20 December 2023
EMADOC-1700519818-1230857
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Casgevy (exagamglogene autotemcel)
EU/3/19/2210 and EU/3/19/2242

Sponsor: Vertex Pharmaceuticals (Ireland) Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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Introductory comment:

The therapeutic indication

- Casgevy is indicated for the treatment of transfusion-dependent β-thalassemia (TDT) in patients 12 years of age and older for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available.
- Casgevy is indicated for the treatment of severe sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs) for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available.

falls within the scope of the two designated orphan conditions "treatment of beta-thalassaemia intermedia and major" and "treatment of sickle cell disease" and are covered in this one document.

1. Casgevy for treatment of beta-thalassaemia intermedia and major - EU/3/19/2210 (EMA/OD/0000146264)

1.1. Product and administrative information

Product	
Designated active substance	Autologous CD34+ haematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene
Other name(s)	--
International Non-Proprietary Name	Exagamglogene autotemcel
Tradename	Casgevy
Orphan condition	Treatment of beta-thalassaemia intermedia and major
Sponsor's details:	Vertex Pharmaceuticals (Ireland) Limited Unit 49 Block 5 Northwood Court Northwood Crescent Dublin 9 D09 T665 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Vertex Pharmaceuticals (Ireland) Limited
COMP opinion	12 September 2019
EC decision	17 October 2019
EC registration number	EU/3/19/2210
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Jan Mueller-Berghaus / Heli Suila
Applicant	Vertex Pharmaceuticals (Ireland) Limited
Application submission	29 December 2022
Procedure start	24 January 2023
Procedure number	EMA/H/C/005763
Invented name	Casgevy
Proposed therapeutic indication	Treatment of transfusion-dependent β-thalassemia (TDT) in patients 12 years of age and older for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available. Further information on Casgevy can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/casgevy
CHMP opinion	14 December 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttila / Enrico Costa
Sponsor's report submission	10 July 2023

COMP discussion	5-7 December 2023
COMP opinion (adoption via written procedure)	20 December 2023

1.2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2019 was based on the following grounds:

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing autologous CD34+ haematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene was considered justified based on in vitro data showing the increased expression of foetal haemoglobin and early clinical data in a patient who achieved transfusion independence with 6 months follow up;

- the condition is life-threatening and chronically debilitating due to the severe anaemia, the need for blood transfusions, and the complications related to these, in particular in beta-thalassaemia major patients;

- the condition was estimated to be affecting approximately 0.8 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous CD34+ haematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that suggest a disease modifying potential of the product in patients restoring clinically acceptable levels of haemoglobin. This would compare favourably to other current methods of treatment. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing autologous CD34+ haematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene as an orphan medicinal product for the orphan condition: treatment of beta-thalassaemia intermedia and major.

1.3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Beta thalassaemias are a group of inherited autosomal recessive disorders caused by genetic mutations that reduce or eliminate the expression of β-globin, which results in an α to non-α globin chain imbalance and decrease in adult haemoglobin (HbA) tetramers in red blood cells (RBCs). Unpaired α-globin chains precipitate, leading to destruction of erythroid precursors and ineffective erythropoiesis (i.e., destruction of RBC precursors in the bone marrow) and peripheral haemolysis. β-thalassaemia is caused by point mutations or, more rarely, deletions in the HBB gene, leading to reduced (β+) or absent (β0) synthesis of the β-chains of haemoglobin.

Historically, individuals with beta thalassemia were classified as having beta thalassemia major, intermedia, and minor (asymptomatic carrier).

Thalassemia major can be of any β0/β0, β0/β+, or β+/β+ genotype that results in a transfusion-dependent phenotype. Thalassemia intermedia is characterized by clinical diversity, is classified as non-transfusion-dependent thalassemia (patients receive occasionally, if any, transfusions) and its diagnosis is based on the severity of the condition rather than the underlying genetic abnormality (results from either the inheritance of 1 or 2 mild β-thalassemia alleles, or alternatively, the co-inheritance of genetic modifiers that reduce the severity associated with inheritance of 2 severe β-thalassemia alleles).

A moderate, mild microcytic anaemia is the characteristic feature of minor beta thalassaemia (also called trait) where the genotype is β/β0 or β/β+ haemoglobin analysis and HbF is up to 5%. Subsequently, β-thalassemia has been classified Transfusion dependent (TD) β-thalassemia and Non-Transfusion Dependent (NTD) β-thalassemia (Taher, 2017).

The COMP has previously considered that individuals with beta thalassaemia trait are not to be included in the proposed orphan condition, because of their limited clinical relevance (Premawardhena A Br J Haematol. 2008;141(3):407).

The approved therapeutic indication "Casgevy is indicated for the treatment of transfusion-dependent β-thalassemia (TDT) in patients 12 years of age and older for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available" falls within the scope of the designated orphan condition "Treatment of beta-thalassaemia intermedia and major".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The COMP has previously considered that the condition is life-threatening and chronically debilitating due to the severe anaemia, the need for blood transfusions, and the complications related to these. This view is still retained.

All of the pathophysiologic features of β-thalassaemias can be linked to the primary imbalance and accumulation of unpaired α-globin chains within the developing erythrocytes, resulting in ineffective erythropoiesis and peripheral haemolysis that lead to clinical complications including chronic anaemia, primary iron overload, and hypercoagulable state (Musallam, 2013a; Taher, 2018a; Sleiman, 2018).

Number of people affected or at risk

The sponsor has conducted a literature search to establish the prevalence estimate for the condition. Two different estimates are provided. One is based on country specific data. The results of this data are summarised below in Table 1.

