30 January 2025
EMA/OD/0000225798
EMADOC-1700519818-1884934
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Rytelo (Imetelstat sodium)
Treatment of myelodysplastic syndromes
EU/3/20/2305

Sponsor: Geron 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
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1. Product and administrative information

Product	
Designated active substance(s)	Imetelstat sodium
Other name(s)	Imetelstat sodium
International Non-Proprietary Name	Imetelstat
Tradename	Rytelo
orphan condition	Treatment of myelodysplastic syndromes
Sponsor's details:	Geron Netherlands B.V. Naritaweg 165 1043 BW Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Parexel International GmbH
COMP opinion	18 June 2020
EC decision	27 July 2020
EC registration number	EU/3/20/2305
Post-designation procedural history	
Transfer of sponsorship	Transfer from Parexel International GmbH to Geron Netherlands B.V. – EC decision of 13 June 2023
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Filip Josephson / Johanna Lähteenvuo
Applicant	Geron Netherlands B.V.
Application submission	08 September 2023
Procedure start	28 September 2023
Procedure number	EMA/H/C/006105/0000
Invented name	Rytelo
Proposed therapeutic indication	Treatment of adult patients with very low to intermediate-1risk myelodysplastic syndromes(MDS) who are transfusion-dependent and had an unsatisfactory response to or are ineligible for erythropoiesis-stimulating agent (ESA) treatment. Update 06/02/2023: The treatment of adult patients with low to intermediate-1 risk myelodysplastic syndromes who are transfusion-dependent and have failed to respond or have lost response or are ineligible for erythropoiesis-stimulating agents. 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/Rytelo

CHMP opinion	12 December 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Darius Matusevicius / Karri Penttila
Sponsor's report submission	15 August 2024
COMP discussion	05-07 November 2024
COMP opinion (adoption via written procedure)	30 January 2025

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2020 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing imetelstat sodium was considered justified based on early clinical data demonstrating achievement of transfusion independence in a proportion of patients with low risk myelodysplastic syndromes;
- the condition is life-threatening and chronically debilitating in particular due to anaemia, thrombocytopenia, and neutropenia, as well as transformation into AML;
- the condition was estimated to be affecting approximately 2 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 imetelstat sodium will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients with low risk condition who were transfusion dependent even after pre-treatment with erythropoiesis stimulating agents and who are ineligible for treatment with lenalidomide did achieve either transfusion independence or reduction of transfusion frequency. The Committee considered that this constitutes a clinically relevant advantage.

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

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing imetelstat sodium as an orphan medicinal product for the orphan condition: treatment of myelodysplastic syndromes.

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

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

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

Condition

Myelodysplastic syndromes (MDS) are a group of clonal haematopoietic stem cell diseases characterised by cytopenias, dysplasia in myeloid cell lines, ineffective haematopoiesis and increased risk of development of acute myeloid leukaemia (AML). MDS affect principally older adults with a median age of 70 years, and most patients are anaemic and transfusion dependent. Benzene and other chemical exposure, cigarette smoking and family history of haematopoietic malignancies have been linked to the aetiology of MDS. Approximately 85% of patients with MDS have primary or idiopathic MDS, and do not have an obvious exposure or cause for the disease (Fenaux 2021). Prognosis is largely based on the marrow blast percentage, number and extent of cytopenias and cytogenetic abnormalities, which are grouped in a recently Revised International Prognostic Scoring system (IPSS/IPSS-R), (Fennaux et al 2014, Ann Oncol 25 s3: iii57-iii69).

The therapeutic indication "*Rytelo is indicated as monotherapy for the treatment of adult patients with transfusion-dependent anaemia due to very low, low or intermediate risk myelodysplastic syndromes (MDS) without an isolated deletion 5q cytogenetic (non-del 5q) abnormality and who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy*" falls within the scope of the designated orphan condition "Treatment of myelodysplastic syndromes".

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

The clinical presentation of MDS is heterogeneous and varies depending on the subtype and severity of the cytopaenia. Anaemia is the most common peripheral erythroid maturation defect, occurring in 80% to 85% of cases (Steensma, 2006). Many patients with MDS who develop anaemia, particularly those with Revised International Prognostic Scoring System (IPSS-R) lower-risk MDS (approximately 40%), become transfusion dependent (Zeidan, 2013; Ades, 2014). Thrombocytopenia is observed in 30% to 45% of patients with MDS and neutropenia in 40% of patients (Steensma, 2006). Symptoms are usually nonspecific but may be suggestive of the cytopenia involved. Fatigue and a decline in activities of daily living or quality of life (QoL) are indicative of anaemia. Recurrent infections may be related to neutropenia, and frequent and unexplained bruising or bleeding is suggestive of thrombocytopenia (Ades, 2014; Foran, 2012; Toma, 2012). Patients with higher-risk MDS present with more severe symptoms (Foran, 2012). Analysis of the bone marrow (BM) and blood samples is central to the diagnosis (Ades, 2014; Fenaux, 2014) and facilitates the exclusion of non-MDS causes of cytopenias (Ades, 2014; Bejar, 2014; Zini, 2017). Analysis of somatic mutations and flow cytometry analysis of BM cells can be useful when a diagnosis of MDS is uncertain (Fenaux, 2014).

The sponsor has not identified any changes on the chronically debilitating or life-threatening nature of MCC since the orphan designation was granted in 2020, despite the more recent approval of luspatercept.

The COMP has previously acknowledged that the condition is chronically debilitating and life threatening as a result of anaemia, thrombocytopenia, and neutropenia, as well as transformation into acute myeloid leukaemia. This view is maintained by the COMP.

Number of people affected or at risk

During the initial orphan designation in June 2020, the COMP accepted that the condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union.

The sponsor has updated their prevalence calculation with epidemiologic data which has become available since the adoption of the initial orphan designation.

To determine a range of plausible estimates for prevalence of MDS in Europe, the sponsor multiplied various estimates of incidence and survival identified in the literature. A commonly cited estimate of MDS incidence is 0.4 per 10,000 person-years (PY) (Sekeres, 2022), which falls within the range of incidence estimates identified in this literature search and serves as the lower estimate for calculations. Additionally, a high, but plausible, estimate of 0.7 per 10,000 PY is presented based on the adjusted values from epidemiologic studies from Greece (0.57 per 10,000 PY), Denmark (0.64 per 10,000 PY) and Italy (0.69 per 10,000 PY) (Avgerinou, 2013; Lauritsen, 2023; Mangone, 2023). Finally, a very high estimate (0.86 per 10,000 PY), using a single period of time from the Northern Italian study, is included (Mangone, 2023). Survival estimates included 2.3 years (28 months based on Dinmohamed, 2014), and estimates for intermediate (3.0 years), low (5.3 years) and very low (8.8 years) risk MDS based on Greenberg, 2012. Results appear in Table 1.

