18 March 2026
EMA/OD/0000272216 and EMA/OD/0000272219
EMADOC-1700519818-3062788
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Pyrukynd (mitapivat)
Treatment of thalassaemia intermedia and major
EU/3/23/2827 (EMA/OD/0000272216)
EU/3/23/2889 (EMA/OD/0000272219)

Sponsor: Agios Netherlands B.V.

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

Introductory comment

The COMP considered that the granted orphan designations "treatment of alpha-thalassaemia intermedia and major" and "treatment of beta-thalassaemia intermedia and major" should be renamed under the umbrella condition of "treatment of thalassaemia intermedia and major". The therapeutic indication "Pyrukynd is indicated in adults for the treatment of anaemia associated with transfusion dependent and non-transfusion-dependent alpha- or beta-thalassaemia" falls entirely within the condition "treatment of thalassaemia intermedia and major".

1. Product and administrative information

EU/3/23/2827

Product	
Designated active substance	Mitapivat sulfate
Other name	-
International Non-Proprietary Name	Mitapivat
Tradename	Pyrukynd
Initial orphan condition	Treatment of beta-thalassaemia intermedia and major
Amended orphan condition (at time of review of criteria for orphan designation)	Treatment of thalassaemia intermedia and major
Sponsor's details:	Agios Netherlands B.V. Zuidplein 36 1077 XV Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Agios Netherlands B.V.
COMP opinion	7 September 2023
EC decision	13 October 2023
EC registration number	EU/3/23/2827
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Enrico Costa / Karri Penttila
Sponsor's report submission	21 May 2025
COMP discussion and adoption of list of questions	7-8 October 2025
Oral explanation	4 November 2025
COMP opinion (adoption via written procedure)	19 November 2025
Appeal to the COMP opinion procedural history	
COMP rapporteur	Ingeborg Barisic / Elisabeth Johanne Rook
Appeal submission	3 February 2026
Ad-Hoc Expert Group Consultation	12 March 2026
Appeal oral explanation cancelled by the COMP	17 March 2026
COMP final opinion	18 March 2026

EU/3/23/2889

Product	
Designated active substance	Mitapivat sulfate
Other name	-
International Non-Proprietary Name	Mitapivat
Tradename	Pyrukynd
Initial orphan condition	Treatment of alpha-thalassaemia intermedia and major
Amended orphan condition (at time of review of criteria for orphan designation)	Treatment of thalassaemia intermedia and major

Sponsor's details:	Agios Netherlands B.V. Zuidplein 36 1077 XV Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Agios Netherlands B.V.
COMP opinion	7 December 2023
EC decision	12 January 2024
EC registration number	EU/3/23/2889
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Enrico Costa / Karri Penttila
Sponsor's report submission	21 May 2025
COMP discussion	4-6 November 2025
COMP opinion (adoption via written procedure)	25 November 2025
Repeal of the COMP opinion adopted on 25 November 2025 and adoption of the final COMP opinion	18 March 2026

Type II variation procedural history

Rapporteur / Co-rapporteur	Alexandre Moreau / Paolo Gasparini
Applicant	Agios Netherlands B.V.
Application submission	8 November 2024
Procedure start	28 November 2024
Procedure number	EMA/H/C/005540/X/0010/G
Invented name	Pyrukynd
Proposed therapeutic indication	Pyrukynd is indicated in adults for the treatment of anaemia associated with transfusion-dependent and non-transfusion-dependent alpha- or beta-thalassaemia. Further information can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Pyrukynd
CHMP opinion	16 October 2025

2. Grounds for the COMP opinion

Orphan medicinal product designation:

- **EU/3/23/2827**

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2023 was based on the following grounds:

"For the purpose of orphan designation, the Committee for Orphan Medicinal Products (COMP) considered at that time that the condition originally proposed by the sponsor should be renamed as "beta-thalassaemia intermedia and major" (hereinafter referred to as "the condition") based on the current understanding of the difference between the different thalassaemias as described in the literature.

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 mitapivat sulfate was considered justified based on preliminary clinical data showing a durable increase in haemoglobin levels over a period of 72 weeks;
- 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 less than 1 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 mitapivat sulfate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary non-clinical data that demonstrate a reduction in iron load in target end organs in a valid model of the condition supporting an important therapeutic effect which can translate into a reduced need for chelating agents. Furthermore, this effect provides a potential benefit over luspatercept as the latter did not show clinically meaningful reductions in iron deposition in target end organs, and on hemolysis. 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 cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing mitapivat sulfate as an orphan medicinal product for the orphan condition: treatment of beta-thalassaemia intermedia and major".

- **EU/3/23/2889**

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2024 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 mitapivat sulfate was considered justified based on preliminary clinical data which showed an increase in haemoglobin levels and a decrease in haemolysis and erythropoietin;
- the condition is chronically debilitating due to a number of problems, including delayed growth during childhood, iron overload, gallstones, cholecystitis, skeletal abnormalities, osteoporosis, and reduced fertility. Other serious types such as Bart's hydrops foetalis syndrome is fatal;
- the condition was estimated to be affecting approximately 1 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 mitapivat sulfate will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo and preliminary clinical data that demonstrate an increase in haemoglobin and reduction in haemolysis and erythropoietin. This is associated with a reduction in iron overload in target end organs and supports an important therapeutic effect which can be translated into a reduced need for chelating agents. 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 cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing mitapivat sulfate as an orphan medicinal product for the orphan condition: treatment of alpha-thalassaemia intermedia and major".

3. Review of criteria for orphan designation at the time of type II variation

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

The applicant had received two orphan medicinal product designations: "treatment of alpha - thalassemia intermedia and major" and "treatment beta-thalassaemia intermedia and major".

Alpha- and beta-thalassaemia result from the defective synthesis of the α- or β-globin chains of adult haemoglobin. In beta-thalassaemia, α-globin aggregates, and in α-thalassaemia/HbH disease, β-globin tetramers aggregate. These toxic globin tetramers precipitate in the red blood cell (RBC) and result in intracellular oxidative stress and damage to the cellular membrane. The direct consequences of accumulation of the toxic α-globin and β-globin tetramers is a net decrease in haemoglobin (Hb)

production and haemolysis. These effects are observed in RBC precursors in the bone marrow, peripheral circulation, and in extramedullary sites (Cappellini et al, 2014).

Patients with αlpha-thalassaemia are clinically classified as having minor, intermedia, or major disease according to severity and transfusion requirements. In intermedia and major, impaired globin-chain synthesis produces unstable haemoglobin tetramers that precipitate in erythroid cells, causing oxidative damage, apoptosis, and ineffective erythropoiesis (Lechauve et al., 2019; Chakraborty et al., 2012; Cappellini et al., 2014). This leads to chronic anaemia, iron overload, and compensatory marrow expansion with extramedullary haematopoiesis, manifesting as splenomegaly, hepatomegaly, and bone deformities (Piel & Weatherall, 2014; Taher et al., 2021; Cappellini et al., 2014).

Beta thalassemia intermedia, which varies in severity but can cause chronic anaemia and may require intermittent transfusions, whereas near-complete or absent β-globin synthesis leads to beta thalassemia major, a severe, transfusion-dependent condition presenting in infancy and associated with life-threatening complications. Across both α and β forms, ineffective red blood cell production and haemolysis lead to anaemia, poor oxygen delivery, bone marrow expansion, splenomegaly, iron overload, and progressive organ damage, with severe forms linked to early mortality.

The approved therapeutic indication "Pyrukynd is indicated in adults for the treatment of anaemia associated with transfusion-dependent and non-transfusion-dependent alpha- or beta-thalassaemia" falls within the scope of the designated orphan condition for the two conditions "treatment of beta-thalassaemia intermedia and major" and "treatment of alfa-thalassaemia intermedia and major".

Initially the two orphan designations were kept separate and hence the specific questions on the beta-thalassaemia development (see List of Questions and appeal below).

However, following the appeal procedure, the COMP concluded that alpha- and beta-thalassemia could be considered as part of a single broader thalassemia condition and that the orphan conditions designated initially for Pyrukynd should be combined and reworded as "treatment of 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

Thalassemia intermedia and major are chronic inherited blood disorders characterized by reduced haemoglobin production, leading to lifelong anaemia and systemic complications; thalassemia intermedia typically causes persistent fatigue, bone deformities, splenomegaly, and progressive iron overload that can damage the heart and liver over time, making it chronically debilitating with potential life-threatening complications, whereas thalassemia major presents in infancy with severe anaemia requiring regular blood transfusions and iron chelation therapy, and without treatment is often fatal in early childhood, while even with modern care it carries significant risks such as heart failure, endocrine dysfunction, and liver disease due to transfusion-related iron overload, making it a profoundly life-threatening condition with substantial impact on quality and length of life.

The COMP considered that the condition is life-threatening and chronically debilitating due to the severe haemolytic anaemia and fatigue, splenomegaly, cardiomyopathy, jaundice, bone deformities and delayed growth, and the regular need for red blood cell transfusions, and the complications related to these transfusions.

Number of people affected or at risk

The sponsor conducted a recalculation of beta-thalassaemia and alpha-thalassemia prevalence to support the orphan designation of mitapivat, focusing exclusively on clinically significant forms of the disease.

For beta-thalassaemia, at the time of initial orphan designation, a systematic literature review (SLR) was performed with Embase, MEDLINE, and the Cochrane Library, covering the period from 1 January 2000 through 2 February 2023, with the objective of identifying country-specific, population-based prevalence studies across the 27 EU member states, Liechtenstein, Norway, and Iceland. At the time of maintenance of the orphan designation and using the same methodology, an updated search, extending the review window to 20 November 2024, was subsequently undertaken using Ovid. This later search did not yield any new population-based prevalence studies appropriate for inclusion.

To assess the robustness of the estimates, a series of sensitivity analyses were performed. These included use of the mean or median prevalence rate from all countries with available data; weighted means based on either overall population size or geographical grouping; medians within geographical groupings; extrapolation of intermedia prevalence from major cases using a 2.6 multiplier; and application of a uniform prevalence rate of 1.1 per 10,000 across the entire study region.

The main analysis yielded an overall prevalence of 0.34 per 10,000 for beta-thalassaemia intermedia and major across the 27 EU member states, Liechtenstein, Norway, and Iceland, corresponding to an estimated 15,526 patients. Sensitivity analyses produced a prevalence range of 0.33–1.1 per 10,000, equating to between 14,814 and 49,688 patients depending on the applied methodology. These can be seen in the Table 1 below. Importantly, all prevalence estimates, including those derived from the most conservative sensitivity analyses, remained below the threshold of 5 per 10,000 that defines a rare condition in the context of orphan designation.