Table 1. Estimates of the Prevalence of Beta Thalassemia in the EEA Using Country-Specific Data

Country	Last year of the historically reported prevalence	Estimate of historically reported prevalence as cases per 10,000	Population at time of the historically reported prevalence[31]	Estimated number of historically reported prevalent cases	Estimate of historically reported incidence as cases per 10,000 live births[17]	Estimated total of live births (2021) [19]	Estimated total of new cases since the historically reported prevalence to 2023	Total population in 2023[31]	Estimated number of prevalent cases in 2023
Italy	2022	1.22	59,037,000	7,185 [21]	0.97	399,431	39	58,871,000	7,224
Greece	2015	1.94	10,806,600	2,099 [15]	0.97	85,303	66	10,341,000	2,165
Germany	2022	0.19	83,369,843	1,600 [28]	0.97	795,492	77	83,295,000	1,677
Cyprus	2015	4.99	1,187,000	592 [14]	0.97	10,150	8	1,260,000	600
France	2019	0.10	64,399,800	668 [29]	0.97	738,594	287	64,757,000	955
Netherlands	2022	0.20	17,564,000	350 [28]	--[a]	179,441	10	17,618,000	360
Sweden	2013	0.49	9,648,932	470 [26]	0.97	114,263	111	10,612,000	581
Norway	2021	0.23	4,405,300	100 [30]	0.97	56,060	11	5,474,000	111
Subtotal for the countries listed above								252,228,000	13,672
Estimated prevalence per 10,000							**~ 0.54 cases per 10,000 individuals**		
Total for the entire EEA								**458,551,212**	**24,856**

The estimate of historically reported prevalence is computed based on the estimated number of reported prevalent cases as a proportion of the population at the time of the historically reported prevalence, The estimate used as the number of beta-thalassemia major for Cyprus and Sweden is actual published estimate for number of cases with βthalassemia in 2015 and 2013 respectively. The estimated incidence for β-Thalassemia reported in Modell and Darlison was used throughout. This will overestimate the incidence, especially considering that a number of countries have implemented prevention measures. The estimated total of new cases since historically reported incidence is derived from multiplying the estimated incidence per 10,000 live births, by estimated total live births reported in 2021, and multiplied by the number of years since the last reported prevalence, assuming comparable annual total live birth rates as in 2021, e.g., France (0.97/10,000) ×(738,594)×(2023-2019).
The estimates do not take into account the disease-related mortality likely resulting in an overestimation of prevalent cases.
Estimates for total populations are based on UN Population Prospects and live births for the countries and EEA are based on reports from the Eurostat database
--[a]The incidence of the Netherlands is based on Giordano et al (2004) indicating that based on predicted frequencies, it is expected that the Netherlands would have 10 new cases per year. This estimate was then multiplied by 1 year (2023 – 2022).

This method proposes a prevalence of 0.54 in 10,000 in the EU/EEA

The second approach is based on modelling by applying an inflated common incidence rate based on Modell and Darlison to each country's 2021 estimate of live births, then multiplying the number of years from last reported prevalence to 2023 to yield an approximate number of new cases since then,

assuming comparable annual live birth rates to 2021. In this analysis, the incidence rate by Modell and Darlison was inflate by tenfold (i.e., 0.97 per 1,000 instead of 0.97 per 10,000) for all countries except Greece and Cyprus which had higher incidence rates, to be conservative in our prevalence estimate.

The results of this approach are presented in Table 2 below.

Table 2. Estimates of the Prevalence of Thalassemia (Syndromes) in the EEA

Country	Last year of the historically reported prevalence	Estimate of historically reported prevalence as cases per 10,000	Population at time of the historically reported prevalence [19]	Estimated number of historically reported prevalent cases	Estimate of historically reported incidence as cases per 1,000 live births[17,18]	Estimated total number of live births (2021)	**Estimated total number of new cases since historically reported prevalence to 2023	Total population in 2023[19]	Estimated number of prevalent cases in 2023
Italy	2013	1.173	59,685,227	7,000	0.97	399,431	3,874	58,871,000	10,874
Greece	2013	2.945	11,003,615	3,241	1.60	85,303	1,365	10,341,000	4,606
Germany	2013	0.186	80,523,746	1500	0.97	795,492	7,716	83,295,000	9,216
Cyprus	2013	7.38	865,878	639	5.50	10,150	558	1,260,000	1,197
France	2013	0.087	65,600,350	571	0.97	738,594	7,164	64,757,000	7,735
Netherlands	2013	0.15	16,779,575	250	0.97	179,441	1,741	17,618,000	1,197
Spain	2013	0.024	46,727,890	113	0.97	336,247	3,262	47,520,000	3,375
Belgium	2013	0.09	11,137,974	100	0.97	118,349	1,148	11,686,000	1,248
Sweden	2015	0.7	9,747,355	682	0.97	114,263	1,108	10,612,000	1,790
Subtotal for the countries listed above								305,960,000	42,033
Estimated prevalence								**~1.37 cases per 10,000 individuals**	
Total for the entire EEA								**458,551,200**	**62,996**

Notes: The estimate of historically reported prevalence is computed based on the estimated number of reported prevalent cases as a proportion of the population at the time of the historically reported prevalence.
The estimated total of new cases since historically reported incidence is derived from multiplying the (tenfold) inflated estimated incidence per 1,000 live births for all countries except Greece and Cyprus (which had higher incidence rates than the inflated value), by estimated live births reported in 2021, and multiplied by the number of years since the last reported prevalence, Italy for example (0.97/1,000) *(399431)*(2023-2013), assuming comparable total annual live birth rates as 2021.
Estimates for total populations is based on the UN Population Prospectus and live births for the countries and EEA are based on reports from the Eurostat database

The final estimate proposed by this approach is 1.37 in 10,000 in the EU/EEA. The sponsor proposes this second estimate as the most conservative and which should be used in this review for the Maintenance of the Orphan Designation.