Table 1. Calculated Estimates of MDS Prevalence Using Varying Incidence and Survival

Survival (Years)	If incidence is 0.4 per 10,000 PY	If incidence is 0.7 per 10,000 PY	If incidence is 0.86 per 10,000 PY	Survival Reference
2.3	0.9	1.6	2.0	Dinmohamed 2014
3	1.2	2.1	2.6	Greenberg 2012
5.3	2.1	3.7	4.6	Greenberg 2012
8.8	3.5	6.2	7.6	Greenberg 2012

The calculated prevalence of MDS ranged from 0.9 to 7.6 per 10,000 persons. The sponsor notes that the two calculated prevalence estimates which exceeded the 5 per 10,000-person threshold are likely an overestimate as they were calculated using the highest incidence estimates found in the literature and the highest survival estimate, which represents the median survival in very low risk MDS patients. Indeed, in all three studies which presented 3-year average survival, fewer than 50% of MDS patients survived to 3 years (Lauritsen, 2023; HMRN, 2024; RARECARENet 2022c) and in all six studies which presented 5-year survival, 33% of fewer patients survived for 5 years (Bonadies, 2017; Lauritsen, 2023; HMRN, 2024; Mangone, 2023; RARECARENet 2022c Roman,2016).

The COMP noted that the three different incidence values used in their calculations pertain to MDS incidence in general, while the four survival values pertain to different MDS risk groups. However, the sponsor also explains that the mean/median MDS survival is around 3 years (i.e. fewer than 50% of MDS patients survived to 3 years as reported by Lauritsen, 2023; HMRN, 2024; RARECARENet 2022c). Furthermore, the incidence value of 0.86 per 10,000 PY appears to be an outlier in a particular part of Italy from the period between 2011-2015. In the subsequent period from 2016-2020 the value in this particular region dropped again to 0.69 (Mangone et al., 2023). Therefore, an incidence figure of approximately 0.7 per 10,000 appears to be sufficiently conservative. Considering this, a final prevalence of approximately 2 per 10,000 persons is considered acceptable and likely to reflect the actual prevalence of the condition in the EU.

The COMP accepted a prevalence of approximately 2 per 10,000 persons, in line with previous orphan designations in this condition.

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

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

Existing methods

The below products are authorised for the treatment of the condition in the EU:

Table 2. Products authorised in the EU indicated for the treatment of MDS

Invented Name (INN)	**Approved MDS Indication in EU***
EPREX/ERYPO (epoetin alfa) -> Anti-anaemic	EPREX is indicated for the treatment of symptomatic anaemia (haemoglobin concentration of ≤10 g/dL) in adults with **low- or intermediate-1-risk primary myelodysplastic syndromes (MDS)** who have low serum erythropoietin (<200 mU/mL).
Reblozyl (Luspatercept) -> Anti-anaemic	Reblozyl is indicated in adults for the treatment of transfusion-dependent anaemia due to **very low, low and intermediate-risk myelodysplastic syndromes (MDS)**.
Vidaza (azacitidine) -> Antineoplastic agents	Vidaza is indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (HSCT) with:**intermediate-2 and high-risk myelodysplastic syndromes (MDS)** according to the International Prognostic Scoring System (IPSS)
Revlimid (lenalidomide) -> Other immunosuppressants	Revlimid as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anaemia due to **low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q** cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

The aim of therapy in lower-risk MDS (LR MDS), which represent the main target patient population of Imeltestat, is to improve anaemia (usually the predominant cytopenia) and decrease transfusion needs, improve other cytopenias, attempt to prolong OS, and reduce the risk of progression without compromising QoL (Fenaux, 2021; Platzbecker, 2021; Volpe, 2022). In patients where cytopenias are mild and asymptomatic, the approach is generally watchful observation. Eventually, ~40% of LR MDS patients will become transfusion dependent.

The ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up for MDS, endorsed by the European Hematology Association (EHA) (van de Loosdrecht, 2022), provide a treatment algorithm supported by either evidence or expert opinions for LR-MDS (Figure 1).

Figure 1. Treatment Algorithm for Lower Risk MDS (sponsor Figure 20)

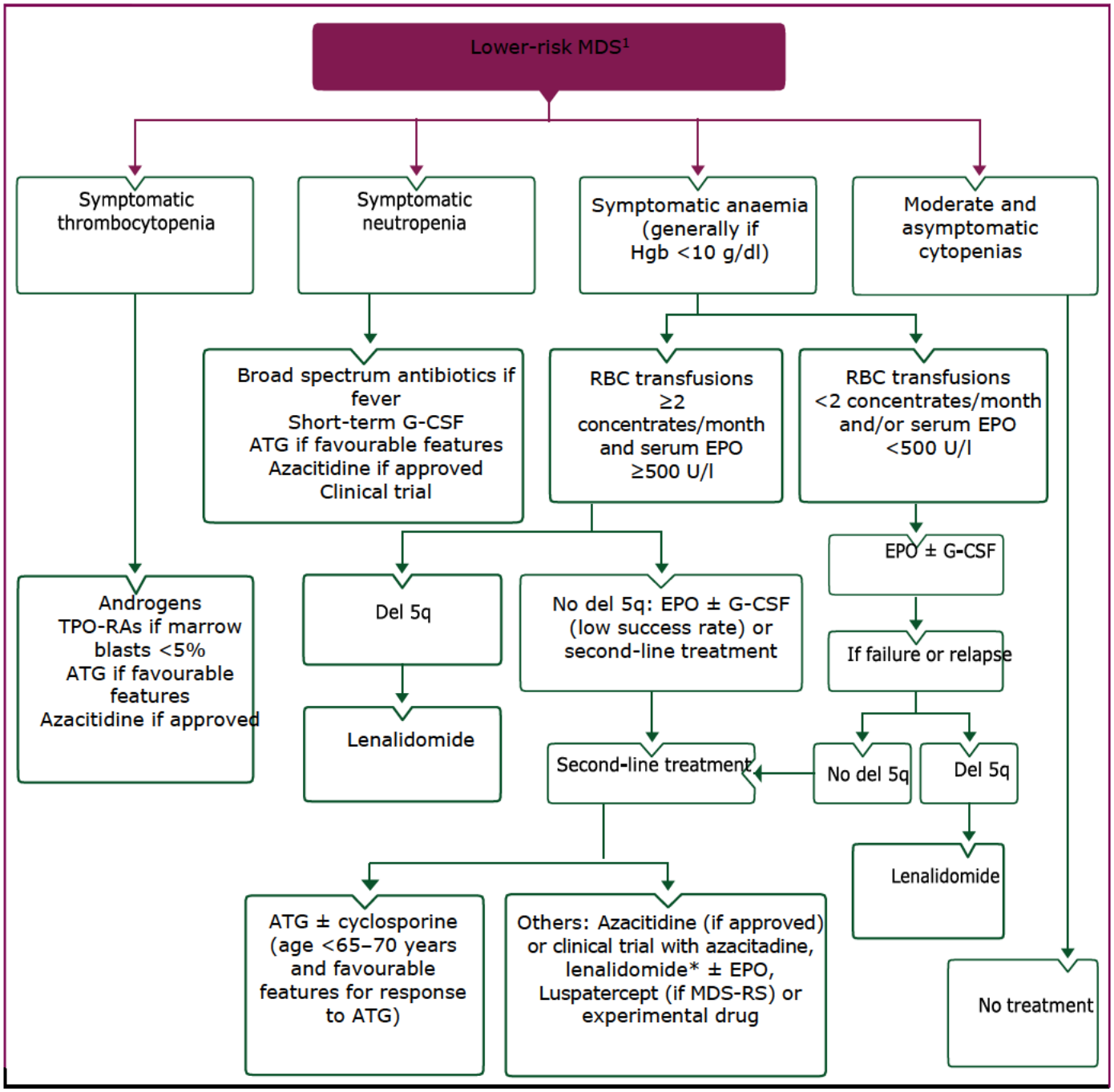

Figure adapted from ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of MDS (Fenaux, 2021).