Table 1. Prevalence of beta-thalassemia intermedia and major in the 27 EU member states and Liechtenstein, Norway, and Iceland; main analysis and sensitivity analyses

Country	2024 Population size*	Year of prevalence estimates	Type of analysis	β-thalassaemia intermedia prevalence/ 10,000**	β-thalassaemia major prevalence/ 10,000**	Estimated β-thalassaemia intermedia and major Prevalence/ 10,000**	Estimated number of patients withβ-thalassaemia intermedia and major**	Prevalence source
Bulgaria	6,445,481	2012	Main Analysis	0.032	0.336	0.368	237	Rare Disease, 2012
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.032; 0.032; 0.032; 0.032; 0.032; 0.869	0.336; 0.336; 0.336; 0.336; 0.336; 0.336;	0.368; 0.368; 0.368; 0.368; 0.368; 1.204	237; 237; 237 237; 237; 776	
Croatia	3,861,967	N/A	Main Analysis	*0.462*	*2.482*	*2.944*	*1,137*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.429; 0.558; 6.450	1.128; 0.072; 0.277; 0.991; 1.512; 2.482	1.380; 0.136; 0.428; 1.419; 2.070; 8.932	533; 52; 165; 548; 800; 3,449	
Cyprus	933,505	2022	Main Analysis	0.700	6.569	7.269	679	(Angastiniotis et al, 2022)
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.700; 0.700; 0.700; 0.700; 0.700; 17.075	6.569; 6.569; 6.569; 6.569; 6.569; 6.569	7.269; 7.269; 7.269; 7.269; 7.269; 23.643	679; 679; 679; 679; 679 2,207	
Greece	10,397,193	2010–2015	Main Analysis	0.696	2.277	2.973	3,091	(Voskaridou et al, 2019)
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.696; 0.696; 0.696; 0.696; 0.696; 5.916	2.277; 2.277; 2.277; 2.277; 2.277; 2.277	2.973; 2.973; 2.973; 2.973; 2.973 ; 8.193	3,091; 3,091; 3,091; 3,091; 3,091; 8,518	
Italy	58,989,749	2016	Main Analysis	0.421	0.747	1.168	6,891	(Angelucci et al, 2017)
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.421; 0.421; 0.421; 0.421; 0.421; 1.939	0.747; 0.747; 0.747; 0.747; 0.747; 0.747	1.168; 1.168; 1.168; 1.168; 1.168; 2.686	6,891; 6,891; 6,891; 6,891; 6,891; 15,846	
Malta	563,443	N/A	Main Analysis	*0.462*	*2.482*	*2.944*	*166*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.429; 0.558; 6.450	1.128; 0.072; 0.277; 0.991; 1.512; 2.482	1.380; 0.136; 0.428; 1.419; 2.070; 8.932	78; 8; 24; 80; 117; 503	
France	68,401,997	2005-2017	Main Analysis	0.036	0.068	0.104	713	(Agouti et al, 2019; Thuret et al, 2010)
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.036; 0.036; 0.036; 0.036; 0.036; 0.173	0.068; 0.068; 0.068; 0.068; 0.068; 0.068	0.104; 0.104; 0.104; 0.104; 0.104; 0.241	713; 713; 713; 713; 713; 1,646	
Portugal	10,639,726	N/A	Main Analysis	*0.022*	*0.042*	*0.064*	*68*	Estimated

			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.024; 0.022; 0.106	1.128; 0.072; 0.277; 0.046; 0.042; 0.042	1.380; 0.136; 0.428; 0.071; 0.064; 0.148	1,469; 145; 455; 75; 68; 157	
Romania	19,064,409	N/A	Main Analysis	*0.022*	*0.042*	*0.064*	*121*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.024; 0.022; 0.106	1.128; 0.072; 0.277; 0.046; 0.042; 0.042	1.380; 0.136; 0.428; 0.071; 0.064; 0.148	2,632; 259; 815; 134; 121; 282	
Slovenia	2,123,949	N/A	Main Analysis	*0.022*	*0.042*	*0.064*	*14*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.024; 0.022; 0.106	1.128; 0.072; 0.277; 0.046; 0.042; 0.042	1.380; 0.136; 0.428; 0.071; 0.064; 0.148	293; 29; 91; 15; 14; 31	
Spain	48,610,458	2014–2017	Main Analysis	0.007	0.016	0.023	112	(Bardon Cancho et al, 2020)
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.007; 0.007; 0.007; 0.007; 0.007; 0.039	0.016; 0.016; 0.016; 0.016; 0.016; 0.016	0.023; 0.023; 0.023; 0.023; 0.023; 0.055	112; 112; 112; 112; 112; 267	
Austria	9,158,750	N/A	Main Analysis	*0.064*	*0.046*	*0.110*	*101*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.078; 0.064; 0.095	1.128; 0.072; 0.277; 0.018; 0.063; 0.046	1.380; 0.136; 0.428; 0.095; 0.127; 0.141	1,264; 124; 392; 87; 116; 130	
Belgium	11,832,049	N/A	Main Analysis	*0.064*	*0.046*	*0.110*	*131*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.078; 0.064; 0.095	1.128; 0.072; 0.277; 0.018; 0.063; 0.046	1.380; 0.136; 0.428; 0.095; 0.127; 0.141	1,633; 161; 506; 113; 150; 167	
Czechia	10,900,555	NR	Main Analysis	*0.064*	*0.046*	*0.110*	*120*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.078; 0.064; 0.095	1.128; 0.072; 0.277; 0.018; 0.063; 0.046	1.380; 0.136; 0.428; 0.095; 0.127; 0.141	1,505; 148; 466; 104; 139; 154	
Denmark	5,961,249	2015	Main Analysis	0.048[#]	0.072[#]	0.120[#]	72	(Hansen et al, 2020)
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.048; 0.048; 0.048; 0.048; 0.048; 0.183	0.072; 0.072; 0.072; 0.072; 0.072; 0.072	0.120; 0.120; 0.120; 0.120; 0.120; 0.255	72; 72; 72; 72; 72; 152	
Estonia	1,374,687	N/A	Main Analysis	*0.064*	*0.046*	*0.110*	*15*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.078; 0.064; 0.095	1.128; 0.072; 0.277; 0.018; 0.063; 0.046	1.380; 0.136; 0.428; 0.095; 0.127; 0.141	190; 19; 59; 13; 17; 19	
Finland	5,603,851	N/A	Main Analysis	*0.064*	*0.046*	*0.110*	*62*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.078; 0.064; 0.095	1.128; 0.072; 0.277; 0.018; 0.063; 0.046	1.380; 0.136; 0.428; 0.095; 0.127; 0.141	774; 76; 240; 53; 71; 79	

Germany	83,445,000	2015	Main Analysis	0.080	0.004	0.084	699	(Borchert et al, 2018)
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.080; 0.080; 0.080; 0.080; 0.080; 0.007	0.004; 0.004; 0.004; 0.004; 0.004; 0.004	0.084; 0.084; 0.084; 0.084; 0.084; 0.011	699; 699; 699; 699; 699; 92	
Hungary	9,584,627	N/A	Main Analysis	*0.064*	*0.046*	*0.110*	*106*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.078; 0.064; 0.095	1.128; 0.072; 0.277; 0.018; 0.063; 0.046	1.380; 0.136; 0.428; 0.095; 0.127; 0.141	1,323; 130; 410; 91; 122; 136	
Ireland	5,343,805	N/A	Main Analysis	*0.064*	*0.046*	*0.110*	*59*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.078; 0.064; 0.095	1.128; 0.072; 0.277; 0.018; 0.063; 0.046	1.380; 0.136; 0.428; 0.095; 0.127; 0.141	738; 73; 228; 51; 68; 76	
Latvia	1,871,882	N/A	Main Analysis	*0.064*	*0.046*	*0.110*	*21*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.078; 0.064; 0.095	1.128; 0.072; 0.277; 0.018; 0.063; 0.046	1.380; 0.136; 0.428; 0.095; 0.127; 0.141	258; 25; 80; 18; 24; 26	
Lithuania	2,885,891	N/A	Main Analysis	*0.064*	*0.046*	*0.110*	*32*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.078; 0.064; 0.095	1.128; 0.072; 0.277; 0.018; 0.063; 0.046	1.380; 0.136; 0.428; 0.095; 0.127; 0.141	398; 39; 123; 27; 37; 41	
Luxembourg	672,050	N/A	Main Analysis	*0.064*	*0.046*	*0.110*	*7*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.078; 0.064; 0.095	1.128; 0.072; 0.277; 0.018; 0.063; 0.046	1.380; 0.136; 0.482; 0.095; 0.127; 0.141	93; 9; 29; 6; 9; 10	
The Netherlands	17,942,942	2002	Main Analysis	*0.064*	0.063	0.127	228	(Giordano et al, 2004)
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.078; 0.064; 0.161	0.063; 0.063; 0.063; 0.063; 0.063; 0.063	0.316; 0.127; 0.214; 0.141; 0.127; 0.224	566; 228; 384; 253; 228; 401	
Poland	36,620,970	N/A	Main Analysis	*0.064*	*0.046*	*0.110*	*404*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.078; 0.064; 0.095	1.128; 0.072; 0.277; 0.018; 0.063; 0.046	1.380; 0.136; 0.428; 0.095; 0.127; 0.141	5,055; 498; 1,566; 349; 465; 518	
Slovakia	5,424,687	N/A	Main Analysis	*0.064*	*0.046*	*0.110*	*60*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.078; 0.064; 0.095	1.128; 0.072; 0.277; 0.018; 0.063; 0.046	1.380; 0.136; 0.428; 0.095; 0.127; 0.141	749; 74; 232; 52; 69; 77	
Sweden	10,551,707	N/A	Main Analysis	*0.064*	*0.046*	*0.110*	*116*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.078; 0.064; 0.095	1.128; 0.072; 0.277; 0.018; 0.063; 0.046	1.380; 0.136; 0.428; 0.095; 0.127; 0.141	1,457; 143; 451; 101; 134; 149	

Liechtenstein	40,023	N/A	Main Analysis	*0.064*	*0.046*	*0.110*	*0.4*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.078; 0.064; 0.095	1.128; 0.072; 0.277; 0.018; 0.063; 0.046	1.380; 0.136; 0.428; 0.095; 0.127; 0.141	6; 1; 2; 0.4; 1; 1	
Norway	5,550,203	N/A	Main Analysis	*0.064*	*0.046*	*0.110*	*61*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.078; 0.064; 0.095	1.128; 0.072; 0.277; 0.018; 0.063; 0.046	1.380; 0.136; 0.428; 0.095; 0.127; 0.141	766; 75; 237; 53; 71; 79	
Iceland	398,940	N/A	Main Analysis	*0.064*	*0.046*	*0.110*	*4*	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5; 6)	0.252; 0.064; 0.151; 0.078; 0.064; 0.095	1.128; 0.072; 0.277; 0.018; 0.063; 0.046	1.380; 0.136; 0.428; 0.095; 0.127; 0.141	55; 5; 17; 4; 5; 6	
TOTAL	**455,195,745**	**N/A**	**Main Analysis**			**0.34†**	**15,526**	
			Sensitivity analyses (1; 2; 3; 4; 5; 6, 7)			**0.75; 0.33; 0.43; 0.33; 0.34; 0.79; 1.1**	**34,327; 14,814; 19,464; 14,720; 15,336; 35,995; 49,688**	

Abbreviations: HbE=haemoglobin E; NR=not reported; N/A=not available.
Notes: Text in *italics* indicates estimated data in countries for which prevalence rate information was not found in the literature, and mean prevalence rate from the countries with reported estimates (by group) was used in the main analysis; countries were grouped according to geography to reflect the varying prevalence of thalassaemia as described in the initial orphan application for mitapivat. * Source is 2024 Eurostat; ** Includes any other variant of β-thalassaemia intermedia and major reported such as HbE; High prevalence group; Middle prevalence group; Low prevalence group; †Calculated as Prevalence Rate=15,526/455,195,745×10,000. #The prevalence estimates for Denmark were corrected from the initial application in a re-examination of the methods and data from the original publication to reflect the true number of patients eligible for prevalence calculations; this adjustment led to lower prevalence estimates for β-thalassaemia intermedia (reduced from 0.055 to 0.044) and β-thalassaemia major (reduced from 0.092 to 0.069) and resulted in the inability to calculate a Denmark-specific estimate for other variants of β-thalassaemia intermedia.
Sensitivity analysis descriptions:
The mean prevalence rate from all countries with reported estimates (without country groupings) was used for the countries for which no data were reported.
As above, the median was used instead of the mean for the countries for which no data were reported.
To account for countries with higher prevalence rates but smaller population sizes, prevalence rate using a weighted mean based on country size was calculated for countries for which no data were reported.
As above, the weighted mean was used for the country grouping based on geography (as opposed to the mean of all countries as described in the main calculation).
As above, the median was used for the country grouping based on geography (as opposed to the median of all countries as described in sensitivity analysis #2).
Prevalence rate of each country for β-thalassaemia intermedia was determined by using the β-thalassaemia major rate and multiplying it by 2.6.
Prevalence rate of 1.1 per 10,000 for β-thalassaemia intermedia and major (based on luspatercept Orphan Maintenance Application [LOMA] median) was applied to the overall population, versus country-specific population. Therefore, country-specific estimates are not reported.

