25 June 2020
EMADOC-1700519818-468538
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Reblozyl (luspatercept)
Sponsor: Celgene Europe B.V.

Note

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

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1. Introductory comment

The approved therapeutic indication encompasses –and lies completely within- two distinct medical entities, for which the sponsor has been granted two separate orphan designations: beta thalassemia (intermedia and major) and myelodysplastic syndromes.

The maintenance of the criteria for orphan designation are discussed separately for each orphan condition, in sections 2 and 3 below.

2. Recombinant fusion protein consisting of a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain for treatment of beta-thalassaemia intermedia and major - EU/3/14/1300 (EMA/OD/0000008931)

2.1. Product and administrative information

Product	
Active substances at the time of orphan designation	Recombinant fusion protein consisting of a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain
International Non-Proprietary Name	Luspatercept
Tradename	Reblozyl
Orphan condition	Treatment of beta-thalassaemia intermedia and major
Sponsor's details:	Celgene Europe B.V. Winthontlaan 6n 3526 KV Utrecht Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	IDEA Innovative Drug European Associates Limited
COMP opinion date	12 June 2014
EC decision date	29 July 2014
EC registration number	EU/3/14/1300
Post-designation procedural history	
Transfer of sponsorship	Transfer from IDEA Innovative Drug European Associates Limited to Celgene Europe Limited – EC decision of 26 February 2015
Transfer of sponsorship	Transfer from Celgene Europe Limited to Celgene Europe B.V. – EC decision of 27 September 2018
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Milena Stain / Ewa Balkowiec Iskra
Applicant	Celgene Europe B.V.
Application submission date	26 April 2019
Procedure start date	23 May 2019
Procedure number	EMA/H/C/004444
Invented name	Reblozyl

Proposed therapeutic indication	Treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy and for the treatment of adult patients with transfusion-dependent anaemia associated with beta-thalassaemia. Further information on Reblozyl can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/reblozyl
CHMP opinion date	30 April 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttila / Ingeborg Barisic
Sponsor's report submission date	23 May 2019
COMP discussion	18-20 May 2020
COMP opinion date	20 May 2020

2.2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2014 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing recombinant fusion protein consisting of a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain was considered justified based on preliminary clinical data showing haemoglobin increase in non-transfusion dependent patients affected by the condition;
- 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 1 in 10,000 people in the European Union, at the time the application was made;
- in addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant fusion protein consisting of a modified form of the extracellular domain of human Activin Receptor IIB linked to the human IgG1 Fc domain may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that treatment of patients with the product may improve anaemia, which is a different aspect to the target of the iron chelation products authorised. The Committee considered that this constitutes a clinically relevant advantage.

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

Beta thalassaemia is characterised by a genetic deficiency in the synthesis of β-globin chains. In turn, a relative excess of α-globin chains leads to increased erythroid precursor apoptosis, ineffective erythropoiesis, extramedullary expansion, splenomegaly and microcytic anaemia (Li et al, Nature Medicine 2010 16, 177–182). The affected beta chain gene is located in chromosome 11 and is an erythroid-specific gene, activated in late stages of erythropoiesis. At the biosynthetic level, the syndromes are categorized by the affected globin chains and in particular on whether there is a partial (β+) or complete (β0) defect in chain production. The most severe form is thalassaemia major, which is characterised by a severe (Hb 3 to 4 g/dl) transfusion dependent microcytic anaemia with genotype β0/ β0 or β0 / β+ and corresponding haemoglobin constitution of HbA2 ≥5%, HbF up to 95% and no HbA. Beta thalassaemia intermedia gives a clinical manifestation of moderate microcytic anaemia, has a genotype of β+/ β+ and on typical values on haemoglobin analysis HbA2 ≥4%, HbF up to 50%. 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%.