ATG = antithymocyte globulin; EPO = erythropoietin; G-CSF = granulocyte colony-stimulating factor; Hgb = haemoglobin; IPSS-R = revised international prognostic scoring system; MDS = myelodysplastic syndromes; MDS-RS = myelodysplastic syndrome with ring sideroblasts; RBC = red blood cell; TPO-RA = thrombopoietin receptor agonist.

[1] IPSS-R very low-, low- and some intermediate-risk. For IPSS-R intermediate-risk MDS patients, whether they should initially receive treatment for lower-risk MDS or higher-risk MDS is also based on other factors including age, comorbidities, importance of cytopenias, somatic mutations, effect of first-line treatment, etc.*Not approved in this setting

The COMP does not consider EPREX/ERYPO (epoetin alfa), Vidaza (azacitidine) and Revlimid (lenalidomide) as satisfactory methods for the purpose of this procedure, as imetelstat is indicated in a patient population which is not fully covered by the indication wordings of these three authorized products:

- As regards EPREX/ERYPO (epoetin alfa), imetelstat is indicated for use in patients who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.
- As regards Vidaza (azacitidine), imetelstat is indicated for use in patients with lower-risk MDS.
- As regards Revlimid (lenalidomide), imetelstat use is not restricted to patients carrying an isolated deletion 5q cytogenetic abnormality.

In conclusion, the COMP considered that significant benefit would only have to be argued versus the authorised product Reblozyl (luspatercept).

Significant benefit

The sponsor claims a clinically relevant advantage of Imetelstat vis a vis Reblozyl (Luspatercept) based on improved efficacy. Five main arguments with corresponding data from the pivotal Phase 3 study MDS3001 with Imetelstat are presented, see below claims 1) to 5).

While Imetelstat is intended for use in patients who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy, this restriction does not apply to Luspatercept. For the purpose of comparing the efficacy of Imetelstat and Luspatercept, the sponsor focuses on the respective pivotal studies in the second-line treatment setting, i.e. study MDS3001 (IMerge) for Imetelstat and the MEDALIST Study for Luspatercept.

Table 3. Comparison of Key Study Design Features between Imetelstat MDS3001 and Luspatercept MEDALIST Studies

	Imetelstat MDS3001 Study	**Luspatercept* MEDALIST Study**
Study Design	Phase 3, double-blind, randomized, placebo-controlled, multicentre	Phase 3, double-blind, randomized, placebo-controlled, multicentre
Total No. of Treated Patients (active and placebo)	N= 177 (118 imetelstat; 59 placebo)	N= 229 (153 Luspatercept; 76 placebo)
MDS Population	IPSS: low or int-1 Non-del 5q, No HMA or Len	IPSS-R very low, low, or intermediate-risk Non-del 5q, no HMA or iMIDs Ring sideroblasts (RS)+ by WHO 2001: $\geq$ 15% RS or $\geq$ 5% with SF3B1 mutation and < 5% blasts in bone marrow
Transfusion dependence and response to prior ESA definitions	RBC transfusions burden $\geq$ 4 units /8 weeks over 16-week pre-study period Relapsed/refractory to ESA or EPO > 500 U/L	RBC transfusion burden $\geq$ 2 units/ 8 weeks over 16-week pre-study period Refractory, intolerant or ESA naïve: EPO > 200 U/L
Primary Endpoint	$\geq$8-week RBC TI	8-week RBC TI within week 1-24

	(*Note: no fixed time period; Day 1 until the start of subsequent anti-cancer therapy (if any)*)	
Key Secondary Endpoints	≥24-week RBC TI Duration of RBC TI (*Note: no fixed time period; Day 1 until the start of subsequent anti-cancer therapy (if any) or discontinuation*)	12-week TI (week 1-24) 12-week TI (week 1-48) 8-week TI (week 1-48)
Primary analysis timepoint	12 months after the last subject is randomized in Phase 3	At 24 weeks for all subjects and 48 weeks for subjects eligible to continue treatment after the Week 25 visit

EPO = epoetin; HMA = hypomethylating agent; Len = lenalidomide; RBC=red blood cell; TI = transfusion independence *Reblozyl EPAR

The sponsor points out the following differences in the baseline characteristics of the enrolled patient population between these studies and notes that these should be considered in the comparative efficacy analyses:

- Enrolment of a broader patient population in MDS3001 due to inclusion of RS- subjects. MEDALIST study was restricted to RS+ patients who are known to have improved long-term outcomes (i.e. OS, transformation to AML) compared with RS- patients (Malcovati, 2020; Patnaik, 2021).
- In the MDS3001 study, 76.4% of the population received ≥ 6 RBC units per 8 weeks at baseline compared with 43.2% of subjects in the MEDALIST study. It is known that higher transfusion burden tends to correlate with worse outcome (Malcovati, 2005; Santini, 2022).
- In the MDS3001 study, 27.0% of the population had serum EPO ≥ 500 U/L at baseline compared with 14.0% of subjects in the MEDALIST study. Patients with EPO ≥ 500 U/L at baseline have low likelihood of response to any further erythropoietin-based treatment (Gascon, 2019).

Table 4. Comparison of Key Baseline Characteristics between Imetelstat Phase 3 MDS3001 and Luspatercept MEDALIST

	Imetelstat MDS3001/Phase 3 (N=178)	**Luspatercept MEDALIST /Phase 3 (N=229)**
WHO classification, n (%)[a]	RS+: 110 (61.8%) RS-: 67 (37.6%)	RS+: 229 (100%) RS-: none
Baseline RBC transfusions, median/8 weeks (range)	6 (4-33)	5 (1-20)
Risk category, n (%)	IPSS: low: 119 (66.9%) Intermediate-1: 59 (33.1%)	IPSS-R[b]: very low, low: 190 (83.0%) Intermediate: 38 (16.6%)
% of subjects enrolled by baseline RBC transfusion need U/8 weeks[c]	< 4 units: 0 4 – 5 units: 42 (23.6%) ≥ 6 units: 136 (76.4%) 6 – 8 units: 100 (56.2%) > 8 units: 36 (20.2%)	< 4 units: 66 (28.8%) 4 – 5 units: 64 (27.9%) ≥ 6 units: 99 (43.2%) 6 – 8 units: 62 (27.0%) > 8 units: 37 (16.2%)
Serum EPO level > 500 U/L, n (%)	48 (27.0%)	32 (14.0%)