The COMP agreed that the prevalence of is approximately 1.1 in 10,00 persons for beta-thalassaemia.

The recalculated prevalence for alpha-thalassemia intermedia and major across the 27 EU member states, Liechtenstein, Norway, and Iceland was 0.90 per 10,000, corresponding to 41,045 patients. See table 2 for country-specific prevalence rate information and extrapolations. Overall, the methodology followed by the sponsor was considered acceptable, and the figure of 1 in 10,000 was accepted for alfa-thalassemia intermedia and major.

Table 2. Prevalence of alpha-thalassemia intermedia and major in the 27 EU member states and Liechtenstein, Norway, and Iceland

Country	2024 Population size*	Year of prevalence estimates	Type of analysis	α-thalassaemia intermedia prevalence/ 10,000	α-thalassaemia major prevalence/ 10,000	Estimated α- thalassaemia intermedia and major prevalence/ 10,000	Estimated number of patients with α- thalassaemia intermedia and major	Prevalence source
Bulgaria	6,445,481	2012	Main analysis	*2.707*	*0.002^*	2.709	1,746	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.582; 2.707	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.583; 2.709	887; 78; 133; 376; 1,746	
Croatia	3,861,967	N/A	Main analysis	*2.707*	*0.002^*	2.709	1,046	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.582; 2.707	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.583; 2.709	532; 47; 80; 225; 1,046	
Cyprus	933,505	2022	Main analysis	5.250	*0.002^*	5.252	490	(Angastiniotis et al, 2022)
			Sensitivity analyses (1; 2; 3; 4; 5)	5.250; 5.250; 5.250, 5.250; 5.250	0.002; 0.002; 0.001; 0.001; 0.002	5.252; 5.252; 5.252; 5.252; 5.252	490; 490; 490; 490; 490	
Greece	10,397,193	2010–2015	Main analysis	0.163	*0.002^*	0.165	171	(Voskaridou et al, 2019)
			Sensitivity analyses (1; 2; 3; 4; 5)	0.163; 0.163; 0.163; 0.163; 0.163	0.002; 0.002; 0.001; 0.001; 0.002	0.165; 0.165; 0.164; 0.164; 0.165	171; 171; 171; 171; 171	
Italy	58,989,749	2016	Main analysis	*2.707*	*0.002^*	2.709	15,978	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.582, 2.707	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.583; 2.709	8,121; 712; 1,220; 3,441; 15,978	
Malta	563,443	N/A	Main analysis	*2.707*	*0.002^*	2.709	153	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.582; 2.707	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.583; 2.709	78; 7; 12; 33; 153	

France	68,401,997	2005–2008	Main analysis	*1.375^*	*0.002^*	1.377	9,417	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.205; 0.119	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.207; 0.121	9,417; 825; 1,414; 1,414; 825	
Portugal	10,639,726	N/A	Main analysis	*1.375^*	*0.002^*	1.377	1,465	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.205; 0.119	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.207; 0.121	1,465; 128; 220; 220; 128	
Romania	19,064,409	N/A	Main analysis	*1.375^*	*0.002^*	1.377	2,625	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.205; 0.119	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.207; 0.121	2,625; 230; 394; 394; 230	
Slovenia	2,123,949	N/A	Main analysis	*1.375^*	*0.002^*	1.377	292	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.205; 0.119	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.207; 0.121	292; 26; 44; 44; 26	
Spain	48,610,458	2014–2017	Main analysis	*1.375^*	*0.002^*	1.377	6,692	Estimated
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.205; 0.119	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.207; 0.121	6,692; 586; 1,005; 1,005; 586	
Austria	9,158,750	N/A	Main analysis	*0.043*	*0.002*	0.045	41	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.027; 0.043	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.028; 0.045	1,261; 110; 189; 26; 41	
Belgium	11,832,049	N/A	Main analysis	*0.043*	*0.002*	0.045	53	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.027; 0.043	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.028; 0.045	1,629; 143; 245; 33; 53	
Czechia	10,900,555	NR	Main analysis	*0.043*	*0.002*	0.045	49	*Estimated*

			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.027; 0.043	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.028; 0.045	1,501; 131; 225; 31; 49	
Denmark	5,961,249	2015	Main analysis	0.074[#]	0.004	0.078	46	(Hansen et al, 2020)
			Sensitivity analyses (1; 2; 3; 4; 5)	0.074; 0.074; 0.074; 0.074; 0.074	0.004; 0.004; 0.004; 0.004; 0.004	0.078; 0.078; 0.078; 0.078; 0.078	46; 46; 46; 46; 46	
Estonia	1,374,687	N/A	Main analysis	*0.043*	*0.002*	0.045	6	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.027; 0.043	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.028; 0.045	189; 17; 28; 4; 6	
Finland	5,603,851	N/A	Main analysis	*0.043*	*0.002*	0.045	25	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.027; 0.043	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.028; 0.045	771; 68; 116; 16; 25	
Germany	83,445,000	2015	Main analysis	*0.043*	*0.002*	0.045	374	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.027; 0.043	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.028; 0.045	11,488; 1,006 1,725; 236; 374	
Hungary	9,584,627	N/A	Main analysis	*0.043*	*0.002*	0.045	43	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.027; 0.043	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.028; 0.045	1,320; 116; 198; 27; 43	
Ireland	5,343,805	N/A	Main analysis	*0.043*	*0.002*	0.045	24	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.027; 0.043	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.028; 0.045	736; 64; 110; 15; 24	
Latvia	1,871,882	N/A	Main analysis	*0.043*	*0.002*	0.045	8	*Estimated*
			Sensitivity analyses	1.375; 0.119; 0.205; 0.027; 0.043	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.028; 0.045	258; 23; 39; 5; 8	

			(1; 2; 3; 4; 5)					
Lithuania	2,885,891	N/A	Main analysis	*0.043*	*0.002*	0.045	13	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.027; 0.043	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.028; 0.045	397; 35; 60; 8; 13	
Luxembourg	672,050	N/A	Main analysis	*0.043*	*0.002*	0.045	3	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.027; 0.043	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.028; 0.045	93; 8; 14; 2; 3	
The Netherlands	17,942,942	2002	Main analysis	0.011	0.001	0.012	21	(Giordano et al, 2004)
			Sensitivity analyses (1; 2; 3; 4; 5)	0.011; 0.011; 0.011; 0.011; 0.011	0.001; 0.001; 0.001; 0.001; 0.001	0.012; 0.012; 0.012; 0.012; 0.012	21; 21; 21; 21; 21	
Poland	36,620,970	N/A	Main analysis	*0.043*	*0.002*	0.045	164	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.027; 0.043	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.028; 0.045	5,042; 442; 757; 103; 164	
Slovakia	5,424,687	N/A	Main analysis	*0.043*	*0.002*	*0.045*	24	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.027; 0.043	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.028; 0.045	747; 65; 112; 15; 24	
Sweden	10,551,707	N/A	Main analysis	*0.043*	*0.002*	0.045	47	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.027; 0.043	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.028; 0.045	1,453; 127; 218; 30; 47	
Liechtenstein	40,023	N/A	Main analysis	*0.043*	*0.002*	0.045	0.2	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.027; 0.043	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.028; 0.045	6; 0.5; 1; 0.1; 0.2	

Norway	5,550,203	N/A	Main analysis	*0.043*	*0.002*	0.045	25	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.027; 0.043	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.028; 0.045	764; 67; 115; 16; 25	
Iceland	398,940	N/A	Main analysis	*0.043*	*0.002*	0.045	2	*Estimated*
			Sensitivity analyses (1; 2; 3; 4; 5)	1.375; 0.119; 0.205; 0.027; 0.043	0.002; 0.002; 0.001; 0.001; 0.002	1.377; 0.121; 0.207; 0.028; 0.045	55; 5; 8; 1; 2	
TOTAL	**455,195,745**	N/A	**Main analysis**			**0.90**†	**41,045**	
			Sensitivity analyses (1; 2; 3; 4; 5)			**1.29; 0.13; 0.21; 0.19; 0.49**	**58,546; 5,795; 9,411; 8,450; 22,349**	

The sponsor, when originally applied for the designation, estimated prevalence rate of thalassemia intermedia and major to 1.36/10,000 (range of 0.55 to 2.13/10,000) in the 27 EU member states as well as Liechtenstein, Norway, and Iceland. After the appeal, the COMP combined the prevalence of alpha and beta thalassemia intermedia and major which resulted in a figure of 2.1 in 10,000, which is within the range of what the sponsor proposed.

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

During the initial evaluation and before the appeal procedure, the sponsor submitted the existing methods for alpha and beta-thalassemia.

There are general approaches to treatment of thalassaemia: transfusion therapy combined with iron chelation therapy; allogeneic stem cell transplant (allo-HSCT), and, where indicated, splenectomy

Reblozyl (luspatercept), and Casgevy (exagamglogene autotemcel) are specifically indicated for the treatment of beta-thalassemia. No products were identified that are authorised for the treatment alpha-thalassaemia specifically.

The sponsor listed the medicinal products approved for the treatment and management of thalassaemia in Table 3.

Table 3. Medicinal products approved for treatment and management of thalassemia

Product	**Member State**	**Indication**
Products for the treatment of β-thalassemia		
Casgevy (exagamglogene autotemcel)	Centrally approved	Indicated for the treatment of transfusion-dependent beta-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.
Reblozyl (luspatercept)[36]	Centrally approved	In adults for the treatment of anaemia associated with transfusion-dependent and non-transfusion-dependent beta-thalassemia For the treatment of adult patients with transfusion-dependent anaemia 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 in thalassemia		
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 paediatric 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 paediatric 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 paediatric patients with other anaemias 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 anaemia, hypoproteinaemia, 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.		

Overall, the following considerations are made regarding the need for comparability between Pyrukynd and other authorised treatments for thalassaemia.

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is recognised as a potentially curative option for patients with transfusion-dependent thalassaemia (TDT). However, its applicability is limited, as fewer than 30% of otherwise eligible patients have access to an HLA-matched related donor. According to TIF recommendations, allo-HSCT should be considered only in young patients with symptomatic TDT who have a matched sibling donor and ideally performed before the development of iron overload. Given these restrictions allo-HSCT is not considered a satisfactory treatment by the COMP.

