not re-freeze. Shelf life after thawing: maximum 4 hours at room temperature (20 °C – 25 °C)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

bluebird bio (Netherlands) B.V.
Stadsplateau 7
WTC Utrecht
3521AZ Utrecht
The Netherlands
Tel: +31 (0) 303 100 450
e-mail: medinfo@bluebirdbio.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1563/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Last Name:
First Name:
Date of Birth:
Patient ID:
DIN:
Lot:
COI ID:
Bag ID:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INFUSION BAG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Skysona 2-30 × 10^6 cells/mL dispersion for infusion
elivaldogene autotemcel ($CD34^+$ cells encoding *ABCD1* gene)
For intravenous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP:
Shelf life after thawing: maximum 4 hours at room temperature (20 °C – 25 °C)

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Last Name
First Name:
Date of Birth:
Patient ID:
DIN:
Lot:
COI ID:
Bag ID:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Approximately 20 mL of cell dispersion per bag.
See Lot Information Sheet for number of infusion bags and $CD34^+$ cells per kg for this patient.

6. OTHER

For autologous use only.

PARTICULARS TO APPEAR ON THE LOT INFORMATION SHEET INCLUDED WITH EACH SHIPMENT FOR ONE PATIENT

1. NAME OF THE MEDICINAL PRODUCT

Skysona 2-30 × 10^6 cells/mL dispersion for infusion
elivaldogene autotemcel ($CD34^+$ cells encoding *ABCD1* gene)
Intravenous use

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Skysona is an autologous $CD34^+$ cell-enriched population that contains haematopoietic stem cells transduced with lentiviral vector encoding *ABCD1* complementary deoxyribonucleic acid for human adrenoleukodystrophy protein (ALDP).

3. DONATION AND PRODUCT CODES

PATIENT INFORMATION

Name (Last, First):
Date of Birth (DD/MM/YYYY):
Weight at First Collection (kg):
Patient ID:

4. BATCH NUMBER, CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT, AND EXPIRY DATE

INFORMATION ON SUPPLIED LOT(S)

The following lot(s) was manufactured and included in the shipment:

Lot Number / COI ID	**DIN** (List all collections)	**Number of Infusion Bags**	**Bag ID** (List each infusion bag)	**Strength** (× 10^6 cells/mL)	**$CD34^+$ Cells** (× 10^6 $CD34^+$ cells)	**Expiry Date** (DD/MM/YYYY)

5. DOSE OF THE MEDICINAL PRODUCT

Total Number of Infusion Bags: __
Dose: {N.N} × 10^6 $CD34^+$ cells/kg

The minimum recommended dose of Skysona is 5.0 × 10^6 $CD34^+$ cells/kg. In clinical studies doses up to 38.2 × 10^6 $CD34^+$ cells/kg have been administered.

6. OTHER SPECIAL WARNING(S), IF NECESSARY

SAVE THIS DOCUMENT AND PREPARE TO HAVE IT AVAILABLE AT THE TIME OF SKYSONA INFUSION.

Read the package leaflet before use.
For autologous use only.

7. SPECIAL STORAGE CONDITIONS

INSTRUCTIONS FOR STORAGE AND USE

Store in the vapour phase of liquid nitrogen at ≤ -140 °C until ready for thaw and administration. Keep infusion bag(s) in the metal cassette(s).
Shelf life after thawing: maximum 4 hours at room temperature (20 °C – 25 °C).
Once thawed do not re-freeze.

8. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

9. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MARKETING AUTHORISATION HOLDER AND NUMBER

bluebird bio (Netherlands) B.V.
Stadsplateau 7
WTC Utrecht
3521AZ Utrecht
The Netherlands
e-mail: medinfo@bluebirdbio.com

10. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1563/001

B. PACKAGE LEAFLET

Package leaflet: Information for the patient or carer

Skysona 2-30 × 10^6 cells/mL dispersion for infusion
elivaldogene autotemcel (autologous $CD34^+$ cells encoding *ABCD1* gene)

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you or your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you/your child is given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask the doctor or nurse.
- If you get any side effects, talk to the doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- The doctor or nurse will give you a Patient Alert Card which contains important safety information about the treatment with Skysona. Read it carefully and follow the instructions on it.
- Carry the Patient Alert Card with you at all times and always show it to any doctor or nurse who sees you or if you go to the hospital.