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 product has received a therapeutic indication for the treatment of

- adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy
- adult patients with transfusion-dependent anaemia associated with Beta-thalassaemia

With regards to beta thalassaemia, it is acknowledged that treatment of "adult patients with transfusion-dependent anaemia associated with Beta-thalassaemia" falls entirely within the orphan condition, "treatment of β-thalassaemia intermedia and major", which would therefore be acceptable for this procedure.

Intention to diagnose, prevent or treat

The medical plausibility has been established based on the positive benefit/risk assessment of the CHMP, please 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.

Beta thalassaemia major causes a hypochromic, microcytic anaemia developing in in the first year of life. Without transfusions, ~85% of patients die by five years of age. Bone marrow expansion due to severe ineffective erythropoiesis results in characteristic deformities of the skull and face, and painful periarticular syndrome with microfractures and osteomalacia. Progressive hepatic, cardiac and endocrine disturbances develop, due to the accumulation of iron from transfusion and its deposition in the tissues.

Number of people affected or at risk

The sponsor performed a literature review and provided a range from 0.06 to 1.1 in 10,000 according to the type of publications used for EU27 and the UK. A table with the used sources is presented below, adopted from the sponsor's documents.

Table 1. Sourced from the sponsor's application.

Country	**2019 Population Estimate (thousands)[1]**	**Calculated Total Number of Patients (N) Based on**	**Calculated Prevalence (per 10,000 population) Based on Affected**	**Actual Reported Prevalence (per 10,000**
Austria	8,858.8	89	0.1	
Belgium	11,467.9	229	0.2	0.06 (Gulbis, 2009)
Bulgaria	7,000.0	1750	2.5	0.3 (Raredis, 2011)
Croatia		163	N/A (0.4)[a]	
Cyprus		4931	56.3	5.9 (Tefler, 2006)
Czech Republic	10,649.8	426	N/A (0.4)[a]	
Denmark	5,806.1	232	0.4	
Estonia	1,324.8	53	N/A (0.4) [a]	
Finland	5,517.9	55	0.1	
France	67,028.0	2681	0.4	0.06 (Thuret, 2010)
Germany	83,019.2	2491	0.3	0.06 (Dickerhoff,
Greece	10,722.3	10293	9.6	2.9 (Voskaridou,
Hungary	9,772.8	391	N/A (0.4) [a]	
Ireland	4,904.2	49	0.1	
Italy	60,359.5	21729	3.6	1.0 (WHO-TIF,
Latvia	1,920.0	77	N/A (0.4) [a]	
Lithuania	2,794.2	112	N/A (0.4) [a]	
Luxembourg	613.9	12	0.2	
Malta	493.6	118	2.4	
Netherlands	17,282.2	864	0.5	0.06 (Giordano,
Poland	37,972.8	1519	N/A (0.4) [a]	
Portugal	10,276.6	103	0.1	0.04 (WHO-TIF,
Romania	19,401.7	582	0.3	
Slovakia	5,450.4	218	N/A (0.4) [a]	
Slovenia	2,080.9	83	N/A (0.4) [a]	

Spain	46,934.6	469	0.1	0.02 (Cela, 2017)
Sweden	10,230.2	614	0.6	
United Kingdom	66,647.1	6665	1.0	0.12 (Modell, 2001)
EU28 total	**513,481,690**	**56,999**	**1.1**[b]	**0.06**[c]

[a] For countries in which prevalence estimates are not available (shaded cells), a median value of 0.4 per 10,000 population is used for the purpose of estimating prevalence in the EU28.

[b] Calculated as: Prevalence = 56,999/513,481,690 x 10,000

[c] Median prevalence across EU countries for which individual prevalence values are available.

Sources: [1] Eurostat, Population on 1 January; [2]: Modell, 2007; Modell, 2008

The conclusion is in line with previous procedures of approximately 1 per 10,000, and was considered acceptable.