Regular red blood cell (RBC) transfusions remain a cornerstone of care for patients with TDT thalassaemia; however, they are associated with a recognised treatment burden and significant long-term risks. Patients requiring frequent transfusions may need RBC units every 2 to 5 weeks to maintain pre-transfusion haemoglobin levels, which can substantially disrupt daily activities, schooling, employment and social functioning (Patterson et al., 2022; Shah et al., 2021; Shah et al., 2019). Transfusions provide short-term correction of anaemia but do not modify the underlying disease process. Transfusion therapy is also associated with well-documented complications, including acute transfusion reactions, transfusion-transmitted infections, alloimmunisation and progressive iron overload, as well as challenges related to blood availability in certain settings. Despite advances in supportive care, individuals dependent on chronic transfusions continue to experience reduced quality of life and higher rates of premature mortality compared with the general population (Borgna-Pignatti et al., 2004; Modell et al., 2000). In this context, transfusion therapy alone cannot be regarded as a satisfactory method of treatment for the purpose of assessing significant benefit, particularly when contrasted with medicinal products intended for use across the broader beta-thalassaemia population, including those who are not transfusion-dependent.

Splenectomy is used as a supportive intervention in selected patients with transfusion-dependent beta-thalassaemia; however, it is associated with a recognised procedural burden and long-term risks. In patients with marked hypersplenism, splenectomy can reduce splenic sequestration of red blood cells and thereby lower transfusion requirements, but this effect is variable, and it does not correct the underlying ineffective erythropoiesis or chronic anaemia.

The procedure is associated with documented complications, including lifelong increased susceptibility to infections with encapsulated bacteria, a higher risk of thromboembolic events, and an increased risk of pulmonary hypertension and other vascular complications. Because of these risks, contemporary international guidelines (such as those of the Thalassaemia International Federation) recommend that splenectomy be reserved for specific indications (for example, hypersplenism with clearly excessive transfusion requirements, symptomatic splenomegaly, or mechanical complications), and it is not recommended as routine management for the broader TDT population.

In this context, splenectomy cannot be regarded as a satisfactory method of treatment for the purpose of assessing significant benefit, given its limited and selected indications, its procedural and long-term risk profile by the COMP.

The iron chelating agents listed in the table above are indicated solely for the management of iron overload resulting from chronic transfusions. Since Pyrukynd is indicated for the treatment of anaemia in adult patients with both non–transfusion-dependent and transfusion-dependent alpha and beta-thalassaemia, its target population only partially overlaps with that of the iron chelators. These agents are therefore not considered satisfactory methods of treatment for the intended indication.

Casgevy (exagamglogene autotemcel) is a gene-editing therapy indicated for the treatment of transfusion-dependent beta-thalassaemia in patients 12 years of age and older for whom haematopoietic stem cell (HSC) transplantation is appropriate and an HLA-matched related HSC donor is not available. As such, its indication is restricted to a specific subgroup of TDT patients eligible for myeloablative conditioning and autologous transplantation. Considering these restrictions, there is no complete therapeutic overlap with Pyrukynd.

In contrast, there is a complete therapeutic overlap between the authorised indication of Pyrukynd and that of Reblozyl (luspatercept), as it is approved for the treatment of anaemia associated with beta-thalassaemia in adults. Consequently, Reblozyl is considered a satisfactory treatment, a justification of significant benefit is required.

Significant benefit (Pyrukynd over Reblozyl)

The sponsor compares Pyrukynd (mitapivat) with Reblozyl (luspatercept) as both products share overlapping therapeutic indications for the treatment of anaemia in adult patients with TDT and non–transfusion-dependent (NTDT) beta-thalassaemia. This comparison is based on a clinically relevant advantage, of both efficacy and safety grounds, and a major contribution to patient care.

Clinically relevant advantage - efficacy comparison

According to the sponsor, results from the BEYOND trial demonstrated that in adults with NTDT beta-thalassaemia, luspatercept achieved its primary endpoint, defined as an increase in haemoglobin (Hb) of ≥1.0 g/dL from baseline sustained from Week 13 through Week 24 in the absence of transfusions (Taher et al., 2022a; Taher et al., 2022b). However, the sponsor notes that luspatercept did not demonstrate a statistically significant improvement in quality of life, as assessed by the NTDT-patient reported outcomes (PRO) Tiredness/Weakness domain.

The sponsor reports that in the mitapivat pivotal Study 017, conducted in adults with NTDT alpha or beta-thalassaemia, all primary and key secondary endpoints were met. The sponsor states that mitapivat improved haemolytic anaemia, with statistically significant and clinically meaningful improvements in haemoglobin response - defined similarly to the BEYOND study - and in fatigue, measured by the FACIT-Fatigue instrument, which was not met for luspatercept. The sponsor further highlights improvement in exercise capacity, with a least-squares mean difference of 23.36 meters (95% CI: 6.90, 39.83) in the 6-minute walk test (6MWT) compared with placebo, exceeding the 20-meter threshold for clinical relevance. Haemoglobin responses were described as durable, lasting up to 23.4 weeks or longer for most responders at the end of the double-blind period.

For transfusion-dependent beta-thalassaemia, the sponsor refers to the BELIEVE trial, in which luspatercept met its primary and key secondary endpoints, demonstrating a reduction in transfusion burden (Cappellini et al., 2020). However, the sponsor highlights that luspatercept did not result in improvement in markers of haemolysis, with a reported mean increase in indirect bilirubin of +6.4 µmol/L after 24 weeks (Cappellini et al., 2021).

In the mitapivat pivotal Study 018, conducted in adults with TDT α- or beta-thalassaemia, the sponsor states that mitapivat met all primary and key secondary endpoints. The study design used transfusion evaluation periods similar to those in BELIEVE but also included extended 36-week evaluation periods (TRR3 and TRR4) to assess durability and depth of transfusion reduction, which demonstrated continued response. The sponsor reports a mean decrease in indirect bilirubin of –9.83 µmol/L at Week 24, indicating an improvement in haemolysis.

The sponsor attributes these findings to mitapivat's mechanism of action, which increases erythrocyte adenosine triphosphate (ATP) production via activation of the pyruvate kinase enzyme, thereby improving red blood cell integrity and reducing ineffective erythropoiesis and haemolysis. In contrast, luspatercept's mechanism of action involves binding to TGF-β superfamily ligands that inhibit late-stage erythropoiesis, thus promoting differentiation of erythroid precursors without directly reducing haemolysis (Suragani et al., 2014; Martinez et al., 2020; Reblozyl SmPC, 2024, Section 5.1).

Clinically relevant advantage – safety comparison

The sponsor refers to data from the BELIEVE study, in which a higher incidence of thromboembolic events was reported in the luspatercept arm compared with placebo (Cappellini et al., 2020). The sponsor also cites data from the BELIEVE and BEYOND studies showing higher rates of extramedullary haematopoiesis (EMH) and hypertension in patients treated with luspatercept compared with placebo (EMA, 2024; Reblozyl SmPC, 2024). As stated by the sponsor, these events are reflected in the product information under Special warnings and precautions for use (Reblozyl SmPC 2024). Long-term

safety follow-up (median treatment duration 153.6 weeks) reportedly did not identify new safety signals (Cappellini et al., 2025).

According to the sponsor, across the mitapivat pivotal thalassaemia studies, the incidence and severity of treatment-emergent adverse events (TEAEs) were similar between treatment and placebo arms, with most TEAEs reported as non-serious and low grade (Grade 1–2). The sponsor acknowledges hepatocellular injury (HCI) as an important potential risk based on a limited number of discontinuations associated with elevated liver enzymes that improved upon treatment cessation. The sponsor considers this risk manageable through routine laboratory monitoring.

In contrast, the sponsor notes that adverse events associated with luspatercept, such as thrombosis, hypertension, and EMH, may only be detected after onset, limiting the possibility for early intervention (Reblozyl SmPC, 2024, Section 4.4).

Major Contribution to Patient Care comparison

The sponsor emphasises that luspatercept requires subcutaneous administration every three weeks under medical supervision, with dose titration based on haemoglobin levels and transfusion history, leading to increased clinical monitoring and health care resource use (Reblozyl SmPC, 2024, Section 4.2). For patients with TDT who already require frequent transfusions, these additional visits contribute to a higher treatment burden.

In contrast, the sponsor highlights that mitapivat is an oral therapy that can be self-administered at home at a fixed dose of 100 mg twice daily, thereby reducing hospital visits and overall treatment burden. The sponsor considers the oral route and simplified dosing regimen to represent a major contribution to patient care, particularly given the chronic nature of thalassaemia management (CADTH, 2021).

The sponsor is reminded, however, that to be regarded as making a major contribution to patient care, a product should be at least equivalent in terms of efficacy, safety, and overall benefit–risk balance compared with authorised medicinal products. Therefore, the sponsor should further justify whether mitapivat and luspatercept can be considered at least equivalent in terms of efficacy, safety and benefit/risk balance.

In summary, according to the sponsor, mitapivat demonstrates broader clinical benefit compared with luspatercept, including improvements in haemolysis, quality of life, and functional capacity, along with a more convenient route of administration that may enhance patient adherence and reduce healthcare resource utilisation.

Overall, based on the sponsor's submission, mitapivat (Pyrukynd) appears to demonstrate favourable efficacy signals relative to luspatercept (Reblozyl) across multiple domains. In patients with NTDT, mitapivat was reported to improve haemoglobin levels consistent with the response definition used in the BEYOND study, along with clinically meaningful improvements in fatigue, as measured by the FACIT-Fatigue instrument, and in functional capacity, as assessed by the 6MWT (Taher et al., 2022a; 2022b). In patients with TDT, mitapivat was associated with a reduction in transfusion burden, including across extended 36-week evaluation periods that were not prespecified in the BELIEVE study for luspatercept, as well as evidence of durable response and improvements in haemolysis, reflected by decreases in indirect bilirubin (AG348-C-018 CSR; Cappellini et al., 2020; 2021). The sponsor attributes these findings to mechanistic differences between the two products: mitapivat, a pyruvate kinase activator, increases ATP production, thereby improving red blood cell integrity and reducing haemolysis, whereas luspatercept, a ligand trap of the TGF-β superfamily, enhances late-stage erythroid differentiation without directly affecting haemolysis (Suragani et al., 2014; Martinez et al., 2020; Reblozyl SmPC, 2024).

However, while these findings are of interest, it remains unclear whether the mitapivat and luspatercept pivotal trial populations are comparable. The available information does not confirm alignment in baseline disease severity, transfusion burden, haemoglobin levels, or genotype distribution (alpha- vs beta-thalassaemia). Moreover, differences in inclusion and exclusion criteria, endpoint definitions, and assessment windows may influence outcomes and limit the validity of any indirect comparison. Without detailed cross-trial adjustment or matching analyses, comparability between study populations cannot be assumed. The sponsor should therefore clarify whether the identified variables - such as disease severity, transfusion burden, haemoglobin level, and genotype – should be considered prognostic factors in the indirect comparison, and if so, account for them in the analytical model.

To enable a robust and transparent indirect comparison, the sponsor should provide:

1. Comprehensive baseline characteristics for *all trials* included in the indirect comparison (not limited to variables used in matching/weighting).
2. An overview of inclusion/exclusion criteria across trials, clearly highlighting commonalities and differences.
3. A timeline alignment analysis describing the start/end of each compared arm, study duration, treatment period, follow-up, and whether (primary) endpoints were collected at comparable timepoints.
4. A justification of covariables selected for matching/adjustment (clinical relevance, prognostic/ effect-modifying roles, data availability, and balance diagnostics).
5. A clear description of the statistical methods used for the indirect comparisons (e.g., MAIC, STC, anchored vs unanchored, IPW/entropy balancing, propensity methods).
6. Modelling approach: state the primary model, all covariates included, interaction terms (if any), and handling of missing data.
7. Assumptions: list the key assumptions, whether they were met, any violations, and the impact (direction/magnitude) of those violations on the estimates.
8. Effective Sample Size (ESS), if applicable: report ESS for every result, if possible.
9. Weights: provide the distribution of raw and standardised weights; discuss the impact of extreme weights (≈0 or >5) on result stability and precision, if applicable.