The COMP accepted the latter proposal and rounded it up to 1.4 in 10,000.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are 3 main approaches to treatment of TDT: transfusion therapy combined with iron chelation therapy; allogeneic stem cell transplant (allo-HSCT), and luspatercept (Reblozyl). The sponsor listed the medicinal products approved for the treatment and management of β-thalassemia in **Table 3**.

The TIF guideline on the management of TDT describes best practices on the screening, diagnosis, treatment, and monitoring of TDT. This includes recommendations for RBC transfusions, iron overload and chelation therapy, allo-HSCT and Reblozyl. Some EU countries also have similar national guidance on these topics.

Table 3. Medicinal Products Approved For Treatment and Management Of β-thalassemia

Product	Member State	Indication
Products for the treatment of β-thalassemia		
Reblozyl (luspatercept)[36]	Centrally approved	In adults for the treatment of anemia associated with transfusion-dependent and non-transfusion-dependent beta-thalassemia For the treatment of adult patients with transfusion-dependent anemia due to very low, low and intermediate-risk myelodysplastic syndromes with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy
Products supporting transfusion therapy		
Ferriprox (deferiprone)[37]	Centrally approved	Monotherapy is indicated for the treatment of iron overload in patients with thalassemia major when current chelation therapy is contraindicated or inadequate. In combination with another chelator is indicated in patients with thalassemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction.
Deferiprone Lipomed (deferiprone)38	Centrally approved	Monotherapy is indicated for the treatment of iron overload in patients with thalassemia major when current chelation therapy is contraindicated or inadequate. In combination with another chelator is indicated in patients with thalassemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload justifies rapid or intensive correction.
Exjade (deferasirox)[39]	Centrally approved	Treatment of chronic iron overload due to frequent blood transfusions (≥7 mL/kg/month of packed red blood cells) in patients with β-thalassemia major aged 6 years and older. For the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups: in pediatric patients with beta thalassemia major with iron overload due to frequent blood transfusions (³7 ml/kg/month of packed red blood cells) aged 2 to 5 years, in adult and pediatric patients with beta thalassemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older in adult and pediatric patients with other anemias aged 2 years and older. For the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassemia syndromes aged 10 years and older.

Desferal (deferoxamine mesylate)[40]	Nationally approved	Monotherapy iron chelation treatment of chronic iron overload • primary and secondary hemochromatosis including thalassemia • transfusional hemosiderosis; in patients in whom concomitant disorders (e.g., severe anemia, hypoproteinemia, renal failure) preclude phlebotomy.
There are also a number of products approved nationally for the treatment of chronic iron overload in patients receiving regular transfusions.		

Allo-HSCT is a potentially curative therapy for TDT. However, it is available to less than 30% of otherwise eligible patients (because it requires an HLA-matched related donor) and is recommended by TIF only in young patients with symptomatic TDT who have a matched sibling donor as early as possible before iron overload. It is not considered a satisfactory treatment by the COMP.

The iron chelating agents presented in the table above are used for managing iron overload. As Casgevy is for the treatment of transfusion dependent βthalassemia (TDT) per se, the target patient population is not considered to be completely overlapping with the iron chelators. Therefore deferoxamine/deferoxamine mesilate (Desferal), deferiprone (Ferriprox) and deferasirox (Exjade), are not considered as satisfactory methods.

The therapeutic indication for Reblozyl is not exactly worded in the same way as the one for Casgevy, it is, however, considered that the target population for Casgevy is so severe that they would all have anaemia and therefore Reblozyl should be considered a satisfactory treatment, hence a justification of significant benefit is needed.

Significant benefit

The sponsor claims that Casgevy offers improved efficacy over Reblozyl in terms of the elimination or reduction in the number of transfusions and improvements in total Hb.

Study 111 is a single-arm, open-label, multi-site, single dose, Phase 1/2/3 study in subjects 12 to 35 years of age who have TDT. Patients had to have a documented homozygous β-thalassemia or compound heterozygous β-thalassemia including β-thalassemia/haemoglobin E (HbE). Transfusion dependence was defined as a history of at least 100 mL/kg/year or 10 units/year of packed red blood cell (RBC) transfusions in the 2 years before signing the ICF or last rescreening (if needed).

The study is ongoing; at time of data cut for interim analysis, n=59 patients have been enrolled, but not all had been treated yet (data cutoff date: 16 April 2023).

Patients recruited into the study were transfusion dependent (A history of at least 100 mL/kg/year or 10 units/year of packed RBC transfusions in the prior 2 years before signing the consent or the last rescreening for patients going through rescreening.)

The primary efficacy endpoint was defined as the proportion of subjects achieving TI12, defined as maintaining weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion. The evaluation of TI12 starts 60 days after last RBC transfusion for post-transplant support or TDT disease management.

Numbers analysed.