What is in this leaflet

1. What Skysona is and what it is used for

Skysona is used to treat a serious genetic disease called cerebral adrenoleukodystrophy (CALD) in children and adolescents younger than 18 years old.

People with CALD have an alteration in the gene that makes a protein called adrenoleukodystrophy protein (ALDP). People with CALD either cannot make this protein or have a protein that does not work well. This leads to the build-up of very long chain fatty acids in the body, particularly in the brain. These fatty acids cause severe damage to brain cells. If untreated, this damage will lead to problems with vision, hearing, talking, walking and/or thinking, and will likely lead to death.

Skysona is a type of medicine called gene therapy. It is made specifically for each patient, using the patient's own blood stem cells.

Cells called stem cells are collected from the patient's blood. They are then modified in a laboratory to insert a working gene for making ALDP. When you/your child is given Skysona, which is made up of these modified cells, the cells will start making ALDP, which will then break down the very long chain fatty acids. This is expected to slow down the progression of the disease.

Skysona is given by a drip (infusion) into a vein (intravenously). For more information on what happens before and during treatment, see section 3, How Skysona is made and given.

2. What you need to know before you or your child is given Skysona

You or your child must not be given Skysona if you or your child:
- are allergic to any of the ingredients of this medicine (listed in section 6).
- are allergic to any of the ingredients in the medicines your child will be given before treatment with Skysona (see section 3).

Warnings and precautions

- Information about cell-based medicinal products, like Skysona, must be kept for 30 years at the hospital. The information kept about you or your child will be your name and the batch number of Skysona received.
- Skysona is made from your or your child's own stem cells and should only be given to you or your child.
- An ingredient of Skysona called dimethyl sulfoxide (DMSO) may cause an allergic reaction, so the doctor or nurse should watch closely during and following the infusion for any signs or symptoms of a reaction.

Before the treatment with Skysona the doctor will

- check the kidneys and liver;
- check for human immunodeficiency virus (HIV);
- discuss possible impacts of the conditioning medicine on fertility (see below under "*Fertility in men and women*");
- prepare for stem cells to be taken (mobilisation) and then clear the cells from your child's bone marrow ready for Skysona to be given (conditioning). For more information on this, including possible side effects of the medicines used, see sections 3 and 4.

After the treatment with Skysona

- Blood counts may remain low for more than 2 months after conditioning and treatment with Skysona. During that time, there may be a risk for bleeding and infection. The doctor will monitor this using blood tests and will tell you when blood counts have returned to safe levels.
- If you require a blood transfusion within the first 3 months after having received Skysona, blood products should be irradiated. This will reduce the white blood cells, called lymphocytes, and minimise the risk of a reaction to the transfusion.
- After treatment with Skysona, you will not be able to donate blood, organs, tissues or cells. This is because Skysona is a gene therapy medicine.
- Adding a new gene into the stem cells could theoretically cause blood cancers (myelodysplasia, leukaemia, and lymphoma). After the treatment, the doctor will monitor you at least every year, which will include a blood test, for at least 15 years and the doctor will check for any signs of cancer of the

blood. Contact the doctor if you have fever, you are more tired than usual, are losing weight without trying, or if you have frequent nosebleeds, bleeding, or bruising.

- Skysona is prepared using parts of HIV, which have been altered so that they cannot cause HIV infection. The virus is used to insert a working gene into your child's blood stem cells.
- Although this medicine will not give an HIV infection, having Skysona in the blood may cause a false positive HIV test result because some HIV tests recognise a piece of HIV that is used to make Skysona. If the patient tests positive for HIV following treatment, please contact the doctor or nurse.