The sponsor is invited to use the following table to present baseline balance before and after adjustment (include ESS for adjusted arms). Add rows for all variables considered (clinical and methodological). For categorical variables, list categories with n (%).

Table 4. Baseline balance before and after adjustment (include ESS for adjusted arms)

Baseline Variables	**Matching Variable**	**Trial 1 Arm A (N=)**	**Trial 1 Arm B (N=)**	**Trial 1 Adjusted Arm A (ESS = n, %)**	**Trial 1 Adjusted Arm B (ESS = n, %)**	**Trial 2 Arm B (N=)**	**Trial 2 Arm C (N=)**
Variable 1 (continuous)	Yes	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Variable 2 (categorical) – Category 1	Yes	n (%) n (%)	n (%) n (%)	n (%) n (%)	n (%) n (%)	n (%) n (%)	n (%) n (%)

Category 2							
Variable 3	Yes	…	…	…	…	…	…
Variable 4	Yes	…	…	…	…	…	…
Variable 5	No	…	…	…	…	…	…
Variable 6	No	…	…	…	…	…	…
Variable 7	No	…	…	…	…	…	…
…	…	…	…	…	…	…	…

4. COMP list of issues

The sponsor has provided an indirect comparison of mitapivat to the authorised treatment, luspatercept. However, it remains unclear whether the study populations enrolled in the respective pivotal trials are comparable given the differences in the placebo response. The information provided does not demonstrate alignment in key baseline characteristics. In addition, potential differences in inclusion and exclusion criteria, endpoint definitions, and assessment timeframes may influence study outcomes and limit the validity of any indirect comparison between the two trials. In the absence of detailed cross-trial adjustment or matching analyses, the assumption of comparability between the mitapivat and luspatercept study populations cannot be substantiated. The sponsor is invited to detail these aspects. In addition, the sponsor is invited to substantiate the claim of a major contribution to patient care and how it was captured in the clinical studies.

Comments on sponsor's response to the COMP list of issues

In writing and during the oral explanation the sponsor defended their position.

The sponsor submitted an indirect treatment comparison (ITC) using a matching-adjusted indirect comparison (MAIC) approach to contextualise the efficacy of mitapivat relative to luspatercept in adults with beta-thalassaemia, in both NTDT and TDT disease settings. An anchored comparison using placebo as the common comparator was implemented.

The analyses were conducted separately for NTDT (ENERGIZE vs BEYOND) and TDT (ENERGIZE-T vs BELIEVE). Outcomes were re-derived, where feasible, to align with the comparator trial definitions. Both analyses used individual patient data (IPD) for the mitapivat studies and published aggregate data for the luspatercept trials.

While the general design of an anchored MAIC is in principle acceptable, the evidence base is limited to single pivotal studies per comparison, and trial-level structural differences (eligibility, endpoint definitions, and assessment windows) constrain interpretability.

Trials included:

- **NTDT population**: mitapivat trial ENERGIZE (Phase 3, double-blind RCT) vs luspatercept trial BEYOND (Phase 2, double-blind RCT), restricted to beta-thalassaemia subgroups.
- **TDT population**: mitapivat trial ENERGIZE-T (Phase 3, double-blind RCT) vs luspatercept trial BELIEVE (Phase 3, double-blind RCT).

Both ENERGIZE and ENERGIZE-T were Phase 3 double-blind randomized trials. BEYOND was Phase 2, while BELIEVE was Phase 3. The sponsor restricted the MAIC dataset to beta-thalassaemia patients and excluded those who did not meet key eligibility criteria of the comparator trials (e.g., recent initiation of iron chelation, thrombocytosis, short pre-randomisation transfusion-free interval). After this filtering and matching, baseline characteristics were generally balanced, supporting adequate alignment on observable covariates of choice.

Despite efforts to harmonise populations, several structural differences were identified in the NTDT comparison. For instance, to ensure Hb stability at baseline and avoid artificial inflation from recent RBC transfusions, BEYOND required two haemoglobin measurements within the 4 weeks before randomisation, excluding any value obtained ≤21 days after transfusion; ENERGIZE required two haemoglobin measurements within the 6 weeks before randomisation, excluding any value obtained ≤56 days after transfusion. When the sponsor attempted to retrospectively apply the BEYOND screening rule, only 44/132 ENERGIZE NTDT patients met the criterion. Enforcing this would have resulted in an unacceptably low effective sample size, preventing meaningful matching.

As a result, Hb endpoints were harmonised only partially. The sponsor acknowledged that NTDT haemoglobin outcomes are not interpretable in the MAIC, and interpretation shifted to endpoints less sensitive to this structural mismatch - namely FACIT-Fatigue and 6MWT.

NTDT comparison (ENERGIZE vs BEYOND)

The sponsor redefined ENERGIZE endpoints to match BEYOND:

- Hb response and mean Hb change (Weeks 12–24).
- FACIT-Fatigue (Weeks 12–24).
- 6-Minute Walk Test (6MWT) (Week 24).

Apart from the Hb baseline definition, these endpoints could be technically aligned. FACIT-Fatigue and 6MWT are therefore considered the only interpretable comparative outputs for NTDT.

TDT comparison (ENERGIZE-T vs BELIEVE)

BELIEVE used two fixed evaluation windows (Weeks 13–24 and 37–48) and prespecified response thresholds (TRR33 and TRR50). ENERGIZE-T used cumulative 12-week windows over 48 weeks (TRR2/3/4 and transfusion independence). To enable comparison, the sponsor recalculated ENERGIZE-T data using BELIEVE's fixed windows.

Endpoints unique to ENERGIZE-T (TRR2/3/4; transfusion independence at Week 48) could not be included because BELIEVE did not collect analogous data.

The indirect comparison generally relies on the assumption of exchangeability, and this can be further refined by assessing three interdependent assumptions - similarity (all studies considered are comparable with respect to possible effect modifiers across all treatments), homogeneity (absence of heterogeneity within treatment contrasts), and consistency (direct vs. indirect evidence). In the present submission, these assumptions are only partially upheld. The assumption used in population-adjusted methods on the conditional constancy of relative effects seems also not to be fulfilled.

First, the similarity assumption is met only in part. The weighting procedure effectively balanced observable baseline characteristics across ENERGIZE/ENERGIZE-T and BEYOND/BELIEVE, suggesting adequate alignment on the covariates available for matching. However, several key inclusion/exclusion criteria from the luspatercept trials could not be applied retrospectively to the mitapivat datasets. Because these criteria could not be matched or adjusted forresidual confounding related to baseline disease activity is likely. This limitation is most pronounced in NTDT, where the Hb endpoints become difficult to interpret across trials. As regards the anchor, the placebo arms should behave similarly across trials, and this appears generally supported after matching, as placebo outcomes aligned reasonably well following reweighting in most cases. Nonetheless, transfusion thresholds, supportive care practices, 6MWT and regional treatment conventions differ between the luspatercept and mitapivat programmes which indicates that the similarity assumption may not hold.

Second, homogeneity cannot be formally assessed, as each treatment contrast is informed by a single clinical trial. Without multiple trials per direct comparison, statistical tests of between-study heterogeneity are not possible, and any unexplained variability at study level cannot be ruled out.

Third, consistency (direct vs. indirect evidence) assessment of direct and indirect evidence is not possible as there is no direct comparison of mitapivat and luspatercept.

In summary, although the methodology may have been correctly implemented and weighting improved baseline alignment, the foundational assumptions of the MAIC are only partially satisfied. The unmatchable haemoglobin-screening rule in NTDT represents a substantive threat to similarity. As a result, the output of the indirect comparison should be viewed as supportive context rather than confirmatory evidence of comparative efficacy.

A frequentist MAIC using propensity-score weighting was applied to mitapivat IPD to match BEYOND/BELIEVE covariates. Weighted estimates were compared to published luspatercept results. Effective sample size decreased after weighting (e.g., NTDT effective sample size (ESS) reduced from 95 to 41), indicating substantial loss of information.

Sensitivity analyses were limited to eligibility-based exclusion, endpoint re-derivation, and Assessment of ESS and weight distribution.

Results of the indirect comparison

NTDT population (ENERGIZE vs BEYOND)

Following matching and endpoint harmonisation, two NTDT endpoints - FACIT-Fatigue and 6MWT - were considered interpretable. Haemoglobin endpoints could not be used for indirect inference due to the unresolvable Hb-screening mismatch between studies.

For FACIT-Fatigue (Weeks 12–24), mitapivat demonstrated after matching a greater improvement versus placebo in ENERGIZE (mean difference +4.0 points; 95% CI 1.0–7.0), whereas luspatercept showed a smaller change versus placebo in BEYOND (+1.4 points; –1.1 to 3.8). The adjusted indirect comparison yielded a treatment difference of +2.7 points (–1.7 to 7.0) in favour of mitapivat. Although this estimate favours mitapivat, the wide confidence interval crossing zero indicates considerable statistical uncertainty. Importantly, within the ENERGIZE beta-thalassaemia subgroup, the FACIT-Fatigue improvement remained significant (+2.81 points; 95% CI 0.27–5.35), supporting internal validity.

A similar pattern was observed for the 6MWT (Week 24) change from baseline. In ENERGIZE, mitapivat improved walking distance relative to placebo by +34.7 m (8.7–60.8) after matching, while in BEYOND luspatercept improved 6MWT versus placebo by +16.2 m (–5.7 to 38.0). The resulting indirect estimate again favoured mitapivat (+18.6 m; –23.5 to 60.7), but the precision was low, and confidence intervals crossed zero. Of note, the mean change from baseline in 6MWT was inconsistent across the Placebo arms of ENERGIZE (10.5 before matching) and BEYOND (-9.0). The results of the placebo arm in ENERGIZE changed to -5.5 after matching. This was not further explained and raises doubts on the suitability of the indirect comparison as the mean difference between before and after matching of the ENERGIZE placebo arm is 16, and the mean difference between the ENERGIZE placebo arm before matching and the BEYOND placebo arm is 19.5 which both have about the same magnitude of the treatment effect of the indirect comparison (18.6) between mitapivat and luspatercept.

Haemoglobin response and mean Hb change - primary mechanistic endpoints for both agents - were declared non-interpretable by the sponsor. Application of the BEYOND Hb-stability requirement to ENERGIZE would have reduced the effective sample size to a level that precluded meaningful

matching. As Hb represents the key driver of clinical benefit in NTDT, this limitation undermines the strength of comparative inference in this population.

Taken together, the NTDT analysis could suggest trends favouring mitapivat across patient-reported and functional endpoints. However, imprecision, reduced effective sample size after weighting, and the inability to evaluate Hb render the comparison exploratory and supportive only, not confirmatory.

TDT population (ENERGIZE-T vs BELIEVE)

The TDT MAIC focused on transfusion reduction response (TRR) endpoints, harmonised to the BELIEVE evaluation windows (Weeks 13–24 and 37–48). Both treatments showed clinically meaningful reductions in transfusion burden versus placebo in their parent trials. The indirect treatment effects were small, and confidence intervals consistently crossed zero, indicating uncertainty around the magnitude of between-treatment differences.