EPO=erythropoietin; IPSS=International Prognostic Scoring System; MDS = myelodysplastic syndromes; MDS-u = MDS unclassifiable; RA=refractory anaemia; RAEB=refractory anaemia with excess of blasts; RARS=refractory anaemia with ring sideroblasts; RBC=red blood cell; RCMD=refractory cytopenia with multilineage dysplasia; RCUD = refractory cytopaenia with unilineage dysplasia; RS = ringed sideroblasts; U=units

[a] RS+ includes RARS or RCMD-RS; RS- includes RA, RCUD-R1, RCUD-RT, RCMD, RAEB-1, RAEB-2, or MDS-u

[b] IPSS-R is an updated version of IPSS that has 5 rather than 3 risk classification levels (very low, low, intermediate, high and very high risk) for MDS based on the incorporation of the depth of cytopenias into the scoring system. Since neither study enrolled higher risk patients (either IPSS Intermediate-2 or IPSS-R High), the risk categories in both studies are similar regardless of the system used.

[c] Prior RBC transfusion burden is defined as the maximum number of RBC units transfused over an 8-week period during the 16 weeks prior to randomization.

The sponsor considers the results of MDS3001 with Imetelstat support the demonstration of significant benefit versus Luspatercept by addressing the following unmet needs:

1) Imetelstat Provides Clinically Meaningful and Durable Continuous Transfusion Independence in both RS+ and RS- LR MDS patients.

As discussed above, the comparison of the efficacy of Imetelstat versus Luspatercept is based on the respective pivotal Phase 3 studies in the second line setting, MDS3001 and MEDALIST. As the

patient populations are different in key parameters including baseline transfusion needs and RS status (Table 4), the sponsor resorts to a comparative efficacy analysis of Imetelstat versus Luspatercept in sub-populations of the study. The sponsor points out that their pivotal Phase 3 study MDS3001 has demonstrated that Imetelstat provides clinically meaningful and durable continuous transfusion independence in both RS+ and RS- low-risk MDS patients, while no RS- patients were included in the pivotal Phase 3 study MEDALIST with Luspatercept.

In the subset of RS+ MDS patients who had a baseline transfusion burden ≥ 4 units / 8 weeks, Imetelstat and Luspatercept have comparable efficacy (Table 5).

Table 5. Imetelstat Efficacy Compared to Luspatercept in ESA R/R Lower Risk MDS who are **RS+** and had a with baseline transfusion burden ≥ 4 units / 8 weeks (Study MDS3001 versus MEDALIST), amended from sponsor Table 15

	MDS3001 Phase 3			**MEDALIST Phase 3**[1,2,3]		
	Imetelstat N=73	**Placebo N=37**	**Imetelstat vs Placebo**	**Luspatercept N=153**	**Placebo N=76**	**Luspatercept vs placebo**
Median baseline transfusion burden;# units/8 weeks (range)	6 (4-19)	8 (4-13)		5 (1-15)	5 (2-20)	
Subjects with baseline transfusion burden ≥ 4 units / 8 weeks	N=73	N=37		N=107	N=56	
≥ 8-week RBC-TI rate (%)*	33 (45.2%)	7 (18.9%)	△26.3%	34 (31.8%)	4 (7.1%)	△24.7%

*At any time, +during 1- 48 weeks for Luspatercept. 1Fenaux, 2019, 2Fenaux, 2020, 3Zeidan, 2022.

ESA = erythropoietin stimulating agent, RBC = red blood cell, R/R = relapsed/refractory, TI = transfusion independence

Imetelstat has also shown to be efficacious in RS- MDS patients in the MDS3001 Phase 3 study (Table 6). Comparative Phase 3 data from the MEDALIST study with Luspatercept is not available, as no RS- patients were included in this study.

Table 6. Imetelstat Efficacy in ESA R/R Lower Risk MDS with Baseline Transfusion Burden ≥ 4 units/8weeks who are **RS-** (Study MDS3001 Phase 3)

	Imetelstat N=44	**Placebo N=23**	**Imetelstat vs Placebo**
Median baseline transfusion burden # units/8 weeks (range)	6 (4-33)	6 (4-13)	
≥ 8-week RBC-TI rate (%)*	14 (31.8%)	2 (8.7%)	**△23.1%**
Median ≥ 8-week TI Duration, weeks	51.6	11.2	HR=0.11
≥ 16-week RBC-TI rate (%)*	10 (22.7%)	0	△22.7%
≥ 24-week RBC-TI rate (%)*	9 (20.5%)	0	△20.5%
≥ 1-year RBC-TI rate (%)*#	6(13.6%)	0	△13.6%
Subjects with baseline transfusion burden ≥ 6 units / 8 weeks	**N=34**	**N=17**	
≥ 8-week RBC-TI rate (%)*	12/34 (35.3%)	1/17 (5.9%)	△29.4%
Median ≥ 8-week TI Duration, weeks	51.6	10.1	HR=0.00

*At any time. # final analysis with clinical cutoff: Oct 2023

ESA = erythropoietin stimulating agent, RBC = red blood cell, R/R = relapsed/refractory, TI = transfusion independence

The COMP emphasized that the 4.1 indication for Luspatercept is no longer restricted for use only in RS+ MDS patients, neither in first- nor in second-line. During the extension of indication procedure for Luspatercept, the CHMP concluded the following based on the totality of data reviewed: "*Although the evidence of a beneficial effect in RS- patients in the previously approved second line setting is very limited, as no RS- patients were included in the pivotal MEDALIST (ACE-536-MDS-001) study, long-term efficacy results from Phase 2 study (A53603/05) indeed indicate a treatment benefit also in RS- patients, albeit again lower compared to RS+ patients. Taken together, these observations enable extrapolation also to the previously approved second line setting and a broad MDS indication*" (CHMP Assessment Report for procedure EMEA/H/C/004444/II/0021, dated 22 February 2024). Considering that the proposed indication for Rytelo is fully included within the wider authorised indication of Rebrozyl (as it also includes the first line of treatment), and both products cover patients regardless of ring sideroblast status (RS+ or RS-), the sponsor is expected to consider all available relevant data to demonstrate a significant benefit for RS+ and/or RS- patients.

2) Clinical Benefit and Efficacy with Imetelstat in RS+ patients with high baseline transfusion burden (≥ 6 units /8 weeks)

While the ≥ 8-week RBC TI rate in RS+ patients is similar between Imetelstat and Luspatercept, the sponsor points out that Imetelstat compares favourably to Luspatercept on important clinical parameters in the further subset of RS+ patients with high baseline transfusion burden (Table 7). The subset of RS+ patients with a HTB represent only 47% (84/178) of the total patient population of study MDS3001 (Imetelstat).