When Skysona treatment cannot be completed or fails
Before receiving Skysona you or your child will be given conditioning medicine in order to remove cells from the existing bone marrow.

If Skysona cannot be given after having the conditioning medicine or if the modified stem cells do not take hold (engraft) in the body, the doctor may give you an infusion of your own original blood stem cells that were collected and stored before the treatment started (see also section 3, How Skysona is made and given). If you or your child get your original cells back, you or your child will not have any treatment benefit.

Other medicines and Skysona
Tell your doctor if you or your child is taking, has recently taken or might take any other medicines.

Your child should not take any medicines for HIV infection from at least one month before having the mobilisation medicines (see also section 3, How Skysona is made and given). If such medicines are needed, the procedure will be postponed.

It is not recommended that **live vaccines** be given within 6 weeks before receiving the conditioning medicine to prepare for Skysona treatment, nor after treatment while the immune system (the body's defence system) is recovering. Talk to the doctor if there is a need to have any vaccinations.

Contraception, pregnancy, breast-feeding and fertility

Contraception in men and women
Women who could become pregnant and men capable of fathering a child must start using an effective method of contraception from before the blood stem cells are collected and continue until at least 6 months after receiving Skysona. Effective methods of contraception include intra-uterine device or a combination of oral contraceptive (also known as the pill) and condoms. Also read the package leaflet for the conditioning medicine for information regarding contraception.

Pregnancy
Skysona must not be given during pregnancy because of the conditioning medicine.

Women who could become pregnant will be given a pregnancy test before starting mobilisation, before given conditioning medicine, and before Skysona treatment in order to confirm that she is not pregnant. If a woman becomes pregnant after treatment with Skysona, she should contact her treating physician.

The added gene from Skysona will not be passed on to the foetus in case of a pregnancy and the unborn child is still at risk of inheriting the original *ABCD1* gene, which, when absent or does not work, causes adrenoleukodystrophy.

Breast-feeding
Skysona must not be given when breast-feeding. It is not known whether the ingredients of Skysona can pass into breast milk.

Fertility in men and women
It may no longer be possible to become pregnant or father a child after receiving conditioning medicine. If you are concerned, you should discuss this with the doctor before treatment.

Driving and using machines
Skysona has no effect on the ability to drive or use machines. However, the mobilisation and conditioning medicines may cause dizziness and tiredness. You or your child should avoid activities requiring balance (for example, cycling or skateboarding) and driving or using machines if you or your child feel dizzy, tired, or unwell.

Skysona contains sodium
This medicine contains 391–1564 mg sodium (main component of cooking/table salt) in each dose. This is equivalent to 20 - 78% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Skysona is made and given

About 2 months before treatment with Skysona, you or your child will be given medicines that will move blood stem cells from the bone marrow into the blood stream (mobilisation). The blood stem cells can then be collected by a machine that separates blood components (apheresis machine). It may take more than 1 session to collect enough blood stem cells both to make Skysona and to store as replacement cells if Skysona cannot be given or does not work.

How you or your child is given Skysona
Skysona is given by a drip (infusion) into a vein, this is often through a central venous catheter. It can only be given in a specialised hospital by doctors who are experienced in treating patients with CALD, transplanting bone marrow, and using gene therapy medicines. Skysona is a one-time treatment. It will not be given again. If Skysona does not work, you will come back to the treatment center and you will receive a transfusion of your original replacement stem cells. These cells do not contain the medicine and therefore your CALD will not be treated.