Table 4. Subject Disposition (Study 111 Enrolled Set)

Disposition/Reason	**Total n (%)**
Enrolled Seta	59
Safety Analysis Setb	59
Started the conditioning regimen	54
FASc	54
PESd	42
Never dosed with any study druge	0
Never dosed with exa-celf	3
Started exa-cel infusion	54 (91.5)
Completed exa-cel infusion	54 (100.0)
Not completed exa-cel infusion	0
On Study 111 and not yet dosed with exa-celg	2 (3.4)
On Study 111 and dosed with exa-cel	31 (52.5)
Completed Study 111h	23 (39.0)
Completed Study 111 and enrolled in long-term follow-up study	23 (100.0)
Discontinued Study 111 after exa-cel infusion	0
Discontinued Study 111 after exa-cel infusion and enrolled in long-term follow-up study	0

Sources: Study 111/Table 14.1.1 and Study 131/Table 14.1.1a (data cutoff date of 16 April 2023)
AE: adverse event; exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; IA3: interim analysis 3; n: size of subset; PES: Primary Efficacy Set; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia; TI12: maintained a weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion
Notes: Percentages were calculated relative to the number of subjects in the Enrolled Set, unless otherwise specified. Percentages of subjects who completed or did not complete exa-cel infusion (and percentages of reasons for not completing exa-cel infusion) were calculated relative to the number of subjects who started exa-cel infusion. Percentages of subjects who completed the study and enrolled in the long-term follow-up study were calculated relative to the number of subjects who completed the study. Percentages of subjects who discontinued the study after exa-cel infusion and enrolled in the long-term follow-up study were calculated relative to the number of subjects who discontinued the study after exa-cel infusion. Percentages for reasons for discontinuing the study after exa-cel infusion were calculated relative to the number of subjects who received exa-cel infusion.
[a] Enrolled Set included all enrolled subjects who signed informed consent and met the eligibility criteria.
[b] Safety Analysis Set included all subjects who started the mobilization regimen.
[c] FAS included all subjects who received exa-cel infusion.
[d] PES included all subjects who have been followed for at least 16 months post exa-cel infusion and for at least 14 months after completion of the RBC transfusions for post-transplant support or TDT management. Subjects who completed the 24 months of follow up in the study post exa-cel infusion were included in this set. In addition, subjects who died or discontinued the study due to exa-cel-related adverse events and had less than 16 months follow-up post exa-cel infusion, or continuously received RBC transfusions for more than 12 months post exa-cel infusion were also included in this set. For a full definition of the PES refer to Study 111/SAP Version 4.3.
[e] Never dosed with any study drug included all subjects who discontinued the study and did not receive any study drugs for mobilization, conditioning, and exa-cel infusion.
[f] Never dosed with exa-cel included all subjects who discontinued the study and did not receive exa-cel infusion.
[g] On study included all subjects who enrolled and had not yet completed (or discontinued) the study.
[h] Completed study included all subjects who completed the Month 24 visit.

The main analyses of all efficacy endpoints were based on the Primary Efficacy Sample (PES) (N = 42). Following infusion with exa-cel, 39 of 42 (92.9%) subjects in the PES achieved TI12 (95% CI: 80.5%, 98.5%; 1-sided P<0.0001 [against a 50% response rate]).

All 39 subjects in the PES who met the primary endpoint remained transfusion free for the duration of follow-up; the mean (SD) transfusion free duration while maintaining weighted Hb ≥9 g/dL was 23.6

(7.8) months, starting 60 days after the last RBC transfusion. The total duration of transfusion free ranged from 13.5 to 48.1 months.

The efficacy and safety of luspatercept were evaluated in a Phase 3, multicenter, randomized, double-blind, placebo-controlled study (BELIEVE). Patients (N=336) aged ≥18 years with TDT-associated anemia who require RBC transfusions (6 to 20 RBC units/24 weeks), with no transfusion-free period >35 days during that period, were randomly assigned in a 2:1 ratio to receive luspatercept or placebo subcutaneously every 21 days for at least 48 weeks. Luspatercept demonstrated a modest clinical benefit in the BELIEVE trial. Only 10.7% of patients treated with luspatercept achieved transfusion independence during any 8-week interval, compared with 1.8% in the placebo arm (odds ratio [OR] 6.76; 95% CI 1.56, 29.28), and only 4.0% of patients treated with luspatercept achieved transfusion independence during any 12-week interval compared with 0% for placebo (OR infinity). Only 21.4% of subjects in the luspatercept arm achieved the primary endpoint of a ≥33% reduction in RBC transfusion from baseline during Weeks 13 to 24. The mean (SD) total Hb level at Week 24 was 9.0 (1.19) g/dL compared to 8.6 (1.07) g/dL for placebo, and at Week 48, 8.5 (1.28) g/dL compared to 7.7 (0.90) g/dL for placebo.

The sponsor also states that Casgevy provides improved efficacy over Reblozyl; 39 of 42 (92.9%) subjects in the PES achieved TI12 and TI6 (95% CI: 80.5%, 98.5%; 1-sided P<0.0001 [against a 50% response rate]) as opposed to 10% over any 8-week period for Reblozyl. Casgevy achieved mean (SD) total Hb levels of 11.4 (2.2) g/dL at Month 3 in the FAS which was maintained with mean ≥12.2 g/dL from Month 6 onward compared to 8.5 (1.28) g/dL after 48 weeks with Reblozyl.

The COMP considered that the product has been shown to achieve durable increase in the level of HbF and transfusion independence in transfusion dependent patients where HLA-matched haemopoietic stem cell transplantation is an option but not available. This was considered the basis of significant benefit as in this patient population Reblozyl cannot achieve durable transfusion independence at the same level than Casgevy. It was also considered by the COMP that Casgevy offers transfusion independence in TDT, whereas Reblozyl reduces the transfusion burden which are two different concepts.

The COMP agreed to recommend that the orphan designation be maintained.

1.4. COMP position adopted on 20 December 2023

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;

- the prevalence of beta-thalassaemia intermedia and major (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 1.4 in 10,000 persons in the European Union, at the time of the review of the designation criteria;

- the condition is life-threatening and chronically debilitating due to the severe anaemia, the need for blood transfusions, and the complications related to these, in particular in beta-thalassaemia major patients;

- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by Casgevy, the assumption that Casgevy may be of potential significant benefit to those affected by the orphan condition as defined in the granted therapeutic indication still holds. The product has been shown to achieve durable increase in the level

of HbF and transfusion independence in transfusion dependent patients where HLA-matched haemopoietic stem cell transplantation is an option but not available.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Casgevy, autologous CD34+ haematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene, exagamglogene autotemcel, for treatment of beta-thalassaemia intermedia and major (EU/3/19/2210) is not removed from the Community Register of Orphan Medicinal Products.