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

The COMP discussed the authorised products that would form the basis for the justification of significant benefit. In particular, it was considered that iron chelators as well as Zynteglo are authorised in the EU for the treatment of beta thalassaemia. Iron chelators (ICT) such as deferasirox, are indicated for certain populations (refer to SmPC for full indication) for the "treatment of chronic iron overload due to frequent blood transfusions... in patients with beta thalassaemia major..." as well as "chronic iron overload requiring chelation therapy...in patients with non-transfusion-dependent thalassaemia syndromes."

Zynteglo has also recently received marketing authorisation and is indicated for the "Treatment of patients 12 years and older with TD β-thalassaemia who do not have a β0/β0 genotype, for whom HSCT is appropriate but a HLA-matched related HSC donor is not available".

Significant benefit

The COMP considered that significant benefit would have to be justified versus the authorised products, which include iron chelators and Zynteglo.

It was firstly noted that the main study encompasses standard of care, including chelators and transfusions. Indeed, it was reported that in the pivotal trial 97.3% of subjects received at least 1 prior iICT (97.3% of subjects in the luspatercept + BSC treatment group and 97.2% of subjects in the placebo + BSC treatment group). The most frequently used prior ICT was deferasirox (60.8% of subjects), followed by deferiprone (39.8%), and deferoxamine mesilate/deferoxamine (36.7%). All subjects, except 1 in the luspatercept + BSC treatment group, used at least 1 concomitant ICT during the study. The most frequently used concomitant ICT was deferasirox (65.1% of subjects), followed by deferiprone (41.0%), and deferoxamine mesilate/deferoxamine (33.7%).

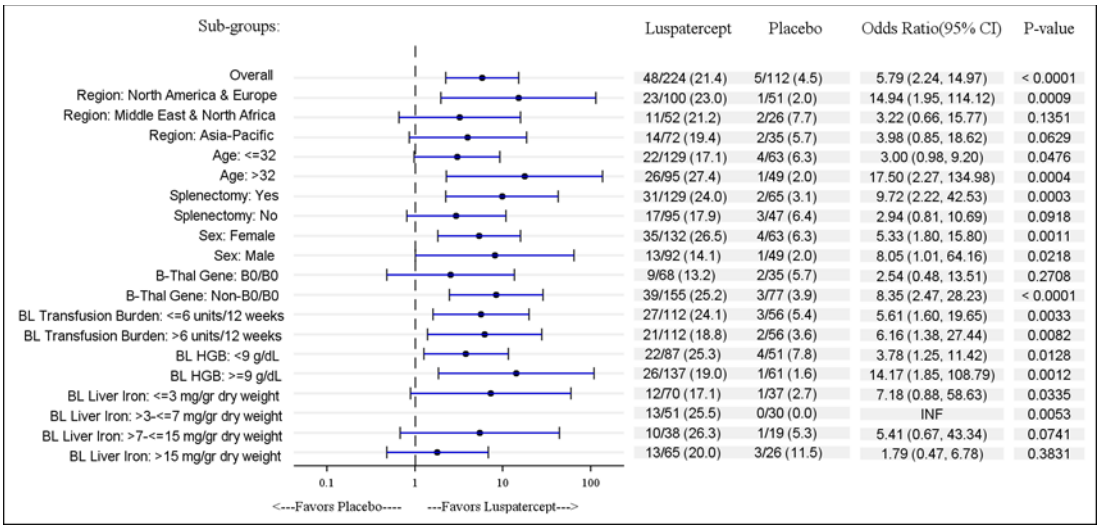
Given that the effects of the product in the pivotal trial have been studied on top of best supportive care versus best supportive care alone, the COMP considered that significant benefit against iron chelators has been justified.

With regards to Zynteglo, the sponsor produced both improved efficacy arguments, on the grounds of a broader patient population of the proposed indication, as well as a safety argument, on the grounds that Zynteglo requires mobilisation/myeloablative conditioning therapies.