Table 5. Across the aligned endpoints:

Endpoint	Indirect RD (Mitapivat – Luspatercept)	95% CI
Global TRR (48 wk construct)	+8.4 %	–9.6 %, 26.5 %
TRR33 W13–24	+3.1 %	–12.6 %, 18.9 %
TRR33 W37–48	+2.5 %	–10.4 %, 15.4 %
TRR50 W13–24	+7.2 %	–2.7 %, 17.1 %
TRR50 W37–48	–1.1 %	–11.0 %, 8.8 %

All point estimates numerically favoured mitapivat except at the later TRR50 interval, where the estimate was essentially neutral. In all cases, the confidence intervals overlapped zero, indicating no statistically significant difference between treatments.

Because ENERGIZE-T captured cumulative TRR and transfusion-independence data over the full 48-week period, while BELIEVE assessed short, non-overlapping 12-week windows, sustained benefit (durability) could not be compared. Additionally, only aggregate level BELIEVE data were available, limiting the depth of harmonisation and consistency.

Across both populations, the direction of effect favoured mitapivat. Nonetheless, the precision of the indirect estimates was limited, driven by small effective sample sizes after weighting, endpoint misalignment, and incomplete availability of comparator endpoints.

In NTDT, the inability to compare haemoglobin, the primary physiological driver of benefit, prevents definitive inference, despite favourable trends in fatigue and functional capacity. In TDT, both treatments reduced transfusion burden, and the magnitude of the indirect differences was small, suggesting no clinically meaningful difference.

Sensitivity analyses were restricted to eligibility alignment, endpoint re-derivation, and inspection of weight distributions. No alternative matching strategies, covariate sets, or model specifications were reported. Although the direction of effect remained stable across sensitivity checks, the limited scope of robustness testing prevents a full assessment of model adequacy or residual confounding.

Overall COMP conclusion

The sponsor has implemented an anchored MAIC in an appropriate technical framework; however, the resulting comparative evidence is weakened by structural limitations of the underlying data and by methodological constraints that could not be resolved.

Despite the apparent alignment of baseline characteristics presented in the summary tables, important differences remain between trial populations that challenge the assumption of exchangeability. In the NTDT analysis, the most consequential issue relates to the haemoglobin baseline requirement. BEYOND mandated two Hb measurements ≥1 week apart within 4 weeks before randomisation, excluding any measurement taken ≤21 days post-transfusion. In contrast, ENERGIZE required two haemoglobin measurements within the 6 weeks prior to randomisation, excluding any value obtained ≤56 days after transfusion. When the BEYOND criterion was retrospectively applied, 44 ENERGIZE beta-thalassaemia subjects (approximately one-third of the NTDT population) would have met the criteria, leading to an insufficient effective sample size. The sponsor therefore adopted the BEYOND post-transfusion exclusion rule of 21 days (rather than 56 days) while not enforcing the 4 weeks pre-randomisation window, meaning that Hb-related endpoints, the primary biological marker of treatment effect, are intrinsically non-comparable and non-interpretable across trials.

Similarly, in the TDT comparison, while demographics appeared generally aligned, clinically relevant baseline differences persisted (e.g., genotype distribution, transfusion burden categorisation, hepatic iron concentration thresholds). Only eight covariates were used for matching, and no formal justification for covariate selection or exclusion was provided prior to the oral explanation. During the oral explanation, the sponsor clarified that inclusion of additional covariates would have resulted in a further reduction of the effective sample size, which reinforces the concern that the MAIC operates with limited overlap between study populations.

A further area of concern is the magnitude of ESS reduction after weighting. For ENERGIZE and ENERGIZE-T, ESS decreased from nominal trial sizes of 114 and 191 patients to 62 and 79, respectively. At treatment-arm level, the loss is more pronounced: in ENERGIZE-T, effective information content was reduced to less than half for mitapivat (39.5%). ESS reductions of this magnitude imply that only a subset of patients meaningfully contributes to the comparison, which increases uncertainty and indicates limited overlap between populations. In light of this, the statement in the sponsor's report that the ESS suggests sufficient overlap between trial populations is not supported; in fact, the substantial ESS reduction itself signals that overlap is limited.

Additionally, inspection of the weighting structure shows skewness in the rescaled weights, suggesting dependence on a small number of highly weighted individuals. Missing baseline covariates led to exclusion of additional patients, but the impact of this step on representativeness and potential bias was neither quantified nor discussed.

Regarding the results, the NTDT comparison shows numerically favourable trends for mitapivat on FACIT-Fatigue and 6MWT; however, haemoglobin outcomes favour luspatercept and are not interpretable due to baseline incompatibility. Confidence intervals are wide and include zero for all aligned endpoints, and in several comparisons the point estimate trends towards luspatercept. In TDT, the aligned TRR endpoints show no statistically significant differences, and indirect treatment effects are small. Matching increased mitapivat responder rates relative to the unweighted dataset, suggesting that weighting alters the clinical profile in a manner that may not reflect the total trial population.

Sensitivity exploration remains very limited and does not address model dependency or residual confounding. Violations of MAIC assumptions - particularly exchangeability - are not discussed.

In summary, the indirect comparison provides only exploratory and supportive evidence. The analysis does not adequately demonstrate that populations are comparable, nor does it establish superiority or robust equivalence of mitapivat relative to luspatercept. Given the methodological limitations;unmatched Hb eligibility criteria, substantial ESS reduction, residual confounding, unequal endpoint availability, and imprecision of estimates, the results are not sufficiently compelling to form a reliable basis for claims of comparative efficacy.

Given the structural differences between the study populations, the COMP considers that the MAIC does not achieve population comparability and therefore cannot support a suitable conclusion on equivalent or comparable efficacy between mitapivat and luspatercept. The sponsor confirmed during the oral explanation that expanding the covariate set would further reduce the effective sample size, reinforcing that the overlap between study populations is limited and that matching could be achieved only by excluding a substantial proportion of the ENERGIZE population. Under these circumstances, the foundational assumptions of the MAIC (similarity/exchangeability and valid comparators) are not met.

Because comparability of the study populations could not be demonstrated, the Committee considered that the indirect comparison data does not allow the establishment of a clinically relevant advantage (superiority) in terms of efficacy and/or safety over the authorised comparator, nor does it support a conclusion that efficacy, safety and overall benefit/risk balance can be regarded as comparable or equivalent. In this context, the Committee recalled the Commission Notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000, which states that:

"To be regarded as making a major contribution to patient care, the product should at least be equivalent in terms of efficacy, safety and benefit/risk balance as compared with authorised medicinal products."

In the present case, a robust demonstration that Pyrukynd achieves at least equivalent efficacy, safety and overall benefit/risk balance compared with luspatercept has not been provided. Consequently, this requirement cannot be considered fulfilled and the criterion for recognising of major contribution to patient care is not met.

5. COMP position adopted on 19 November 2025

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 1.1 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, in particular in beta-thalassemia major patients.
- In view of the fact that a satisfactory method for the treatment of the condition has been authorized in the European Union (luspatercept), the existence of significant benefit over the authorized method of treatment should be established at the stage of the granting of marketing authorization. The sponsor claims that Pyrukynd is of significant benefit to those affected by the orphan condition does not hold.
- In the absence of direct comparative clinical data, the sponsor submitted an indirect treatment comparison to support the claim of significant benefit. Following assessment, the Committee

concluded that this indirect comparison does not provide sufficiently robust evidence to demonstrate clinically relevant advantage based on improved efficacy or safety. While the analytical approach was, in principle, acceptable, the underlying clinical datasets could not be made sufficiently comparable. Key eligibility criteria and primary efficacy endpoints differed between trials and could not be harmonised without substantial loss of information. As a consequence, the comparative analyses relied mainly on secondary or partially aligned endpoints, with results characterised by high degree of uncertainty. Such limitations also prevented a reliable assessment of comparative efficacy and, therefore, the Committee was unable to conclude that efficacy is comparable to, or superior to, that of the authorised comparator.

- In addition, the study populations were not considered sufficiently distinct to support an argument that the product targets a broader or more difficult-to-treat population than the authorised comparator. In accordance with the Commission Notice on the application of Regulation (EC) No 141/2000, a medicinal product can be considered to be of major contribution to patient care only when it demonstrates at least equivalent efficacy, safety and overall benefit–risk compared with authorised alternatives. As equivalent (or superior) efficacy has not been demonstrated, significant benefit based on a major contribution to patient care cannot be established.

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 not satisfied.

The Committee for Orphan Medicinal Products has recommended that Pyrukynd, mitapivat sulfate, mitapivat for treatment of beta-thalassaemia intermedia and major (EU/3/23/2827) is removed from the Community Register of Orphan Medicinal Products.

6. Appeal to the negative opinion adopted on 19 November 2025

Grounds for appeal

The sponsor presented detailed grounds for appeal (EMA/OD/0000314274) on 3 February 2026.

A summary of the grounds of appeal

Ground #1: The benefits of Pyrukynd were underappreciated, due to artificially splitting the orphan condition and without regard for the full therapeutic indication

(1) While alpha and beta thalassaemia are caused by different mutations in the alpha or beta globin genes, both share a common pathophysiology driven by the imbalance of the globin chains. This imbalance leads to ineffective erythropoiesis and chronic haemolytic anaemia, translating into similar clinical manifestations. Consequently, the fundamental treatment goal is the same for patients with alpha-thalassaemia and for patients with beta-thalassaemia: improving anaemia and reducing transfusion burden

(2) There is no evidence that Pyrukynd would be ineffective in other parts of the condition. To the contrary, Pyrukynd has demonstrated effectiveness in patients with alpha-thalassaemia and in patients with beta-thalassaemia

The need to frame orphan conditions by reference to both (a) the breadth or specificity of differing mechanisms of action and (b) differing target populations of different types of medicinal products, has

been expressly recognised by the EMA in its Statement on the amended policy on orphan designations for inherited retinal dystrophies (EMADOC-628903358-34665, "IRD Statement"). In that context, the EMA clarified that three options for orphan designation should be available depending on whether a medicinal product (i) is broadly applicable across phenotypes, (ii) targeted to a specific genetic defect, or (iii) does not fit neatly within either category. The IRD Statement thus confirms that a product with a broad, genotype-agnostic mechanism of action may warrant a correspondingly broad orphan condition, distinct from more narrowly defined conditions applicable to genotype-restricted therapies. This approach is intended to ensure that orphan designations appropriately reflect the actual therapeutic scope of a medicinal product and do not inadvertently exclude otherwise treatable patient populations. That same logic must be applied to thalassaemia.

The orphan condition of Pyrukynd, and the assessment of its benefits, must be aligned with its genotype-independent mechanism of action, its clinical effectiveness and its therapeutic indication, which all apply across the thalassaemia spectrum. There are no scientific or legal grounds to define the orphan condition for Pyrukynd, or the benefits of Pyrukynd, by reference to Reblozyl, which has a different, narrower, therapeutic indication and orphan condition – all confined to the beta-thalassaemia pathophysiology. Treating these two fundamentally different products as if they warranted the same genotype-based orphan condition risks misaligning the orphan designation and significant benefit assessment with the therapeutic reality of Pyrukynd and is not justified from a scientific or regulatory perspective.

As a result of the COMP's requirement to split the Sponsor's originally proposed condition into 'alpha' and 'beta' conditions, the COMP proceeded to assess the benefit of Pyrukynd considering in isolation the subset of patients with beta-thalassaemia based on the incorrect assertion that there is a complete therapeutic overlap between the authorised indication of Pyrukynd and that of Reblozyl (luspatercept). On the contrary, Reblozyl is authorized only for beta-thalassaemia and not authorized for alpha-thalassaemia (Reblozyl SmPC) whereas Pyrukynd has received a positive opinion for an indication that encompasses both alpha- and beta-thalassaemia. The incorrect assertion regarding complete therapeutic overlap between the authorized indication of Pyrukynd and that of Reblozyl led to the incorrect conclusion.