2. Casgevy for treatment of sickle cell disease - EU/3/19/2242 (EMA/OD/0000146415)

2.1. Product and administrative information

Product	
Designated active substance(s)	Autologous CD34+ haematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene
Other name(s)	--
International Non-Proprietary Name	Exagamglogene autotemcel
Tradename	Casgevy
Orphan condition	Treatment of sickle cell disease
Sponsor's details:	Vertex Pharmaceuticals (Ireland) Limited Unit 49 Block 5 Northwood Court Northwood Crescent Dublin 9 D09 T665 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Vertex Pharmaceuticals (Ireland) Limited
COMP opinion	5 December 2019
EC decision	9 January 2020
EC registration number	EU/3/19/2242
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Jan Mueller-Berghaus / Heli Suila
Applicant	Vertex Pharmaceuticals (Ireland) Limited
Application submission	29 December 2022
Procedure start	24 January 2023
Procedure number	EMA/H/C/005763
Invented name	Casgevy

Proposed therapeutic indication	Treatment of severe sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso occlusive crises (VOCs) for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA) matched related HSC donor is not available. Further information on Casgevy can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/casgevy
CHMP opinion	14 December 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttila / Enrico Costa
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COMP opinion (adoption via written procedure)	20 December 2023

2.2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2019 was based on the following grounds:

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing autologous CD34+ hematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11a* gene was considered justified based on ex vivo data showing reduced cell sickling and on early clinical data showing sustained elevation of foetal haemoglobin;

- the condition is chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, acute chest syndrome, chronic kidney disease, pulmonary hypertension and susceptibility to infections, and life-threatening with reduced survival;

- the condition was estimated to be affecting approximately 1.3 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous CD34+ hematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene will be of significant benefit to those affected by the condition. The sponsor has provided early clinical data that demonstrate that a single treatment resulted in consistent elevation of HbF production over 4 months follow up, which reduced the need for transfusions and any need for the use of hydroxyurea. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing autologous CD34+ hematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene as an orphan medicinal product for the orphan condition: treatment of sickle cell disease.

2.3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Sickle cell disease (SCD) is characterised by haemolytic anaemia, vaso-occlusion and progressive end-organ damage. SCD is caused by a point mutation in the haemoglobin (Hb) β-chain, converting the glutamic acid residue at position 6 to a valine residue. The mutation leads to sickle haemoglobin (HbS) following deoxygenation in the microvasculature. HbS polymerization leads to decreased red blood cell (RBC) deformability, morphologic sickling of RBCs, decreased RBC survival, microvascular obstruction and the clinical complications of SCD. Patients suffer from unpredictable and recurrent episodes of severe pain often leading to significant psychosocial and occupational disability. In addition to painful crises, a systemic vasculopathy leads to chronic and progressive tissue injury across multiple organ systems. Multiple pathophysiologic mechanisms likely contribute to the systemic vasculopathy, including, chronic haemolytic anaemia. The consequences include cognitive dysfunction and stroke, increased susceptibility to infections, cardiopulmonary complications, renal dysfunction, leg ulcers, priapism in males, and increased mortality.

The approved therapeutic indication "*Casgevy is indicated for the treatment of severe sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso occlusive crises (VOCs) for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA) matched related HSC donor is not available."* falls within the scope of the designated orphan condition "Treatment of sickle cell disease".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The COMP considered that the condition is chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, acute chest syndrome, chronic kidney disease, pulmonary hypertension, leg ulcers and susceptibility to infections, and life-threatening with reduced survival.

Number of people affected or at risk

The sponsor has used published scientific articles to establish the prevalence of sickle cell disease. The findings per country are summarised below.

Specific European countries: Prevalence of Sickle Cell Disease

France

Prevalence: Prevalence of SCD in France is likely ~26,100 cases, the midpoint of 19,800 and 32,400 prevalent SCD patients reported by a French nationwide claim database study. The large variation is due to different coding iteration used in the insurance data analysis. Previously, the number of SCD cases in France has been estimated at approximately 14,000, with a recent medical claims analysis using 2016 data pointing to approximately 13,509 SCD cases in France. In 2013, approximately 10,000 cases of sickle cell syndromes were reported in France.

Incidence: Based on newborn screening data for 5.4 million newborns from 1995 to 2016 across France and the French territories, 7,644 cases were diagnosed, which produces an estimate of 1.42 cases per 1,000 newborns. In 2016, the incidence of SCD in France was estimated at 1 in 1,836 newborns (i.e., approximately 0.55 cases per 1,000 newborns).

Other historical reports have estimated varying rates of incidence. In 2005, the incidence of SCD in France was approximately 1 case per 2,795 newborns (i.e., 0.358 per 1,000 newborns), and from 1997 to 2007, there were 3,890 newborn cases of SCD in France. In a 2013 report, the incidence of sickle cell syndromes in France was estimated at approximately 0.0018 cases per 1,000 live births.

Germany

Prevalence: The number of prevalent cases in Germany in 2015 was estimated at approximately ~3,200 based on Germany's health insurance data and is consistent with historical estimates. In 2010, approximately 3,085 cases of SCD were estimated in the Ulm Longitudinal Study. Angastiniotis et al. reported approximately 3,000 cases of sickle cell syndromes in Germany in 2013.