With regards to the argument of improved efficacy, the sponsor noted that the pivotal study ACE-536-B-THAL-001 included both patients with the β0/β0 genotype, and without the β0/β0 genotype, also referred to as non-β0/β0. Out of 336 patients in the study, a total of 103 (30.7%) of subjects were β0/β0, and 232 (69.0%) were non-β0/β0.

In the β0/β0 population, there was a non-statistically-significant trend in the primary endpoint (≥ 33% Reduction from Week 13 to Week 24 compared to baseline (see figure below).

Figure 1. Study ACE-536-B-THAL-001: Forest Plot of RBC Transfusion Burden Reduction (≥ 33% Reduction) From Baseline from Week 13 to Week 24 (ITT Population).



Importantly, rolling analyses have also been used to measure the responses within any consecutive 12-week or 24-week interval throughout the entire study period. With regards to those analyses statistically significant differences have been reported, as per the table below. A clinically relevant advantage on the basis of effects in the βo/βo population may therefore be considered acceptable. This is also in line with the broadly articulated therapeutic indication as accepted by the CHMP, which encompasses the βo/βo population.

Table 2. RBC Transfusion Burden Reduction (≥ 33% or ≥ 50% Reduction from Baseline) During Any Rolling Interval (12-week or 24-week) in Study ACE-536-B-THAL-001 in the β0/β0 subpopulation (ITT)

Endpoint	**Luspatercept + BSC[a]** **(N = 68)**	**Placebo + BSC[a]** **(N = 35)**	**Treatment Difference**	
	Number of Responders n (%)	Number of Responders n (%)	Odds Ratio[b] (95% CI)	P-value[b]
RBC transfusion burden reduction (≥ 33% reduction from baseline) During Any Rolling 12-week Interval Throughout the Entire Study Period up to Efficacy Cutoff Date	48 (70.6)	11 (31.4)	5.08 (2.07, 12.48)	0.0002
RBC transfusion burden reduction (≥ 33% reduction from baseline) During Any Rolling 24-week Interval Throughout the Entire Study Period up to Efficacy Cutoff Date	26 (38.2)	1 (2.9)	35.34 (3.42, 365.75)	< 0.0001
RBC transfusion burden reduction (≥ 50% reduction from baseline) During Any Rolling 12-week Interval Throughout the Entire Study Period up to Efficacy Cutoff Date	27 (39.7)	2 (5.7)	10.41 (2.27,47.82)	0.0005
RBC transfusion burden reduction (≥ 50% reduction from baseline) During Any Rolling 24-week Interval Throughout the Entire Study Period up to Efficacy Cutoff Date	7 (10.3)	1 (2.9)	4.01 (0.45, 36.13)	0.1929

Moreover, the sponsor argues effects in patients eligible for HSCT- in order to juxtapose to the authorised indication of Zynteglo. Towards this end, they performed a post-hoc analysis on patients with severe iron overload, based on iron overload parameters (LIC >15 mg/g dw and myocardial T2*< 10ms at baseline, as reflected on the SmPC of Zynteglo), and reporting statistically significant effects in transfusion burden compared to control. Indicatively, with regards to RBC transfusion burden reduction (≥ 33% reduction from baseline) during any 12-week interval throughout the entire study, the difference was 70.8% for the treated patients, versus 26.9% for controls (OR 6.49, p0.0002). This argument would also support effects outside the therapeutic indication of Zynteglo.

In addition to the argument of improved efficacy, there was also a claim for improved safety over Zynteglo, based on the need for progenitor mobilisation and myeloablative conditioning therapies. The COMP considered that such safety arguments are difficult to support at this point in time, given the lack of a full juxtaposition of the safety profiles of the compared products.

In their deliberation, the COMP considered that the reduction of transfusion burden in the βo/βo population, as well as on top of iron chelation therapy, would constitute a clinically relevant advantage of improved efficacy versus the authorised products.

