Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Luspatercept

Proprietary Product Name: Reblozyl

Sponsor: Celgene Pty Ltd

April 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations 4

I. Introduction to product submission 6

Submission details 6

Product background 7

Regulatory status 13

Product Information 14

II. Registration timeline 14

III. Submission overview and risk/benefit assessment 15

Quality 15

Nonclinical 15

Clinical 17

Risk management plan 46

Risk-benefit analysis 47

Outcome 59

Attachment 1. Product Information 60

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ActRIIB	Activin receptor type-2B
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
$AUC_{avg,0\text{-}15wk}$	Average area under the concentration-time curve from 0 to 15 weeks
AUC_{ss}	Area under the concentration-time curve at steady state
CI	Confidence Interval
CL/F	Apparent clearance
CMI	Consumer Medicines Information
CPD	Certified Product Details
ECOG	Eastern Cooperative Oncology Group
ESA	Erythropoiesis stimulating agent
EU	European Union
G-CSF	Granulocyte colony stimulating factor
GM-CSF	Granulocyte-macrophage colony stimulating factor
GDF	Growth differentiation factor
GLP	Good Laboratory Practices
GVP	Good Pharmacovigilance Practices
Hb	Haemoglobin
HSCT	Haematopoietic stem cell transplantation
ICH	International Council for Harmonisation
IgG1	Immunoglobin G1
IPSS-R	Revised International Prognostic Scoring System
IWG	International Working Group

Abbreviation	Meaning
K_a	Absorption rate constant
MDS	Myelodysplastic syndrome(s)
MDS-RS	Myelodysplastic syndromes with ring sideroblasts
PBS	Pharmaceutical Benefits Scheme
PD	Pharmacodynamic(s)
PI	Product Information
PK	Pharmacokinetic(s)
PopPK	Population Pharmacokinetic(s)
RBC	Red Blood Cell Count
RMP	Risk Management Plan
SC	Subcutaneous
SD	Standard deviation
TGF-β	Transforming growth factor beta
TIF	Thalassaemia International Federation
T_{max}	Time of maximum concentration
V/F	Apparent volume of distribution
V1/F	Apparent central volume of distribution
VCR	Victorian Cancer Registry

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Product name:	Reblozyl
Active ingredient:	Luspatercept
Decision:	Approved
Date of decision:	27 August 2021
Date of entry onto ARTG:	30 August 2021
ARTG number:	334510, and 334511
, *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Sponsor's name and address:	Celgene Pty Ltd Level 2/4 Nexus Court Mulgrave VIC 3170
Dose form:	Powder for injection
Strengths:	25 mg and 75 mg
Container:	Type I glass vial
Pack size:	One vial
Approved therapeutic use:	*Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia (requiring 2 or more RBC units over 8 weeks) due to very low, low and intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS)* *Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia associated with beta thalassaemia.*
Route of administration:	Subcutaneous
Dosage:	The recommended starting dose of Reblozyl is 1 mg/kg once every 3 weeks by subcutaneous injection.

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Reblozyl treatment should be initiated and monitored under the supervision of a physician experienced in the treatment of haematological diseases.

Treatment with Reblozyl should be continued or modified based upon clinical and laboratory findings. Treatment should be continued as long as the patient is deriving clinical benefit from treatment.

Patients must have their haemoglobin assessed and have results available prior to each administration. If an red blood cell transfusion occurred prior to dosing, the pre-transfusion haemoglobin must be considered for dosing purposes.

If the predose haemoglobin is ≥ 115 g/L in the absence of transfusion for at least 3 weeks, delay dosing until the haemoglobin is ≤ 110 g/L.

For further information regarding dosing, refer to the Product Information.

Pregnancy category: D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Celgene Pty Ltd (the sponsor) to register Reblozyl (luspatercept) 25 mg and 75 mg, powder for injection (vials) for the following proposed indication:

> *Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia (requiring 2 or more RBC units over 8 weeks) due to very low, low and intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.*
>
> *Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia associated with beta thalassaemia.*

Myelodysplastic syndromes

Myelodysplastic syndromes include a group of clonal myeloid neoplasms characterised by cytopenias due to ineffective haematopoiesis, abnormal blood and marrow cell morphology. In approximately 30% of patients with myelodysplastic syndrome abnormal

cell morphology results in the potential for clonal evolution and the development of acute myeloid leukaemia.[2, 3]

In the United States of America (USA), estimates of age-adjusted incidence was 4.9 per 100,000 individuals during 2007–2011.[4] An analysis of 64 cancer registries from European countries indicates that the incidence of myelodysplastic syndrome was 1.5 per 100,000 individuals per year in 1995–2002.[5] The annual incidence of myelodysplastic syndrome reported by the Haematological Malignancy Research Network (HMRN) in the United Kingdom (UK) between 2010 and 2016 is 3.5 per 100,000.[6] In Australia, the incidence of myelodysplastic syndrome in 2015 was estimated to be 5.5 per 100,000.[7] Myelodysplastic syndrome is most commonly diagnosed in patients with a median age > 70 years at diagnosis and is reported more frequently in men versus women.[8, 9]