Table 7. Imetelstat Efficacy Compared to Luspatercept in ESA R/R Lower Risk MDS who are **RS+** and had a with **baseline transfusion burden ≥ 6 units / 8 weeks** (Study MDS3001 versus MEDALIST), amended from sponsor Table 15

	MDS3001 Phase 3			**MEDALIST Phase 3**[1,2,3]		
	Imetelstat N=57	**Placebo N=27**	**Imetelstat vs Placebo**	**Luspatercept N=66**	**Placebo N=33**	**Luspatercept vs placebo**
≥ 8-week RBC-TI rate+ (%)	25 (43.9%)	3 (11.1%)	△ 32.8%	12 (18.2%)	2 (6.1%)	△ 12.1%
Median ≥ 8-week TI duration, weeks	42	8.9	HR=0.04	26.9	Not reported	Not reported
Median Hgb peak in ≥ 8-week TI period, g/dL	11.0	8.9	△ 2.1	9.9	9.5	△ 0.4

*At any time, +during 1- 48 weeks for Luspatercept. 1Fenaux, 2019, 2**Fenaux, 2020**, 3Zeidan, 2022.
ESA = erythropoietin stimulating agent, RBC = red blood cell, R/R = relapsed/refractory, TI = transfusion independence

In addition, the sponsor presents a **Matching Adjusted Indirect Comparison (MAIC) Analysis** in this patient subset. The anchored MAIC analysis shows that in the patients with ESA R/R LR MDS who are RS+ with high transfusion burden (≥ 6 units /8 weeks), the odds ratio of achieving ≥ 8-week RBC-TI rate in Imetelstat vs Luspatercept is 1.86 with 95% CI (0.22, 16.16), which means the odds of achieving ≥ 8-week RBC-TI with Imetelstat treatment is 1.86 times greater than the odds of achieving ≥ 8-week RBC-TI with Luspatercept treatment. The effective sample size of this analysis was 55.0 (reduction 23.7% from unweighted sample). Due to the small sample size, lack of availability of Luspatercept summary data and the methodology assumptions, the sponsor notes that it is crucial to interpret the results of the MAIC analysis with caution.

The COMP noted that no details of the MAIC analysis were provided including matching criteria and assumptions used for the comparison of the efficacy outcomes between Imetlestat vs Luspatercept.

3) Imetelstat Does Not Worsen Fatigue in Setting of Fewer RBC Transfusions

In terms of PRO instruments, the following exploratory endpoints were included in the phase 3 study MDS3001 (IMerge) for Imetelstat: Assessment of Quality of Life in Myelodysplasia Scale (QUALMS), Functional Assessment of Cancer Therapy - Anemia-Related Effects (FACT-An), the FACIT Fatigue and the EuroQol- EQ-5D-5L (EQ-5D-5L).

The sponsor states that the FACIT Fatigue demonstrated a consistent trend towards improvement with Imetelstat as compared to placebo, in patients who achieve high rates of durable TI, regardless of RS status or baseline transfusion burden. Also, the QUALMS total score provides an overall perspective on the experience of patients with MDS, beyond fatigue. The QUALMS total score showed a similar pattern as the FACIT Fatigue score, with improvement over the course of the study in the Imetelstat group and stability in the placebo group, suggesting that the QoL improvement trend observed in the imetelstat group extends beyond fatigue.

The COMP noted that comparative data for these PRO tools were not presented for Luspatercept. This makes a conclusive comparison on fatigue and QoL not possible. The COMP also took note of the CHMP conclusion in that the difference in FACIT-Fatigue score between the Imetelstat and the placebo group was not nominally statistically significant, and the analysis was not controlled for the type I error.

4) Imetelstat provides a clinical benefit in patients who have progressed on existing therapies, including those who received previous treatment with Luspatercept (n=35).

The sponsor states that in the Imetelstat study program overall, 35 (16.9%) of 207 Imetelstat-treated subjects received Luspatercept prior to study entry, including 5 of 38 subjects in the target population of the Phase 2 portion, 7 of 118 subjects in the Phase 3 portion and 23 of 51 subjects in the QTc substudy. Of the 35 Imetelstat -treated subjects who received Luspatercept prior to study entry in MDS3001(including Phase 2, Phase 3 and QTc substudy), ≥ 8-week and ≥ 24-week RBC TI rates were 28.6% and 20.0%, respectively. Additionally, 68.6% of subjects achieved ≥ 4 units RBC reduction/8 weeks, while 28.6% had ≥ 1.5 g/dL Hgb rise/8 weeks. HI-E 2018 rate was 25.7%, demonstrating that RBC TI and improvements in Hgb were achieved in subjects who were transfusion dependent after prior Luspatercept treatment (Table 8).

Table 1. Efficacy in Imetelstat Treated Subjects who Received Prior Luspatercept in MDS3001

	Total Imetelstat **N=207**
Patients with prior Luspatercept, n	35
RBC TI Rate	
≥ 8-week TI, n (%)	10 (28.6%)
≥ 24-week TI, n (%)	7 (20.0%)
≥ 4 units RBC reduction/8 weeks, n (%)	24 (68.6%)
≥ 1.5 g/dL Hgb rise /8 weeks, n (%)	10 (28.6%)
HI-E per IWG2018, n (%)	9 (25.7%)

HI-E = hematologic improvement-erythroid, HTB = high transfusion burden, LTB = low transfusion burden, RBC = red blood cell, TI = transfusion independence

The COMP noted that only 7 out of these 35 patients were actually part of the phase 3 study, which had the main objective to demonstrate efficacy in a defined patient population. The majority of these 35 patients previously treated with Luspatercept were derived from a QTc study which has a different objective. It is also not clear what type of response to Luspatercept these patients had or which baseline characteristics at time of inclusion in the QTc and phase 2 study these patients had. No details were provided for this pooled patient subset. Therefore, a conclusion could not be derived by COMP, on this claim. In particular, details on the MDS treatment history are required and the use of ESA prior to Luspatercept administration. Furthermore, patient details on the response to Luspatercept treatment and their respective subsequent response to Imetelstat need to be detailed by the sponsor.

5) In addition, the sponsor emphasizes their products potential for disease modification

The sponsor further argues that Imetelstat has the potential for MDS disease modification based on their data on cytogenetic responses, reduction in mutation burden, improvement in bone marrow morphology. The COMP took note of the sponsors argument and data but concluded that these data are not sufficient to substantiate a significant benefit over Luspatercept and the long-term implications in terms of a clinical benefit remain to be demonstrated.

Overall COMP conclusion:

The COMP considered that the data submitted are insufficient to establish a significant benefit of Imetelstat over Luspatercept. Therefore, the significant benefit of Imetelstat over Luspatercept needs to be further substantiated.

With regards to the 35 patients treated with Luspatercept prior to treatment with the sponsors product, it should be clarified what their MDS treatment history was (ESA prior to Luspatercept yes or no), as well as their response to Luspatercept treatment and subsequent response to Imetelstat.

As regards the efficacy in RS negative patients, a comparison of the efficacy of Imetelstat to all available data in RS negative patients with Luspatercept.

Furthermore, additional details of the MAIC analysis are required, including matching criteria and assumptions used for the comparison of the efficacy outcomes between Imetelstat vs Luspatercept.

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

In their written responses and during the oral hearing, the sponsor maintained their view in that imetelstat meets the qualifying criteria for significant benefit over luspatercept and supports their position with additional analyses, as summarized below.