2.4. COMP position adopted on 20 May 2020

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 approximately 1 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;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Reblozyl may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical data that support a reduction in transfusion burden, in a population that is broader than the one covered by the currently authorised products. The COMP considers that this constitutes a clinically relevant advantage.

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 Reblozyl, recombinant fusion protein consisting of a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain, luspatercept, for treatment of beta-thalassaemia intermedia and major (EU/3/14/1300) is not removed from the Community Register of Orphan Medicinal Products.

3. Recombinant fusion protein consisting of a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain for treatment of myelodysplastic syndromes - EU/3/14/1331 (EMA/OD/0000009353)

3.1. Product and administrative information

Product	
Active substances(s) at the time of orphan designation	Recombinant fusion protein consisting of a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain
International Non-Proprietary Name	Luspatercept
Tradename	Reblozyl
Orphan condition	Treatment of myelodysplastic syndromes
Sponsor's details:	Celgene Europe B.V. Winthontlaan 6n 3526 KV Utrecht Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	IDEA Innovative Drug European Associates Limited
COMP opinion date	10 July 2014
EC decision date	22 August 2014
EC registration number	EU/3/14/1331
Post-designation procedural history	
Transfer of sponsorship	Transfer from IDEA Innovative Drug European Associates Limited to Celgene Europe Limited – EC decision of 19 June 2015
Transfer of sponsorship	Transfer from Celgene Europe Limited to Celgene Europe B.V. – EC decision of 27 September 2018
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Milena Stain / Ewa Balkowiec Iskra
Applicant	Celgene Europe B.V.
Application submission date	26 April 2019
Procedure start date	23 May 2019
Procedure number	EMA/H/C/004444
Invented name	Reblozyl

Proposed therapeutic indication	Treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy and for the treatment of adult patients with transfusion-dependent anaemia associated with beta-thalassaemia. Further information on Reblozyl can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/reblozyl
CHMP opinion date	30 April 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttila / Ingeborg Barisic
Sponsor's report submission date	23 May 2019
COMP discussion	18-20 May 2020
COMP opinion date	20 May 2020

3.2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2014 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing recombinant fusion protein consisting of a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain was considered justified based on preliminary clinical data showing dose-dependent increase in haemoglobin in treated patients affected by the condition;
- the condition is life-threatening and chronically debilitating due to the development of anaemia, thrombocytopenia, neutropenia and progression to acute myelogenous leukaemia;
- the condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made;
- in addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant fusion protein consisting of a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain may be of significant benefit to those affected by the condition. The Committee considered that the product acts through a novel mechanism of action, which may allow for the treatment of anaemia as a prominent symptom of the proposed condition as supported by preliminary clinical data in patients affected by the condition. The Committee considered that this constitutes a clinically relevant advantage.

3.3. 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

Myelodysplastic syndromes (MDS) are a group of clonal haematopoietic stem cell diseases characterised by cytopenias, dysplasia in myeloid cell lines, ineffective haematopoiesis and increased risk of development of acute myeloid leukaemia.

They affect principally older adults with a median age of 70 years, and most patients are anaemic and transfusion dependent. Benzene and other chemical exposure, cigarette smoking and family history of haematopoietic malignancies have been linked to the aetiology of MDS.

Prognosis is largely based on the marrow blast percentage, number and extent of cytopenias and cytogenetic abnormalities, which are grouped in a recently Revised International Prognostic Scoring system (IPSS/IPSS-R)(Fennaux et al 2014, Ann Oncol 25 s3: iii57-iii69).

The product has received a therapeutic indication for the treatment of

- adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy
- adult patients with transfusion-dependent anaemia associated with Beta-thalassaemia

The indication for the treatment of "adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy" falls entirely within the scope of the designated orphan condition "treatment of myelodysplastic syndromes".

Intention to diagnose, prevent or treat

The medical plausibility has been established based on the positive benefit/risk assessment of the CHMP, please see EPAR.