Incidence: The incidence of SCD was estimated at 1 in 1,368 (i.e., 0.731 per 1,000) newborns in Germany in 2015, with the incidence in the southwest of Germany estimated at 1 in 12,613 (i.e., 0.079 per 1,000). Other reports from Germany have reported an incidence of approximately 0.04 cases per 100 newborns and an expected incidence of approximately 0.0001 per 1,000 live births.

Italy

Prevalence: Prevalence estimate for SCD in Italy has a large range. The most recent study in Italy using administrative databases based on hospitalization diagnosis's projected estimate is ~8,000 prevalent cases in 2018. However, reports from the Italian SITE (Societa' Italiana Talassemie ed Emoglobinopatie)'s website by treatment center tallies to ~2,400 SCD cases. Previously, the number of prevalent cases of sickle cell syndromes in Italy was reported at approximately 6,000 in 2013, and approximately 829 in 2001.

Incidence: In 2018, it was reported that 4 (i.e., 0.07%) incident cases were identified from screening 5,439 newborns in the Monza and Padova regions of Italy, and all 4 were immigrants of African origin. Angastiniotis et al. estimated the expected incidence of SCD at 0.11 per 1,000 live births in Italy. Incidence based on administrative database analysis in 2018 was 1.09 per 100,000 in females and 0.76 per 100,000 among males.

Spain

Prevalence: The number of prevalent cases of SCD in Spain was estimated at 615 in 2017 based on REPHem. Angastiniotis et al. reported over 200 cases of sickle cell syndromes in Spain in 2013.

Incidence: Angastiniotis et al. reported the expected incidence of sickle cell syndromes at approximately 0.0011 cases per 1,000 live births. Based on the REPHem, the incidence of SCD was

estimated at 0.03 cases per 1,000 newborns. Another report of the incidence of SCD in Spain indicated approximately 0.01 cases per 100 newborns. Spain's new born screening program found 0.12 SCD cases per 1,000 births in 2016. It was also reported that in the period between 2006 and 2010, the average number of new SCD cases in Spain was approximately 42.2 cases per year.

Portugal

Prevalence: TIF's 2022 report estimated there are 800 SCD cases in Portugal, based on input from local experts.

Belgium

Prevalence: TIF's 2022 report estimated SCD cases in Belgium to be ~500 cases. Previously, the estimated number of cases of sickle cell syndromes in Belgium was reported as approximately 400 in 2013. A 2005 through 2006 survey of hemoglobinopathies found approximately 346 cases of SCD in Belgium.

Incidence: The incidence of sickling disorders in Belgium has been reported at 1 per 2,329 (i.e., 0.429 per 1,000) newborns. Other reports of the incidence of SCD in Belgium indicated 1 in 1,559 (i.e., 0.641 per 1,000) newborns. Angastiniotis et al. estimated the expected incidence of sickle cell syndromes at 0.0035 cases per 1,000 live births.

Netherlands

Prevalence: The number of prevalent cases of SCD in the Netherlands has been estimated as approximately 2,000 in 2022; as approximately 750 in 2013; and as approximately 800 in 2002.

Incidence: The incidence of SCD in the Netherlands has been reported at approximately 0.06 cases per 100 newborns. Prior estimates of incidence of SCD in the Netherlands included approximately 50 new cases born annually; 2.1 cases per 10,000 newborns; and an expected incidence of approximately 0.0008 per 1,000 live births.

Sweden

Prevalence: The number of prevalent cases of SCD in Sweden is currently estimated by TIF at approximately ~584. In 2013, Angastiniotis et al. estimated approximately 100 cases of sickle cell syndromes in Sweden.

Incidence: Expected incidence SCD in Sweden was reported as approximately 0.00021 cases per 1,000 live births.

Greece

Prevalence: Based on the National Registry of Hemoglobinopathies in Greece, it is estimated that there are approximately 1,032 individuals with SCD in Greece. TIF reports a slightly higher estimate at ~1,100 cases.

Incidence: Expected incidence of SCD in Greece was reported as approximately 0.009 cases per 1,000 live births.

Cyprus

Prevalence: Prevalent cases in Cyprus is currently estimated to be 40 to 60 cases.

Incidence: Expected incidence of SCD in Cyprus was reported as approximately 0.0018 cases per 1,000 live births.

Denmark

Incidence: TIF estimated that there are ~110 cases of SCD in Denmark in 2022.[37] The PHG Foundation estimated incidence of SCD in Denmark as approximately 0.05 cases per 1,000 live births in 2013, while reporting the incidence across Western Europe as approximately 0.09 cases per 1,000 live births. In the same year, Angastiniotis et al. estimated an expected incidence of 0.00004 cases per 1,000 live births in Denmark.

Ireland

Prevalence: The prevalence of SCD in children below the age of 15 years among African and Asian immigrants in Ireland was reported as approximately 200 cases per 100,000.

The presentation of the data varies by country and is summarized in table 5 below.

Table 5. Estimates of the Prevalence of SCD in the EEA Based on Largest Available Estimates From the Literature

Country	Last year of the historically reported prevalence	Estimate of historically reported prevalence as cases per 10,000	Population at time of the historically reported prevalence[46]	Estimated number of historically reported prevalent cases	Estimate of historically reported incidence as cases per 10,000 live births[47]	Estimated annual total of live births (2021)	Estimated total of new cases since the historically reported prevalence to 2023	Total population in 2023[46]	Estimated number of prevalent cases in 2023
France	2016	4.079	63,989,300	26,100[24]	14.156	738,594	7,319	64,757,000	33,419
Italy	2018	1.332	59,877,400	7,977[34]	7.354	399,431	1,469	58,871,000	9,446
Germany	2015	0.390	82,073,200	3,200[30]	4.000	795,492	2,546	83,295,000	5,746
Netherlands	2022	1.139	17,564,000	2,000[37]	1.000	179,441	18	17,618,000	2,018
Greece	2022	1.059	10,385,000	1,100[37]	0.351	85,303	3	10,341,000	1,103
Spain	2017	0.132	46,584,200	615[48]	1.000	336,247	202	47,520,000	817
Portugal	2022	0.779	10,271,000	800[37]	1.000	79,582	8	10,248,000	808
Sweden	2022	0.554	10,549,000	584[37]	2.100	114,263	24	10,612,000	608
Belgium	2022	0.429	11,656,000	500[37]	6.000	118,349	142	11,686,000	642
Cyprus	2022	0.480	1,251,000	60[37]	0.018	10,150	0	1,260,000	60
Subtotal for the countries listed above								316,208,000	54,666
Estimated prevalence per 10,000								1.729 cases per 10,000 individuals	
Applying that prevalence (i.e., 1.729 cases per 10,000 individuals) to total population of the entire EEA region								458,551,212	79,274