Rytelo decreases transfusion dependence patients with no further authorised treatment options

The sponsor presented additional details as regard the population subset of 32 low-risk myelodysplastic syndrome (LR MDS) patients with red blood cell (RBC) transfusion dependent anemia who were treated with Rytelo during their late stage clinical development and who had exhausted all authorized treatment options, i.e. erythropoietin stimulating agents (ESA) and luspatercept.

Among the 32 subjects, 5 (15.6%) were from the Phase 2 MDS3001 study, 7 (21.9%) were from the Phase 3 MDS3001 study, and 20 (62.5%) were from the Phase 3 MDS3001 QTc substudy. Of the 20 subjects from the QTc substudy, 13 were randomized to imetelstat and 7 were initially randomized to the placebo group and crossed over to imetelstat after 2 cycles of placebo treatment. Key differences in the baseline disease characteristics of the 32 subjects compared to those of the MDS3001 Phase 3 study population are the proportion of ring sideroblast positive (RS+) subjects, time since diagnosis and most notably, baseline RBC transfusion burden (Table 9). In particular, the median baseline transfusion burden for this patient population was 9 RBC units /8 weeks (range 4-19 units/ 8 weeks) and is 50% greater than the median baseline transfusion burden of 6 RBC units/ 8 weeks from MDS3001 Phase 3. Furthermore, 75% of these subjects had a > 6 units/8 weeks RBC transfusion requirement (Table 9). The median baseline transfusion burden of 9 units /8 weeks is indicative of advanced LR MDS which is associated with poor survival and high risk of transformation to AML (Granfeldt Østgård, 2015; Steensma, 2015). It is also accompanied by significant fatigue due to anemia and co-morbidities, poor quality of life, reliance on and frequent interactions with healthcare resources and additional long-term complications associated with chronic transfusions and iron overload leading to end organ damage (De Zern, 2017; Singhal, 2017; Germing, 2019; De Swart, 2020; Platzbecker, 2021; Volpe, 2022). Therefore, although there is overall consistency for demographic and most disease characteristics between the 32 subjects and those treated in MDS3001 Phase 3, where differences in disease characteristics did exist, they indicate that the post-ESA/luspatercept patients' disease was more advanced and thus more difficult to treat and less likely to achieve RBC-TI. In summary this cohort of 32 LR MDS subjects with RBC transfusion dependent anemia who had failed both ESA and luspatercept treatment have no treatment options available.

Table 9 Disease Characteristics at Baseline for Imetelstat Treated Subjects Who Had Failed Prior Luspatercept and Prior ESA Therapies (modified from sponsor Table 1)

	MDS3001 Main Study		**MDS3001 QTc Substudy**		
	Phase 2 (N=5)	**Phase 3 (N=7)**	**Imetelstat (N=13)**	**Crossover Imetelstat [a] (N=7)**	**Total (N=32)**
Time since initial diagnosis (years)					
Mean (SD)	4.966 (1.5771)	5.551 (3.7836)	6.367 (4.9036)	3.292 (3.0329)	5.297 (3.9497)
Median (Min, Max)	4.553 (3.20, 7.51)	5.424 (2.21, 13.31)	5.569 (0.63, 19.39)	3.080 (0.77, 9.54)	4.523 (0.63, 19.39)
Prior RBC transfusion burden based on CRF					
Mean (SD)	8.8 (2.28)	11.0 (5.16)	8.8 (3.63)	8.4 (3.64)	9.2 (3.80)
Median (Min, Max)	8.0 (6, 12)	10.0 (6, 19)	9.0 (4, 16)	9.0 (4, 15)	9.0 (4, 19)
≤ 6 units	1 (20.0%)	2 (28.6%)	3 (23.1%)	2 (28.6%)	8 (25.0%)
> 6 units	4 (80.0%)	5 (71.4%)	10 (76.9%)	5 (71.4%)	24 (75.0%)
WHO classification					
RS+ (RARS/RCMD-RS/MDS/MPN-RS-T)	4 (80.0%)	6 (85.7%)	12 (92.3%)	7 (100.0%)	29 (90.6%)
RS- (Others)	1 (20.0%)	1 (14.3%)	1 (7.7%)	0	3 (9.4%)
Serum erythropoietin (EPO) level (mU/mL)					
≤ 500 mU/mL	2 (40.0%)	3 (42.9%)	11 (84.6%)	5 (71.4%)	21 (65.6%)
> 500 mU/mL	3 (60.0%)	3 (42.9%)	2 (15.4%)	2 (28.6%)	10 (31.3%)
Missing	0	1 (14.3%)	0	0	1 (3.1%)
Pretreatment Hgb level (g/L)					
Mean (SD)	79.7 (8.66)	81.9 (5.17)	76.8 (6.84)	73.8 (3.80)	77.7 (6.64)
Median (Min, Max)	79.0 (71, 92)	83.0 (74, 88)	76.5 (65, 87)	74.0 (68, 79)	77.0 (65, 92)

ESA = erythropoiesis-stimulating agent; IPSS= International Prognostic Scoring System; RBC = red blood cell; WHO = World Health Organization.

[a] Only data after crossover from placebo is included.

[b] Derived by sponsor based on central lab cytogenetic data and local lab results for bone marrow blasts, hemoglobin, platelets, and neutrophils.

Note: For Phase 2 and Phase 3, the data cut-off is 13 Oct 2023; For QTc substudy, the data cut-off is 13 Oct 2024.

Regarding prior luspatercept dosing, 18 (56.3%) subjects received the maximum dose of luspatercept treatment at 1.75 mg/kg as the highest dose of treatment, 7 (21.9%) had a highest dose of treatment of < 1.75 mg/kg and for 7 (21.9%) subjects, the highest dose (mg/kg) of treatment was not recorded.

On-study exposure to imetelstat was consistent with MDS3001 Phase 3 study. Median imetelstat exposure was 34.6 weeks (range 7 – 133) for a median of 7.5 cycles (2 – 33) and more than half of the 32 subjects (56.3%) received > 6 cycles of imetelstat (Table 10). Efficacy and transfusion data were assessed throughout the treatment phase up to the first transfusion in the post-treatment follow-up.