When	What is done	Why
About 2 months before Skysona infusion	Mobilisation medicine is given	To move the blood stem cells from your child's bone marrow into the blood stream.
About 2 months before Skysona infusion	Blood stem cells are collected	To make Skysona and to store some stem cells as replacement cells, if needed.
At least 6 days before Skysona infusion	Conditioning medicine is given in a hospital	To prepare the bone marrow for treatment by destroying cells in the bone marrow so they can be replaced with the modified cells in Skysona.
Start of Skysona treatment	Skysona is given by a drip (infusion) into a vein. This will be in a hospital and will take less than 60 minutes for each	To add blood stem cells containing the ALDP gene into the bone marrow.

	infusion bag. The number of bags will vary by patient.	
After Skysona infusion	You or your child will likely remain in the hospital for about 3–6 weeks	To recover and be monitored until the doctor is satisfied that it is safe to leave the hospital.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects are related to the mobilisation medicine and blood stem cell collection or to the conditioning medicine used to prepare the bone marrow for treatment with Skysona. You should discuss possible side effects due to the mobilisation medicines and conditioning medicine with the doctor. You should also read the package leaflets for these medicines.

Tell the doctor or nurse immediately if you or your child is having any side effects after receiving the treatment. The side-effects below usually happen within the first few days and several weeks after receiving treatment but can also develop much later.

Mobilisation and blood stem cell collection

Very common side effects (may affect more than 1 in 10 people)
- low level of potassium seen in a blood test

Common side effects (may affect up to 1 in 10 people)
- low level of blood platelets, which may lead to bleeding
- low level of red blood cells which may lead to fatigue
- low level of magnesium seen in a blood test
- headache
- high blood pressure
- feeling sick (nausea), being sick (vomiting)
- tingling sensation in the mouth
- itchy skin
- pain in bones, arms and legs

Conditioning Medicine

Very common side effects (may affect more than 1 in 10 people)
- low level of white blood cells, sometimes with fever, which may lead to an infection
- low level of red blood cells which may lead to fatigue
- low level of blood platelets, which may lead to bleeding
- fever
- soreness of the mouth
- nosebleeds
- blood tests showing decrease in magnesium, potassium, or phosphate, increase of liver enzymes
- headache
- decreased appetite

- stomach pain, constipation, diarrhoea
- feeling sick (nausea), being sick (vomiting)
- unusual hair loss or thinning
- dark patches on skin
- high blood pressure

Common side effects (may affect up to 1 in 10 people)
- various kinds of infections in different parts of the body that may be caused by viruses, bacteria, or fungi. These may include an infection of the bloodstream or venous catheter infections, infection of the gastrointestinal system, ear infection, thrush, anal yeast infection, respiratory infection. These may cause symptoms such as feeling hot (feverish), chilly or sweaty, cough, diarrhoea, and vomiting.
- impaired function of the adrenal glands which may result in dangerously low blood pressure
- low level of oxygen in the blood measured by a monitor
- high level of antidiuretic hormone which leads to water retention in the body
- inflammation of the digestive tract lining (which runs from the mouth to the anus), small tear in tissue that lines the anus (anal fissure), inflammation or itching of anus
- blood in stool, spots on the skin from bleeding under the skin, bleeding in eye, increase in time to clot your blood
- stomach irritation
- urinary incontinence, blood in urine, discomfort when passing urine, urinary tract pain
- sore throat, pain in the mouth, rectum, penis, lymph nodes
- slow or fast heart rate
- fast breathing
- excessive sweating
- blood test showing decrease in antibodies
- blood tests showing decrease in sodium, blood test showing increase in alkaline phosphatase, lactate dehydrogenase
- low blood sugar
- cough
- runny nose
- decrease in skin sensation in legs
- dry, peeling or itchy skin, rash, diaper rash, sore on the scrotum
- involuntary movement (tremor)
- decrease in reflexes
- allergic reaction to platelet transfusion
- dislike of swallowing medication
- swelling in face or body (oedema)
- tiredness, trouble sleeping
- weight increased or decreased

Skysona

Common side effects (may affect up to 1 in 10 people)
- low level of white blood cells, which may lead to an infection

- low level of red blood cells which may lead to fatigue
- low level of blood platelets, which may lead to bleeding
- viral infection in bladder. This may cause symptoms such as feeling hot (feverish), chilly or sweaty, blood in urine, pain in lower stomach, and in small children also vomiting.
- vomiting

Reporting of side effects
If you or your child experience any side effects, talk to the doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Skysona

This information is intended for healthcare professionals only. This information is shared for the patient's awareness only.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer container and infusion bag.