Within the context of the significant benefit comparison, the COMP did not sufficiently consider the benefits of Pyrukynd's unique ability to treat thalassaemia patients, regardless of genotype and transfusion dependency, as a clinically relevant advantage.

Ground #2: the COMP did not take into account the totality of the evidence in its significant benefit assessment or the major contributions to patient care of Pyrukynd, a self-administered oral treatment.

The sponsor argues that, in its significant benefit assessment for beta-thalassaemia, the COMP did not adequately consider the totality of the evidence submitted or the cumulative patient-care advantages of mitapivat (Pyrukynd), particularly those linked to its oral, self-administered mode of administration. In the Negative Beta Opinion (19 November 2025), the COMP concluded that the sponsor's indirect treatment comparison was not sufficiently robust to demonstrate a clinically relevant advantage in efficacy or safety, citing limited comparability of the underlying trial datasets, differences in eligibility criteria and primary endpoints, reliance on secondary or only partially aligned endpoints, and consequent high uncertainty. The COMP further stated that the trial populations were not sufficiently distinct to support claims that mitapivat targets a broader or more difficult-to-treat population than the authorised comparator, and considered that, without demonstration of at least equivalent efficacy, significant benefit could not be established on the basis of major contribution to patient care.

In response, the sponsor states that the indirect comparisons were undertaken because the COMP requested cross-trial matching analyses to compare the mitapivat studies (ENERGIZE in non–transfusion-dependent alpha/beta-thalassaemia and ENERGIZE-T in transfusion-dependent alpha/beta-thalassaemia) with the luspatercept studies (BEYOND in non–transfusion-dependent beta-thalassaemia and BELIEVE in transfusion-dependent beta-thalassaemia). The sponsor contends that the limitations highlighted by the COMP are inherent to the forced matching of studies that were intentionally designed to enrol different and broader patient populations in the mitapivat programme, and that the resulting small effective sample sizes after matching both increased uncertainty and reduced interpretability.

The sponsor also challenges the weight given by the COMP to residual uncertainty in indirect comparisons, arguing that Commission guidance anticipates that rare-disease development may preclude adequately powered direct comparative trials and allows alternative approaches, including indirect comparisons using external data, even when endpoints are imperfectly aligned. On this basis, the sponsor argues that methodological limitations should not be determinative and that the assessment should instead consider whether the overall evidentiary record, supports meaningful benefit for patients.

Substantively, the sponsor maintains that mitapivat demonstrates benefits that were not captured in, or are not reflected from, the luspatercept development programme, and that these benefits should be considered as part of the overall significant benefit assessment. For non–transfusion-dependent thalassaemia, the sponsor highlights statistically significant improvements versus placebo in fatigue measured by FACIT-Fatigue (including within the beta-thalassaemia subgroup), noting that although treated as secondary by the COMP, this outcome was a key secondary endpoint included in a pre-specified testing strategy and is presented in the mitapivat SmPC, whereas corresponding fatigue results are not presented in the luspatercept SmPC.

Table 6. PYRUKYND: facit-fatigue results in subjects with non-transfusion-dependent thalassaemia

	Placebo	**Mitapivat**
Subjects with alpha- or beta-Thalassaemia		
Average change from baseline in FACIT-Fatigue Score from Week 12 Through Week 24		
n	54	109
LS Mean (SE)	1.46 (0.955)	4.85 (0.732)
95% CI	(-0.43, 3.34)	(3.41, 6.30)
Difference in LS Mean (SE) (Mitapivat-Placebo)		3.40 (1.110)
95% CI		**(1.21, 5.59)**
Subjects with beta-Thalassaemia		
Average change from baseline in FACIT-Fatigue Score from Week 12 Through Week 24		
n	36	76
LS Mean (SE)	1.71 (1.056)	4.52 (0.727)
95% CI	(-0.38, 3.81)	(3.08, 5.96)
Difference in LS Mean (SE) (Mitapivat-Placebo)		2.81 (1.283)
95% CI		**(0.27, 5.35)**

Both results are statistically significant: lower bound of 95% CI for the difference is above 0.

The sponsor also emphasizes improvements in markers of haemolysis (including reductions in indirect bilirubin and lactate dehydrogenase with confidence intervals excluding no effect), which they state were considered clinically meaningful and reflected in the mitapivat SmPC, and for which analogous results are not presented in the luspatercept SmPC. In addition, the sponsor points to improvements in functional capacity, describing a clinically relevant improvement in six-minute walk distance for mitapivat versus placebo (with confidence intervals excluding no effect) and contrasting this with a smaller, non-clinically relevant difference reported for luspatercept, with no corresponding inclusion in the luspatercept SmPC. For transfusion-dependent thalassaemia, the sponsor argues that mitapivat demonstrated durability of transfusion reduction using an endpoint capturing reduction in transfused red blood cell units over a 36-week standardised period (TRR3), which is reflected in the mitapivat SmPC; they contend that luspatercept trials did not pre-define an analogous durability endpoint, and that the COMP's focus on endpoints shared with the comparator trials necessarily excluded consideration of endpoints unique to mitapivat, thereby limiting recognition of differentiated benefit.

Table 7. PYRUKYND: durability of transfusion burden reduction in subjects with transfusion-dependent thalassaemia

	Placebo	**Mitapivat**
Subjects with alpha- or beta-Thalassaemia	N=87	N=171
TRR3 responders, n (%)	1 (1.1)	25 (14.6)
Difference in response rate (Mitapivat vs Placebo), %		13.4
95% CI		**(7.7, 19.1)**
Subjects with beta-Thalassaemia	N=84	N=161
TRR3 responders, n (%)	1 (1.2)	19 (11.8)
Difference in response rate (Mitapivat vs Placebo), %		10.6
95% CI		**(1.9, 16.9)**

Both results are statistically significant: lower bound of 95% CI for the difference is above 0.
TRR3 is defined as a ≥33% reduction in transfused RBC units from Week 13 through Week 48 compared with the baseline transfusion burden standardized to 36 weeks.

Mechanistically, the sponsor argues that these clinical effects are consistent with mitapivat's distinct mode of action, namely activation of red blood cell pyruvate kinase with consequent increases in intracellular ATP, which is presented as directly targeting downstream pathophysiology common to thalassaemia, including red blood cell fragility, chronic haemolysis, and ineffective erythropoiesis, thereby translating into improvements in haemoglobin, fatigue, and functional capacity. In contrast, the sponsor characterises luspatercept as acting through modulation of TGF-β superfamily signalling to promote late-stage erythroid precursor differentiation, which is presented as potentially increasing erythroid output in certain beta-thalassaemia populations but not directly addressing chronic haemolysis as a key driver of disease burden. The sponsor presents this mechanistic differentiation as relevant when interpreting the pattern of clinical benefits and when considering significant benefit "in the context of the condition as a whole".

Regarding "major contribution to patient care", the sponsor disputes the COMP's interpretation that such a contribution can only be recognised after demonstration of at least equivalent efficacy and overall benefit–risk. The sponsor argues that the Orphan Regulation framework permits demonstration of significant benefit either by clinically relevant advantage or by major contribution to patient care, and that the Commission Notice envisages a broader, multi-factor assessment incorporating efficacy, safety, quality of life, treatment burden, and practical aspects of use, particularly given evidence-generation constraints in rare diseases. The sponsor also cites CHMP conclusions in an assessment dated 16 October 2025 indicating that, for the claimed indication, Pyrukynd provides a significant clinical benefit over existing therapies based on major contribution to patient care and that the CHMP

consensus supported significant clinical benefit in comparison with existing therapies. The sponsor also refers an expert statement asserting that mitapivat's trials were the first to include the full spectrum of thalassaemia patients irrespective of genotype or transfusion need, that mitapivat improved haemoglobin and transfusion burden and reduced fatigue, and that oral administration may reduce treatment burden and improve long-term management. In addition, the sponsor refers a patient organisation letter emphasising the perceived importance of oral therapies for lifelong conditions, reductions in hospital dependence and organisational burden, and the relevance of tolerability for long-term treatment engagement and quality of life.

The sponsor concludes that the COMP should reassess significant benefit for beta-thalassaemia by considering the totality of evidence, including clinical outcomes beyond those directly comparable to the authorised comparator trials, the mechanistic rationale for differentiated benefit, and the major contribution to patient care associated with oral administration, consistent with the approach that the sponsor states is reflected in CHMP's assessment.

7. Ad-Hoc Expert Group consultation 12 March 2026

An Ad-Hoc Expert Group (AHEG) was consulted.

In the context of the re-examination procedure for this application, the AHEG was asked to provide its views on the following issues and concluded accordingly:

1. Please discuss whether alpha and beta thalassemia are separate entities or could be considered as one orphan condition (thalassaemia). Consider disease specific characteristics (e.g., pathophysiological, histopathological, clinical characteristics (signs and symptoms, treatment and medical practice) and international classification criteria.

Historically, alpha- and beta-thalassemia have been considered distinct conditions, largely reflecting their underlying genetic defects affecting the alpha- or beta-globin genes. However, several experts considered that this distinction may reflect historical perspectives.

From a pathophysiological perspective, it was highlighted that haemoglobin functions as a single molecular complex requiring the coordinated production of globin chains. In thalassemia, disease manifestations arise from an imbalance in globin chain production, irrespective of whether the primary defect affects alpha- or beta-globin synthesis. Experts emphasised that this imbalance represents the central disease mechanism and leads to ineffective erythropoiesis and haemolytic anaemia, which are shared features across thalassemia syndromes. By contrast, it was noted that not all haemoglobinopathies would necessarily be approached in the same manner e.g. haemophilia A and B.

Alpha- and beta-thalassemia share a common pathophysiological mechanism centred on globin chain imbalance within the haemoglobin molecule.

Up to 20% of patients may present with combined abnormalities affecting both alpha- and beta-globin chains, which further supports the view that strict separation between the two forms may not always reflect clinical reality. In addition, migration and increasing genetic admixture have contributed to a broader spectrum of presentations, reinforcing the concept of thalassemia as a heterogeneous continuum.

From a clinical perspective, experts agreed that a classification based on clinical severity—particularly the distinction between transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT)—is widely used and may provide a more practical framework for describing patient populations than a purely gene-based categorisation.

At the same time, it was acknowledged that genotypic classification remains important for clinical understanding, diagnosis, and patient management, particularly in the current era of genomic medicine. While genetics plays a key role in defining specific variants, several experts considered that, for the purposes of disease classification in the orphan designation context, grouping alpha- and beta-thalassemia within a single broader thalassemia condition could be scientifically justified.

Experts also noted that international disease classification systems often place thalassemia within a broader category of haemoglobin disorders, reflecting shared biological and clinical characteristics.

Conclusion: The majority of experts supported the view that alpha- and beta-thalassemia could be considered as part of a single broader thalassemia condition, based on the shared underlying mechanism involving imbalance of globin chains within the haemoglobin molecule. However, some experts noted that genetic definitions remain clinically relevant and should continue to be recognised in patient characterisation and medical practice.

2. Does the AHEG consider that the available data indicate benefit with Pyrukynd versus Reblozyl (luspatercept) in the targeted population (beta thalassemia) and is one of the two study populations more difficult to treat?

A direct comparison between the two products is not currently available, as the studies have been conducted separately and with different trial designs and patient populations. Consequently, any comparison between the two treatments is indirect and should be interpreted with caution.