Table 10 Summary of Treatment Exposure to Imetelstat for Imetelstat Treated Subjects Who Had Failed Prior Luspatercept and Prior ESA Therapies

	MDS3001 Main Study		**MDS3001 QTc Substudy**		
	Phase 2 (N=5)	**Phase 3 (N=7)**	**Imetelstat (N=13)**	**Crossover Imetelstat [a] (N=7)**	**Total (N=32)**
Treatment duration (weeks)					
Mean (SD)	65.46 (47.992)	48.78 (43.724)	38.64 (22.301)	38.92 (25.777)	45.11 (32.930)
Median (Min, Max)	55.14 (13.9, 133.3	22.29 (16.1, 131.9)	37.00 (7.0, 75.6)	29.29 (8.1, 70.6)	34.64 (7.0, 133.3)
Number of cycles received					
Mean (SD)	13.4 (9.79)	11.6 (10.69)	8.8 (4.90)	9.4 (6.27)	10.3 (7.37)
Median (Min, Max)	12.0 (4, 24)	6.0 (4, 33)	7.0 (2, 16)	8.0 (2, 18)	7.5 (2, 33)
1-3 cycles	0	0	2 (15.4%)	2 (28.6%)	4 (12.5%)
4-6 cycles	2 (40.0%)	4 (57.1%)	3 (23.1%)	1 (14.3%)	10 (31.3%)
7-12 cycles	1 (20.0%)	0	5 (38.5%)	1 (14.3%)	7 (21.9%)
≥ 13 cycles	2 (40.0%)	3 (42.9%)	3 (23.1%)	3 (42.9%)	11 (34.4%)

SD = Standard Deviation

[a] Only data after crossover from placebo is included.Note: For Phase 2 and Phase 3, the data cut-off is 13 Oct 2023; For QTc substudy, the data cut-off is 13 Oct 2024.

Following treatment with imetelstat as third line in these 32 subjects, responses were achieved that were comparable to the total MDS3001 study patient population with 34.4% achieving ≥ 8-week RBC-TI with a median duration of ~70 weeks and 25% of subjects achieving ≥ 24-week RBC-TI (Table 11). Furthermore, additional clinical benefit was observed with 71.9% of subjects experiencing a reduction in transfusion burden of ≥ 4 RBC units/8 weeks (Table 11). Ten of the 32 subjects were specified as luspatercept "treatment failure" by the investigator on the prior therapy eCRF, and of these 10 subjects, 40% achieved ≥ 8-week RBC-TI, and 30% of subjects achieving ≥ 24-week RBC-TI.

Table 11 Summary of Response to Imetelstat for Subjects Who Had Failed Prior Luspatercept and Prior ESA Therapies

	MDS3001 Main Study		MDS3001 QTc Substudy		
	Phase 2 (N = 5)	**Phase 3 (N = 7)**	**Imetelstat (N = 13)**	**Crossover Imetelstat [a] (N = 7)**	**Total (N = 32)**
Response					
8-week TI, n(%)	3 (60.0%)	1 (14.3%)	4 (30.8%)	3 (42.9%)	11 (34.4%)
Median Duration of TI [b] (weeks) (95% CI)[b]	69.6 (17.00, NE)	NE (NE, NE)	47.9 (40.57, NE)	NE (14.71, NE)	69.6 (14.71, NE)
24-week TI, n(%)	2 (40.0%)	1 (14.3%)	3 (23.1%)	2 (28.6%)	8 (25.0%)
HI-E per IWG2006, n (%)	4 (80.0%)	3 (42.9%)	10 (76.9%)	6 (85.7%)	23 (71.9%)
≥ 4 units RBC reduction/8 weeks, n (%)	4 (80.0%)	3 (42.9%)	10 (76.9%)	6 (85.7%)	23 (71.9%)
≥ 1.5 g/dL Hgb rise /8 weeks, n (%)	3 (60.0%)	1 (14.3%)	4 (30.8%)	3 (42.9%)	11 (34.4%)
HI-E per IWG2018, n (%)	3 (60.0%)	1 (14.3%)	3 (23.1%)	4 (57.1%)	11 (34.4%)

Hgb = hemoglobin; HI-E = hematologic improvement-erythroid; IWG = International Working Group; NE= not evaluable; RBC = red blood cell; TI = transfusion independence.

[a] Only data after crossover from placebo is included.

[b] Based on Kaplan-Meier product limit estimates of the 8-week TI responders.

Note: For Phase 2 and Phase 3, the data cut-off is 13 Oct 2023; For QTc substudy, the data cut-off is 13 Oct 2024.

Despite failure with ESA and luspatercept, following treatment with imetelstat, the majority of these subjects went on to have a reduction in the need for transfusions, which is of clinical importance when the transfusion burden is very high, and even more importantly, over a third were completely independent of transfusions for a median of 70 weeks. In addition, there were other markers of clinical benefit (e.g. hematologic improvement-erythroid, HI-E, and increase in hemoglobin, Hgb). In the absence of imetelstat, these subjects would have remained transfusion dependent without other approved therapeutic options. The COMP considered that this data supports a clinically relevant advantage of Rytelo over luspatercept.

Improved efficacy of Rytelo versus luspatercept

The sponsor also maintains their claim of improved efficacy of Rytelo versus luspatercept in terms of achieving more durable red blood cell (RBC) transfusion independence (RBC-TI) and improved efficacy in under-served subpopulations, such as patient with high transfusion burden. In support, the sponsor presents several comparative datasets of Rytelo and luspatercept, including a summary of the key efficacy data in RS+ patients with LR MDS in Table 12. For the RS+ patients with LR MDS and a transfusion burden of ≥ 4 units/8 weeks there is not much difference in the delta of ≥ 8-week RBC transfusion independence (TI) rates between placebo and active compound between imetelstat and luspatercept , with both around 25%. However, there was a longer duration of continuous TI seen with imetelstat. For the RS+ patients with LR MDS and a higher transfusion burden of ≥ 6 units/8 weeks there is a difference in the delta of ≥ 8-week RBC transfusion independence (TI) rates between

placebo and active compound between imetelstat and luspatercept , of around 20% in favour of imetelstat. For this particular subset the sponsor also conducted an anchored MAIC analysis, however, the confidence interval for the odds ratio is extremely wide, from 0.22 to 16.16 which generated uncertainty over the robustness of these findings.

Table 22 Key Data in Support of Significant Benefit for Imetelstat Over Luspatercept in RS+ patients

	MDS3001 Phase 3			**MEDALIST Phase 3**			
	Imetelstat	**Placebo**	**Imetelstat vs Placebo**	**Luspatercept**	**Placebo**	**Luspatercept vs placebo**	**Imetelstat vs Luspatercept**
RS+ ≥ 4 units/8 weeks							
≥ 8-week RBC-TI rate (%)	33/73 (45.2%)	7 /37 (18.9%)	△26.3%	34/107[#] (31.8%)	4 /56 (7.1%)	△24.7%	+13%
Median ≥ 8-week TI duration, weeks	46.9	16.9	HR=0.32	29.9 [a]*	17.4 [a]	NR	+17 weeks
RS+ ≥ 6 units/8 weeks							
≥ 8-week RBC-TI rate (%)	25 /57 (43.9%)	3/27 (11.1%)	△32.8%	12/66* (18.2%)	2/33 (6.1%)	△12.1%	+26% OR 1.86 (0.22, 16.16)[b]
Median ≥ 8-week TI duration, weeks	42	8.9	HR=0.04	26.9*	NR	NR	+15 weeks

≥ 8-week RBC-TI at any time reported for imetelstat, *≥ 8-week RBC TI within 48 weeks (Zeidan, 2022) and [#]≥ 8-week RBC-TI any time (Fenaux, 2019) reported for luspatercept in MEDALIST
[a] based on ≥ 2 units/8 weeks
[b] based on MAIC analysis with details in Question 4
HR=hazard ratio; OR=odds ratio; NR=not reported