Sources: References (Leleu H, 2021; Kunz JB, 2021; De Franceschi L, 2022; Thalassemia International Federation. 2023; Bardón E, 2023)
EEA: European Economic Area; SCD: sickle cell disease
Note: The estimates above use the largest reported prevalence and incidence based on literature and assumes no SCD cases were lost to mortality to produce an estimation of the highest likely prevalence in the EEA region.

From this collection of heterogeneous data, the sponsor concludes that across France, Italy, Germany, Portugal, Netherlands, Greece, Spain, Sweden, Belgium, and Cyprus, it was estimated that there are approximately 54,666 SCD cases out of a total population of 316,208,000, i.e., a prevalence of 1.729 cases per 10,000 individuals.

The proposed prevalence of 1.7 in 10,000 patients have sickle cell disease in the EU/EEA was accepted by the COMP.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

At present there are three medicinal products authorized for patients with SCD in the European Union/EEA, two of which contain the active substance hydroxycarbamide (hydroxyurea [HU]):

- Siklos (hydroxycarbamide) is centrally approved in the EU for the prevention of recurrent painful VOCs including acute chest syndrome in adults, adolescents and children older than 2 years suffering from symptomatic Sickle Cell Syndrome.
- Xromi (hydroxycarbamide) is indicated for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients over 2 years of age.
- Oxbryta is indicated for the treatment of haemolytic anaemia due to sickle cell disease (SCD) in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide.

Adakveo (crizanlizumab) which was indicated for the prevention of recurrent vaso-occlusive crises (VOCs) in SCD patients aged 16 years and older was withdrawn from the market in August 2023.

Casgevy is indicated for the treatment of severe sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs) for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available. In the pivotal study, one of the inclusion criteria was subjects with severe SCD, defined by the occurrence of at least 2 VOC events per year during the 2-year period before screening, while receiving appropriate supportive care (e.g., pain management plan and HU).

Oxbryta is not considered a satisfactory method for the target population of Casgevy as it is for the treatment of haemolytic anaemia specifically. However, the indication for the two HUs is broader than the indication for Casgevy and therefore Siklos and Xromi are both considered satisfactory methods for the target population of Casgevy and have to be considered for significant benefit.

Allo-HSCT is the only potentially curative option for SCD. However, allo-HSCT is limited in availability to the 18% of patients with SCD who have a suitable HLA-matched related sibling donor and is therefore not considered a satisfactory method.

There are no specific European Guidelines for the treatment of Sickle Cell Anaemia in adults. There are however guidelines for the treatment of children (*ENERCA clinical recommendations for disease management and prevention of complications of sickle cell disease in children Mariane de Montalembert, Alina Ferster, Raffaella Colombatti, David C Rees, Beatrice Gulbis; European Network for Rare and Congenital Anaemias Am J Hematol. 2011 Jan;86(1):72-5. doi: 10.1002/ajh.21865.).* There are specific recommendations published about the place of haematopoietic stem cell transplantation in the US: *American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation Julie Kanter et al, 28 September 2021, Vol 5, Number 18 3668-3689).* The authors acknowledge in this article the curative nature of HSCT and that improvements in outcomes when it is used have progressed. They also acknowledge that authorised treatments available to date are reducing the need for its use to more severe patients and that this patient population is becoming smaller.

Significant benefit

Protocol assistance for the justification for specific benefit was not sought, although scientific advice for the clinical trial design was received in September 2020 (EMEA/H/SA/4534/1/2020/ PA/ADT/III).

The sponsor argued that Casgevy provides improved efficacy in terms of VOC elimination or marked reduction, increases in total Hb and elimination in the need of transfusions. This is based on Study 121 (*A Phase 1/2/3 Study to Evaluate the Safety and Efficacy of a Single Dose of Autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (CTX001) in Subjects With Severe Sickle Cell Disease (Protocol CTX001-121)),* a single-arm, open-label, multi-site, single dose, Phase 1/2/3 study in subjects 12 to 35 years of age who have severe SCD. Severe SCD was defined by the occurrence of at least 2 of the following events each year during the 2-year period before screening, while receiving appropriate supportive care (e.g., pain management plan, hydroxyurea if indicated):

- Acute pain event that required a visit to a medical facility and administration of pain medications (opioids or intravenous [IV] non-steroidal anti-inflammatory drugs) or red blood cell (RBC) transfusions
- Acute chest syndrome, as indicated by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms, pain, or fever
- Priapism lasting >2 hours and requiring a visit to a medical facility
- Splenic sequestration, as defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in hemoglobin (Hb) concentration of ≥2 g/dL

The primary efficacy endpoint was the proportion of subjects who have not experienced any severe VOCs for at least 12 consecutive months (VF12) after exa-cel infusion. The evaluation of VF12 starts 60 days after last RBC transfusion for post-transplant support or SCD disease management.