Chronically debilitating and/or life-threatening nature

The COMP has accepted that MDS is associated with both morbidity and mortality as a result of anaemia, thrombocytopenia, and neutropenia, as well as transformation into AML. The seriousness of the proposed condition is acknowledged.

Number of people affected or at risk

The sponsor proposes an estimate of up to 2 in 10,000, unchanged from the orphan designation.

After providing the results of a literature and database search, the sponsor calculates the prevalence from crude incidence, by assuming a more or less stable incidence over the duration of the disease.

- Firstly, reference to databases was made. The crude incidence for MDS based on HAEMACARE data was cited as 0.18 per 10,000 persons (Sant, 2010). With reference to Rarecare, incidence was 0.15 and overall prevalence was 0.5 per 10,000 persons (Visser, 2012). Data from the Dusseldorf MDS Registry reported the crude point prevalence of MDS to be 1.14 per 10,000 (Neukirchen, 2011). With reference to HMRN (UK based network) the annual crude incidence rate was 0.3 per 10,000 persons between 2010 and 2016 and partial prevalence at 3,5, and 10 years was respectively 0.6, 0.82, and 1.05 per 10,000 persons (HMRN, 2019). It can be commented herein that MDS is a disease of the elderly, usually after the 6th decade of life, and therefore the 10-year partial prevalence would be a proxy for the estimate of complete prevalence. It can be additionally commented here that NORDCAN also gives a compete prevalence of approximately 1 per 10,000.
- Secondly, a list of publications providing country specific data was conducted. Incidence is derived from literature searches, which give a range of 0.23 to 1.26 per 10,000. The highest incidence of 1.26 per 10,000 estimate comes from a very old study by Williams (Br J Haematol 1994;87:743-5), that may be considered outdated. The search also gives a highest reported prevalence of 2.4 per 10,000 citing a Greek study by Avgerinou et al (Ann Hematol 2013;92:877-87)
- Thirdly, an indirect estimation of prevalence is performed, by way of the methodology outlined below, using the literature studied and assuming a duration of up to 5.3 years. The table examines four scenarios and proposes the 1.22-2.02 as more credible as it is also in line with the literature search.

Table 3.

Row	Parameter	Value (source reference or calculation)
1	EU28 population (2019)	513,481,690
2	MDS crude incidence range (per 10,000) across epidemiological studies	0.23 – 1.26 (Table 8)
3	Extrapolation of the number of new cases of MDS diagnosed annually in the EU28, based upon measured incidence rates	11,810 – 64,699 (Row 1 x Row 2)/10,000
4	Median life expectancy (years) for patients initially diagnosed with MDS	1.6 – 5.3
5	Extrapolated prevalence of MDS: Assumptions: Lowest incidence and shortest survival Lowest incidence and longest survival Highest incidence and shortest survival Highest incidence and longest survival	Row 2 x Row 4 **0.37** **1.22** **2.02** **6.68**

An overall conclusion of approximately 2 was considered acceptable, in line with the previous considerations of the committee, and the above three analyses.

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

Several products are authorised for the treatment of the condition:

- Azacitidine is authorised for the treatment of non-eligible for HSCT patients with intermediate-2 and high-risk myelodysplastic syndromes. Decitabine covers among others secondary AML.
- Lenalidomide is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.
- Imatinib is indicated for the treatment of adult patients with myelodysplastic / myeloproliferative diseases (MDS / MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements. The sponsor notes that as per the WHO classification of 2016, MDS/MPN, also referred to as MDS/MPD, is a separate condition to MDS and has therefore been excluded for the purpose of SB exercise.
- Eprex is indicated for the treatment of symptomatic anaemia (haemoglobin concentration of ≤10 g/dL) in adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (<200 mU/mL).