Store at or below -140 °C for up to six months.

Keep infusion bag(s) in the metal cassette(s).

Do not re-freeze after thawing.

Do not thaw the product until it is ready to be used. Once thawed, store at room temperature (20 °C - 25 °C) and use within 4 hours.

6. Contents of the pack and other information

What Skysona contains
- The active substance of Skysona consists of your child's own blood stem cells that contains functional copies of the ALDP gene. The concentration per bag is 2-30 × 10^6 blood stem cells per millilitre.
- The other ingredient is a solution used to preserve frozen cells (see section 2, Skysona contains sodium).

This medicine contains genetically modified human blood cells.

What Skysona looks like and contents of the pack
Skysona is a colourless to white to red dispersion of cells including shades of white or pink, light yellow, and orange. The medicine is supplied in one or more clear infusion bags, each packed in a transparent pouch inside a closed metal container. Skysona may be packaged in one or more 20 mL bags, depending on the total number of cells present. One or more bags may be given to obtain the full dose.

The patient's name and date of birth, as well as coded information identifying you or your child as the patient, are printed onto each infusion bag and each metal container.

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This leaflet was last revised in <{MM/YYYY}>.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Precautions to be taken before handling or administering the medicinal product

- This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Skysona should take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.
- Keep the infusion bag(s) in the metal cassette(s) and store in the vapor phase of liquid nitrogen at ≤ -140 °C until ready for thaw and administration.

Preparation for infusion

- Skysona is shipped from the manufacturing facility to the infusion centre storage facility in a cryoshipper, which may contain multiple metal cassettes intended for a single patient. Each metal cassette contains one infusion bag with Skysona. A patient may have multiple infusion bags.
- Remove each metal cassette from liquid nitrogen storage and remove each infusion bag from the metal cassette.
- Confirm that Skysona is printed on the infusion bag(s).
- Confirm that patient identity matches the unique patient identification information located on the Skysona infusion bag(s) and on the Lot Information Sheet. Skysona is intended solely for autologous use. Do not infuse Skysona if the information on the patient-specific label on the infusion bag does not match the intended patient.
- Ensure that you have the correct number of infusion bags and confirm each infusion bag is within the expiry date using the accompanying Lot Information Sheet.
- Each infusion bag should be inspected for any breaches of integrity before thawing and infusion. If an infusion bag is compromised, follow the local guidelines for handling of waste of human-derived material and contact bluebird bio immediately.

Thawing

- If more than one infusion bag is provided, thaw and administer each infusion bag completely before proceeding to thaw the next infusion bag.
- Do not sample, alter, irradiate, or refreeze the medicinal product.
- Thaw Skysona at 37 °C in a water bath or dry bath. Thawing of each infusion bag takes approximately 2 to 4 minutes. Do not over thaw the medicinal product. Do not leave the medicinal product unattended and do not submerge the infusion ports in a water bath.
- After thaw, mix the medicinal product gently by massaging the infusion bag until all of the contents are uniform.

Administration

- Expose the sterile port on the infusion bag by tearing off the protective wrap covering the port.

- Access the medicinal product infusion bag and infuse per the administration site's standard procedures for administration of cell therapy products. Do not use an in-line blood filter or an infusion pump.
- Infuse Skysona as soon as possible and store for no more than 4 hours at room temperature (20 ºC – 25 ºC) after thawing.
- Administer each infusion bag of Skysona via intravenous infusion over a period of less than 60 minutes.
- Flush all Skysona remaining in the infusion bag and any associated tubing with at least 50 mL of sodium chloride 9 mg/mL (0.9%) solution for injection to ensure as many cells as possible are infused into the patient.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and all material that has been in contact with Skysona (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.

Accidental exposure

In case of accidental exposure, local guidelines on handling of human-derived materials should be followed, which may include washing of the contaminated skin and removal of contaminated clothes. Work surfaces and materials which have potentially been in contact with Skysona must be decontaminated with appropriate disinfectant.