While these data were acknowledged by the COMP, they did not allow for a clear interpretation and conclusion mainly owing to uncertainty over the exact follow-up duration periods in the MEDALIST Phase 3 study with luspatercept vs the one in the MDS3001 Phase 3 study with Rytelo and the differential definition of the primary endpoint. The difference is related to the time period in which the >=8 week TI need to be achieved. A potential bias due to different follow-up duration periods could therefore not be fully excluded. Of note, the data for the treatment comparisons with luspatercept from the MEDALIST Phase 3 study were based on data reported from three different sources, Fenaux 2019 (presentation only), Fenaux 2020 (the primary analysis in NEJM) and Zeidan 2022 (a long-term follow-up in Blood), (see also legends of Tables 7 and 12):

	Reference	Publication/ Presentation	Clinical cut-off date	Median Treatment Duration, months (range)	Median Follow-up Time, months	Endpoint of 8 week TI
1	Fenaux 2019	ASH 2019 Oral presentation	July 1, 2019	11.7 (1.4 – 39.6)	Not reported	Anytime
2	Fenaux, 2020	NEJM 2020	May 8, 2018	11.3 (1.4 – 26.2)	14 (reported in EPAR only)	Week 1-24
3	Zeidan 2022	Blood 2022	July 1, 2019	Not reported	26.4	Week 1-48

Fenaux (2019) is a presentation only. They report the primary analysis result of MEDALIST (Primary endpoint previously reported: 37.9% luspatercept versus 13.2% placebo patients achieved RBC-TI ≥ 8 weeks during Weeks 1–24), but they also report results of RBC-TI ≥ 8 weeks achieved during the entire treatment period (without a restriction to the first 24 weeks), after a median follow up duration of 26.4 months, so apparently, there was no restriction (47.7% luspatercept versus 15.8% placebo patients achieved RBC-TI ≥ 8 over the entire treatment period) (Zeidan 2022).

Fenaux (2020) is the key publication in the NEJM where the primary analysis is reported, restricted to 24 weeks only (this period of time (1 through 24 weeks) was chosen to reduce potential bias due to loss of patients receiving placebo without an early response) : "During the first 24 weeks of the trial, 58 patients (38%) in the luspatercept group had transfusion independence for 8 weeks or longer, as compared with 10 (13%) in the placebo group". Please note that at the time of the data cut-off, 45.8% of the patients in the luspatercept arm remained on treatment versus 7.9% of the patients in the placebo arm.

Zeidan (2022) is a follow-up publication in Blood where longer-term results are reported, i.e. 1-48 weeks. "Median follow-up times for the current analysis were 26.4 and 26.1 months for luspatercept and placebo, respectively, compared with 13.9 months and 14.3 months for the primary analysis. Approximately 3 times as many patients receiving luspatercept vs placebo achieved RBC-transfusion independence (RBC-TI) for ≥8 weeks during weeks 1 to 48 (69/153 [45.1%] vs 12/76 [15.8%].

This reporting is further complicated by the use of subgroups with e.g. high or normal transfusion burden patients in the (sub-)analyses.

The COMP concluded that uncertainty over a potential bias due to different durations of follow-up periods could not be excluded to allow a clear interpretation of the results presented. An efficacy analysis which used the same definition of endpoints (restricted to the time period 1-24 weeks) has not been presented by the sponsor.

Imetelstat shows improved efficacy in under-served subpopulations of RS- patients

The sponsor notes that LR MDS with the RS- pathology comprises the majority (60%) of the LR MDS patient population and these patients have poorer outcomes than LR MDS patients who are RS+. The Phase 3 MEDALIST study that led to the initial approval of luspatercept recruited only RS+ subjects. Therefore, the sponsor cited data with luspatercept in RS- patients with LR MDS from the single-arm Phase 2 PACE-MDS study (Platzbecker, 2022). According to the sponsor this patient population is comparable to those treated with imetelstat in in the Phase 3 study MDS3001 in terms of the post-ESA setting and the similar endpoints analysed in these studies. The response rate of ≥ 8-week RBC-TI reported for imetelstat in the Phase 3 study MDS3001 was 31.8% (i.e. 14 out of the 44 RS- patients), while the one reported for luspatercept in the Phase 2 PACE-MDS study (Platzbecker, 2022) was 34.5% (i.e. 10 out of the 29 RS- patients). However, the sponsor considered that this comparison was not appropriate due to the higher number of patients with higher baseline transfusion burden in the

MDS3001 study. As the RBC-TI responses were not reported for the RS- LR MDS subjects with baseline TB ≥ 4 RBC units/8 weeks in the Phase 2 PACE-MDS study, the rate of ≥ 8-week RBC-TI in subjects with RS- and baseline TB ≥ 4 RBC units/8 weeks was extrapolated by the sponsor, assuming the proportion of RS- responders in the combined RS+ and RS- responders with baseline TB ≥ 4 RBC units/8-weeks is the same as the proportion in the combined RS+ and RS- responders with baseline TB ≥ 2 RBC units/8-weeks. As such, given that 10 (31.3%) RS- subjects had ≥ 8-week RBC-TI out of the total 32 RBC-TI responders in RS+ and RS- subjects combined, it would be extrapolated that 31.3% of the 12 RBC-TI responders who had TB ≥ 4 units/8 weeks were RS-, which corresponds to n= 3.75 (10/32*12=3.75). Therefore, the ≥ 8-week RBC-TI rate (%) in the 16 RS- subjects with TB ≥ 4 units / 8 weeks is extrapolated to be 3.75/16 or 23.4%. This extrapolated response rate of 23.4% in the subset of 16 RS- patients is much lower than the one reported by Platzbecker, 2022 for the whole RS- population of 29 patients treated with luspatercept (34.5%). The COMP considered the assumption made by the sponsor for their extrapolation exercise as hypothetical and not a valid basis to draw a conclusion of improved efficacy of imeltestat in RS- patients with LR MDS.

In conclusion, the COMP considered that Rytelo is of significant benefit to those affected by the condition as it was able to decreased red blood cell transfusion dependence in a subset of patients whose anaemia could not be sufficiently controlled with authorized treatment options, i.e. patients who failed prior treatment with erythropoiesis stimulating agents and with luspatercept. The Committee considered that this constitutes a clinically relevant advantage.

4. COMP position adopted on 30 January 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 myelodysplastic syndromes (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to the development of anaemia, thrombocytopenia, neutropenia and progression to acute myelogenous leukaemia;
- although satisfactory methods for the Treatment of the condition have been authorised in the European Union, the claim that Rytelo is of significant benefit to those affected by the orphan condition is established. Rytelo decreased red blood cell transfusion dependence in a subset of patients whose anaemia could not be sufficiently controlled with authorized treatment options. The Committee considered that this constitutes a clinically relevant advantage.

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

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

The Committee for Orphan Medicinal Products has recommended that Rytelo, imetelstat sodium, imetelstat for treatment of myelodysplastic syndromes (EU/3/20/2305) is not removed from the Community Register of Orphan Medicinal Products.