The therapies target different aspects of disease pathophysiology and may therefore be considered complementary. While luspatercept primarily promotes erythroid maturation, mitapivat acts through activation of pyruvate kinase in red blood cells and targets the underlying chronic anaemia associated with beta thalassemia.

Regarding clinical outcomes, improvements in haemoglobin levels and reductions in transfusion burden observed with mitapivat may translate into clinically meaningful benefits for patients. In addition, improvements in patient-reported outcomes, including quality of life and fatigue scores (e.g. FACIT fatigue), were considered relevant and should not be disregarded. The available data were described as consistently indicating improvements in these parameters, suggesting that amelioration of chronic anaemia may lead to increased energy levels and improved daily functioning in patients.

However, patient-reported outcomes can be challenging to interpret, as they rely on subjective patient assessment and may be influenced by individual perception. Nevertheless, the consistency of the trends across available datasets was considered supportive of a positive effect.

The safety profile of luspatercept has become better characterised since its approval, with specific warnings included in the Summary of Product Characteristics, e.g. risks related to thrombosis, hypertension and extramedullary haematopoiesis. As a result, clinical use of luspatercept may require careful monitoring. In contrast, the safety profile of Pyrukynd seems to be mainly characterised by manageable symptoms based on the currently available data, although long-term data remain limited. It will be important to monitor complications such as iron overload and extramedullary haematopoiesis for Pyrukynd as well.

There is a trend towards reduction of iron overload with mitapivat which is considered as potentially clinically relevant.

Combination studies involving mitapivat and luspatercept are currently underway, reflecting the possibility that therapies with different mechanisms of action may have synergistic effects. In addition, patients with chronic anaemia who have adapted to low haemoglobin levels and remain non-

transfusion dependent may particularly benefit from treatments targeting the underlying metabolic mechanisms of the disease.

It cannot be concluded whether one population was inherently more difficult to treat than the other, although differences in trial design and baseline characteristics complicate interpretation.

Conclusion:

Despite the limitations of indirect comparisons, the available data suggest a benefit of mitapivat compared with luspatercept in the targeted population with beta thalassemia. It is unlikely that mitapivat would demonstrate inferior efficacy to luspatercept, with similar performance anticipated for the primary endpoint and potentially more favourable outcomes for certain secondary endpoints, including patient-reported outcomes. However, two experts emphasised that the currently available evidence does not allow a definitive comparison between the two treatments.

3. Please discuss the clinical relevance of the improvements in fatigue and endurance outcomes observed with Pyrukynd.

Assessment of quality of life (QoL) in clinical trials presents certain methodological limitations. Patient-reported outcomes may vary substantially between individuals, as patients differ in their perception of symptoms and in their expectations or comfort with new treatment regimens. Consequently, interpretation of QoL-related endpoints requires careful consideration.

Regarding endurance measures, one expert indicated that the clinical relevance of the improvements observed in the 6-minute walk test (6MWT) may not always be straightforward to interpret from the patient perspective. However, other experts emphasised that the study design ensured appropriate comparability between the treatment and placebo groups, including selection of placebo participants within the same baseline range as the treated population, thereby minimising concerns regarding imbalance between study arms.

Several participants stressed that improvements in fatigue and endurance are particularly relevant in the context of chronic anaemia. Patients with long-standing anaemia often adapt to their condition and may perceive their reduced functional capacity as their normal baseline. When treatment improves haemoglobin levels and energy, patients may experience a new level of baseline functioning, which can be difficult to fully capture using conventional before-and-after assessments.

The observed improvements in both the 6MWT (> 20 metres) and patient-reported fatigue scores, such as those measured by the FACIT fatigue scale, are clinically meaningful in patients with non-transfusion-dependent thalassemia (NTDT). In contrast, these endpoints may be less informative in patients with transfusion-dependent thalassemia (TDT).

Conclusion:

The improvements in fatigue and endurance outcomes observed with mitapivat are clinically relevant for patients with non-transfusion-dependent thalassemia (NTDT), although interpretation of quality-of-life endpoints should take into account the inherent limitations of patient-reported outcome measures and the adaptive nature of chronic anaemia.

4. Does the AHEG consider that the available data overall supports a major contribution of patient care (MCPC) for Pyrukynd versus Reblozyl in the targeted population (beta thalassemia)?

Mitapivat is administered orally, which is an important advantage from a patient care perspective, as it may reduce the need for hospital visits and allow greater flexibility for patients in daily disease management.

However, the practical relevance of this advantage may vary depending on the patient population and healthcare setting. For example, in patients with transfusion-dependent thalassemia (TDT), luspatercept is often administered during scheduled transfusion visits. In such cases, the treatment does not necessarily require additional hospital travel or appointments, which may reduce the practical advantage of an oral therapy.

Healthcare delivery practices differ between countries and healthcare systems. In some settings, transfusion services and other specialist care may be delivered at different locations, potentially increasing the logistical burden associated with injectable treatments. In such circumstances, an oral therapy will offer a more substantial benefit.

Some patients with thalassemia may already receive multiple concomitant medications to manage complications or comorbidities, such as endocrine disorders, hypertension or iron overload. For these patients, the addition of another oral medication may increase the daily treatment burden. Therefore, while the oral route of administration represents an advantage for many patients, its overall benefit should be considered in the context of individual patient circumstances.

Furthermore, the oral route of administration is considered advantageous for many patients, including paediatric populations.

Conclusion:

Overall, the available data support a major contribution to patient care (MCPC) for Pyrukynd compared with Reblozyl in the targeted population with beta thalassemia. However, it was acknowledged that the extent of this benefit may vary across patient groups and healthcare settings. In particular, for some patients with TDT who receive Reblozyl during routine transfusion visits, the reduction in hospital burden associated with oral administration may be less pronounced.

Comments on the grounds of appeal

COMP position on Ground #1

It is noted that the orphan condition is in concept more general than the "therapeutic indication" as defined in the product labelling (SmPC section 4.1). The orphan condition is established at initial orphan designation when the product is still under development. Although the condition should reflect a medical entity, a more general defined orphan condition allows that relevant patient subsets who may benefit from treatment with a new product will be covered by the orphan condition and included in the clinical development/studies. In contrast, the therapeutic indications in the product information (labelling) precisely define the target population for prescribers, based on the confirmatory evidence from studies and a positive benefit-risk, at the time of marketing authorisation. Furthermore, when evaluating an application for designation, the COMP should consider an orphan condition in broad terms in order to avoid designations relating to artificial subsets of a particular condition.

While alpha and beta-thalassaemia are caused by mutations in different globin genes (HBA versus HBB), they share a common downstream pathophysiological mechanism characterised by imbalanced globin chain synthesis, precipitation of unmatched globin chains, oxidative damage to erythroid precursors. This leads to comparable clinical signs and symptoms of both subsets, namely anaemia due to ineffective erythropoiesis, chronic haemolytic anaemia and compensatory marrow expansion, which together drive the major clinical consequences of disease including splenomegaly, skeletal abnormalities, growth delay, increased intestinal iron absorption and progressive systemic iron overload.

Moreover, up to 20% of patients may present with combined abnormalities affecting both alpha- *and* beta-globin chains. Clinically, these patients cannot always be clearly diagnosed and distinguished as having either alpha- or beta-thalassaemia, which further supports the need for a broader umbrella orphan condition.

In clinically significant forms, both conditions demonstrate largely overlapping pathological features such as hypochromic red blood cells due to reduced synthesis of alpha or beta chains of hemoglobin, haemolytic anaemia and marked erythroid hyperplasia with intramedullary destruction of red cell precursors. In addition, they are associated with a comparable complication spectrum affecting hepatic, cardiac and endocrine function, resulting in similar long-term morbidity.

Furthermore, standard of care is aligned across severe alpha and beta-thalassaemia and include regular red blood cell transfusion, iron chelation therapy, splenectomy in selected cases, and potentially curative allogeneic haematopoietic stem cell transplantation, while emerging therapeutic approaches increasingly target shared downstream processes such as ineffective erythropoiesis or globin chain imbalance rather than the causative mutation itself.

Finally, international classification systems such as ICD-11 maintained by the World Health Organization recognise alpha and beta-thalassaemia as subtypes within the broader disease group "thalassaemia". Notwithstanding their distinct genetic aetiologies, for the purpose of orphan designation, they may be considered manifestations of a single rare haematological disorder.

Based on the above, and in line with the view of the AHEG, the COMP concluded that alpha- and beta-thalassemia should be considered as part of a single broader thalassemia condition and that the orphan conditions designated initially for Pyrukynd should be combined and reworded as "treatment of thalassaemia intermedia and major".

The COMP would like to highlight that "mild-moderate" fits into intermedia (Ben Salah N, Bou-Fakhredin R, Mellouli F, Taher AT. Revisiting beta thalassemia intermedia: past, present, and future prospects. Hematology. 2017 Dec;22(10):607-616).

COMP conclusion

Considering that Pyrukynd is indicated to treat both alpha- and beta-thalassemia, while Reblozyl is authorized only for the treatment of beta-thalassemia, Reblozyl is not considered a satisfactory treatment option for the overall target population. Therefore, a justification of significant benefit versus Reblozyl is not required. Based on this, the COMP considered that the orphan designation for Pyrukynd should be maintained and cancelled the oral explanation.

COMP position on Ground #2

Since the orphan condition changed from "treatment of alpha-thalassaemia intermedia and major" and "treatment of beta-thalassaemia intermedia and major" into "treatment of thalassaemia intermedia and major", ground 2 was not deemed relevant anymore.

COMP conclusion on grounds #1 and #2

The COMP considered that the orphan designation for Pyrukynd should be maintained.

8. COMP final position on review of criteria for orphan designation adopted on 18 March 2026

Based on the assessment of the detailed grounds for appeal and the argumentations presented by the sponsor, the COMP concluded that:

- the orphan indications should be combined and reworded as "treatment of thalassemia intermedia and major";
- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of thalassaemia syndromes (hereinafter referred to as "the condition") is estimated to remain below 5 in 10,000 and was concluded to be approximately 2.1 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 haemolytic anaemia and fatigue, splenomegaly, cardiomyopathy, jaundice, bone deformities and delayed growth, and the regular need for red blood cell transfusions, and the complications related to these transfusions;
- there is, at present, no satisfactory treatment that has been authorized in the European Union for patients affected by the entirety of the condition.

The COMP, having considered the detailed grounds for appeal submitted by the sponsor and all the supporting data 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 of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The COMP recommends that Pyrukynd, mitapivat sulfate, for treatment of thalassaemia intermedia and major, EU/3/23/2827 and EU/3/23/2889 is not removed from the Community Register of Orphan Medicinal Products.

APPENDIX 1

Divergent position on the final COMP opinion expressed by some members of the COMP

- Alpha and beta thalassaemia are two distinct inherited blood disorders caused by mutations in different genes, each affecting the production of different components of haemoglobin. They differ in their underlying mechanisms of globin imbalance, clinical presentation, severity, and prevalence. Consequently, for the purposes of orphan drug development, they should be regarded as two separate conditions.
- In the target population of beta thalassaemia, the applicant did not provide comparative evidence against currently authorised treatments. The indirect comparisons with luspatercept are inconclusive and do not allow any conclusions to be drawn regarding comparative efficacy, whether superior or equivalent.
- The absence of evidence demonstrating comparable efficacy also means that the claim of a major contribution to patient care cannot be supported.

Therefore, the COMP members listed below consider that the evidence provided is insufficient to justify an assumption of significant benefit required for maintaining orphan designation.

COMP members expressing divergent position:

Sine Buhl Naess-Schmidt (Denmark)

Enrico Costa (Italy)