The study is ongoing; at time of data cut for interim analysis, n=63 patients have been enrolled, but not all had been treated yet (data cutoff date: 16 April 2023).

Baseline characteristics of the patient population are summarised below.

Table 6. Subject Disposition (Study 111 Enrolled Set)

Disposition/Reason	**Total n (%)**
Enrolled Seta	59
Safety Analysis Setb	59
Started the conditioning regimen	54
FASc	54
PESd	42
Never dosed with any study druge	0
Never dosed with exa-celf	3
Started exa-cel infusion	54 (91.5)
Completed exa-cel infusion	54 (100.0)
Not completed exa-cel infusion	0
On Study 111 and not yet dosed with exa-celg	2 (3.4)
On Study 111 and dosed with exa-cel	31 (52.5)
Completed Study 111h	23 (39.0)
Completed Study 111 and enrolled in long-term follow-up study	23 (100.0)
Discontinued Study 111 after exa-cel infusion	0

Disposition/Reason	Total n (%)
Discontinued Study 111 after exa-cel infusion and enrolled in long-term follow-up study	0

Sources: Study 111/Table 14.1.1 and Study 131/Table 14.1.1a (data cutoff date of 16 April 2023)
AE: adverse event; exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; IA3: interim analysis 3; n: size of subset; PES: Primary Efficacy Set; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia; TI12: maintained a weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion
Notes: Percentages were calculated relative to the number of subjects in the Enrolled Set, unless otherwise specified. Percentages of subjects who completed or did not complete exa-cel infusion (and percentages of reasons for not completing exa-cel infusion) were calculated relative to the number of subjects who started exa-cel infusion. Percentages of subjects who completed the study and enrolled in the long-term follow-up study were calculated relative to the number of subjects who completed the study. Percentages of subjects who discontinued the study after exa-cel infusion and enrolled in the long-term follow-up study were calculated relative to the number of subjects who discontinued the study after exa-cel infusion. Percentages for reasons for discontinuing the study after exa-cel infusion were calculated relative to the number of subjects who received exa-cel infusion.
[a] Enrolled Set included all enrolled subjects who signed informed consent and met the eligibility criteria.
[b] Safety Analysis Set included all subjects who started the mobilization regimen.
[c] FAS included all subjects who received exa-cel infusion.
[d] PES included all subjects who have been followed for at least 16 months post exa-cel infusion and for at least 14 months after completion of the RBC transfusions for post-transplant support or TDT management. Subjects who completed the 24 months of follow up in the study post exa-cel infusion were included in this set. In addition, subjects who died or discontinued the study due to exa-cel-related adverse events and had less than 16 months follow-up post exa-cel infusion, or continuously received RBC transfusions for more than 12 months post exa-cel infusion were also included in this set. For a full definition of the PES refer to Study 111/SAP Version 4.3.
[e] Never dosed with any study drug included all subjects who discontinued the study and did not receive any study drugs for mobilization, conditioning, and exa-cel infusion.
[f] Never dosed with exa-cel included all subjects who discontinued the study and did not receive exa-cel infusion.
[g] On study included all subjects who enrolled and had not yet completed (or discontinued) the study.
[h] Completed study included all subjects who completed the Month 24 visit.

The main analyses of all efficacy endpoints were based on the Primary Efficacy Set (PES) (N = 29).

Twenty-eight of 29 (96.6%) subjects in the PES achieved VF12, i.e. absence of severe VOCs for at least 12 consecutive months after exa-cel infusion (data cut off 16 April 2023). All (100%) subjects in the PES achieved HF12, i.e. were free of hospitalizations for at least 12 consecutive months.

Primary Efficacy Endpoint: Following infusion with exa-cel, 28 of 29 (96.6%) subjects in the PES in Study 121 achieved VOC free for a continuous 12-month period (VF12; 95% CI: 82.2%, 99.9%; P< 0.0001 [against a 50% response rate]).

Key Secondary Efficacy Endpoint: Following infusion with exa-cel, 29 of 29 (100%) subjects in the PES in Study 121 achieved inpatient hospitalization free for severe VOC for a continuous 12-month period (HF12; 95% CI: 88.1%, 100.0%; P<0.0001 [against a 50% response rate]).

Mean (SD) proportion of total Hb comprised by HbF (HbF%) was 37.3% (9.0%) at Month 3, increased and was generally maintained with mean ≥40% from Month 6 through the duration of follow-up.

The COMP considered that the absence of VOCs in a patient population that had severe SCD - as defined by at least two events of severe VOCs annually in the two prior years to treatment while receiving appropriate supportive care (e.g., pain management plan, HU) - and absence of hospitalizations accompanied by an increase of HbF that can only be attributed to Casgevy is compelling, self-standing evidence of efficacy and therefore a clinically relevant advantage had been shown.

COMP considered sufficient data had been submitted to support the significant benefit in this patient population and recommended maintaining the orphan designation.

2.4. COMP position adopted on 20 December 2023

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of sickle cell disease (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 1.7 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, acute chest syndrome, chronic kidney disease, pulmonary hypertension and susceptibility to infections, and life-threatening with reduced survival;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by Casgevy, the assumption that Casgevy may be of potential significant benefit to those affected by the orphan condition as defined in the granted therapeutic indication still holds. The pivotal study recruited subjects with severe SCD, defined by the occurrence of at least 2 vasocclusive crisis events per year during the 2-year period before screening, while receiving appropriate supportive care (e.g., pain management plan and hydroxy urea). This represents a patient population inadequately treated with currently approved medicinal products and who responded to Casgevy.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Casgevy, autologous CD34+ hematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene, exagamglogene autotemcel, for treatment of sickle cell disease (EU/3/19/2242) is not removed from the Community Register of Orphan Medicinal Products.