The relevant ESMO guideline was published in 2014 (Fennaux et al Ann Oncol (2014) 25 (suppl 3): iii57-iii69.). As per this publication, it is customary to separate MDS into 'higher risk' MDS (corresponding to IPSS high or intermediate-2) and 'lower risk' (corresponding to IPSS low or intermediate-1). In high risk patients, hypomethylating agents (azacitidine) and AML-like intensive chemotherapy are used for patients not eligible for allogeneic SCT. For lower risk patients, the main priority is generally the treatment of cytopaenias, mainly of anaemia (usually the predominant cytopaenia), and the improvement in quality of life. Anaemia, because of failure of specific treatments, often eventually requires repeated RBC transfusions, leading to potential iron overload.

Significant benefit

Significant benefit is argued versus both medicinal products, as well as non-medicinal interventions of red blood cell (RBC) transfusions (where a major contribution to patient care is put forward) and HSCT. The COMP considered that significant benefit would have to be argued versus the authorised products azacitidine, lenalidomide, and epoetin alfa.

- Versus azacitidine, which is authorised for intermediate-2 and high-risk patients, the target population is argued by the sponsor to be different. This was accepted by the COMP. Indeed, the pivotal trial is performed in very low, low, or intermediate ring sideroblast positive (RS+) MDS patients who require RBC transfusions, thereby extending the population to lower risk MDS patients.
- Lenalidomide is authorised only for patients with isolated deletion 5q cytogenetic abnormality, the latter representing a distinct subset of MDS with reference to the 2016 WHO classification for myeloid malignancies (Blood 2016, 127 (20): 2391–2405). In comparison, a key exclusion

criterion in the pivotal study of luspatercept was MDS associated with del 5q cytogenetic abnormality.

- With regards to epoetin alfa, it was also pointed out that the effects in ACE-536-MDS-001 were observed in a population where the use of epoetin alfa is not applicable. In particular, in the inclusion criteria patients would be refractory to (nonresponse or response that is no longer maintained), intolerant of, or ineligible for (serum EPO > 200 U/L) erythropoietin stimulating agents (ESA) (if previously received, must have discontinued ≥ 4 weeks prior to date of randomization).

It was therefore considered that the accepted indication was covering additional populations compared to the authorised products. The pivotal study ACE-536-MDS-001 examined the efficacy and safety of luspatercept versus placebo in subjects with anaemia due to Revised International Prognostic Scoring system (IPSS-R) very low, low, or intermediate ring sideroblast positive (RS+) MDS who require RBC transfusions. In addition, subjects were refractory to (nonresponse or response that is no longer maintained), intolerant of, or ineligible for ESA (defined as serum erythropoietin (EPO) > 200 U/L). A total of 229 subjects were randomized in a 2:1 ratio to the luspatercept (N = 153) or placebo (N = 76) treatment groups. In this population, the primary endpoint was the proportion of subjects who are RBC transfusion free over any consecutive 56 day (i.e., 8-week) period (Week 1 to Week 24) which was met in 37.9% of patients in the active group versus 13.2% in placebo (Odds Ratio 5.065, p<0.0001).

Effects have therefore been described in a population different to the target indications of the other authorised products. Significant benefit was therefore considered justified on the basis of achievement of transfusion independence in a population that includes lower risk patients and those ineligible for treatment with ESA.

3.4. COMP position adopted on 20 May 2020

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 myelodysplastic syndromes (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life threatening as a result of anaemia, thrombocytopenia, and neutropenia, as well as transformation into acute myeloid leukaemia;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Reblozyl may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has presented clinical data demonstrating achievement of transfusion independence in a population that includes lower risk patients and those ineligible for treatment with erythropoietins. This is broader than the populations already covered by the authorised products. The COMP considered that this constitutes a clinically relevant advantage.

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 Reblozyl, recombinant fusion protein consisting of a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain, luspatercept, for treatment of myelodysplastic syndromes (EU/3/14/1331) is not removed from the Community Register of Orphan Medicinal Products.