Myelodysplastic syndrome is associated with high mortality with median time of survival from diagnosis of 75 months (range, 1.7 to 350 months) with 2- and 5-year survival probabilities of 86% and 61%, respectively. Median survival was lower in transfusion-dependent compared with transfusion-independent patients (44 versus 97 months).[10] In Australia the 5-year survival rate for myelodysplastic syndrome was reported to be 37.3% during the period between 2011 to 2015.[7]

Myelodysplastic syndromes can be classified as primary myelodysplastic syndrome (if no cause can be found) and secondary myelodysplastic syndrome (cause can be identified, for example prior cancer treatment);[11] although cause of myelodysplastic syndrome is known only in 15% of cases.[11, 12] In approximately 30% of paediatric patients with myelodysplastic syndrome, the disease is due to an inherited predisposition, such as Down's syndrome, Fanconi anaemia, and neurofibromatosis.[11, 12] In adult patients without inherited predisposition, myelodysplastic syndrome may be attributed to a number of factors, including older age, prior treatment with chemotherapy agents or radiotherapy, and exposure to environmental irritants.[11, 12, 13]

Myelodysplastic syndromes may be further classified using the World Health Organization (WHO) classification system (2016) which incorporates the following diagnostic parameters: cell morphology, cytopenias, myeloblast percentage, ring sideroblasts as a

[2] Bejar, R. et al. Recent developments in myelodysplastic syndromes, *Blood* 2014; 124:2793-2803.
[3] Da-Silva-Coelho, et al. Clonal evolution in myelodysplastic syndromes, *Nat Commun*, 2017; 8: 15099.
[4] Cogle, C., Incidence and burden of the myelodysplastic syndromes, Curr Hematol Malig Rep, 2015;10(3): 272-281.
[5] Visser, O. et al, Incidence, survival and prevalence of myeloid malignancies in Europe, Eur J Cancer, 2012; 48(17): 3257-3266.
[6] Haematological Malignancy Research Network (HMRN). Incidence Available from: https://www.hmrn.org/statistics/incidence. Accessed March 2019.
[7] Australian Institute of Health and Welfare 2018. Cancer Data in Australia; Australian Cancer Incidence and Mortality (ACIM) books: myelodysplastic syndromes. Canberra: AIHW. Australian Institute of Health and Welfare 2019. Australian Cancer Database (ACD). Available from: https://www.aihw.gov.au/about-our-data/our-data-collections/australian-cancer-database.
[8] Ma, X. Myelodysplastic syndromes incidence and survival in united states, Cancer 2007; 109: 1536–1542.
[9] Ma, X. Epidemiology of myelodysplastic syndromes, Am J Med, 2012; 125: S2–S5.
[10] Germing, U. et al. Survival, prognostic factors and rates of leukemic transformation in 381 untreated patients with MDS and del(5q): a multicenter study. Leukemia 2012; 26: 1286-1292.
[11] Fenaux, P. Myelodysplastic syndromes: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann Oncol, 2014; 25 Suppl 3: iii57-69.
[12] Ades, L. et al. Myelodysplastic syndromes, *Lancet* 2014; 383: 2239-2252.
[13] Foran, J. et al. Clinical presentation, diagnosis, and prognosis of myelodysplastic syndromes, *Am J Med* 2012; 125: S6-13.

percentage of bone marrow erythroid elements,[14] and molecular genetic information.[15] According to this classification system, myelodysplastic syndrome can be categorised as myelodysplastic syndrome with single lineage dysplasia, myelodysplastic syndrome with multi-lineage dysplasia, myelodysplastic syndrome with ring sideroblasts (MDS-RS),[16] myelodysplastic syndrome with excess blasts (MDS-EB), myelodysplastic syndrome with isolated del(5q), or myelodysplastic syndrome unclassifiable (MDS-U). However, there are prognostic limitations to above classification system due to highly variable outcomes of different WHO-classified myelodysplastic syndrome groups and additional risk-based stratification systems have been devised with the International Prognostic Scoring System (IPSS-R);[17]and WHO-classification based Prognostic Scoring System (WPSS) used most commonly. The IPSS-R provides discriminatory risk factor assessment for evaluating clinical outcomes (survival duration and time to progression to acute myeloid leukaemia) among patients with myelodysplastic syndromes,[17] and is used in the initial planning of therapeutic options.[18] Bone marrow cytogenetics, bone marrow blast percentage, and cytopenias remain the basis of the IPSS-R with further refinement of these categories to provide more meaningful classifications on which to assess clinical outcome in myelodysplastic syndrome. The IPSS-R defines 5 risk groups: very low, low, intermediate, high, and very high. Lower-risk groups (very low, low, and intermediate categories) account for > 75% of patients with MDS.[17]

Many patients with MDS are asymptomatic and a lack of specific symptoms among patients with lower-risk MDS is a major diagnostic challenge.[13] Diagnosis is often made during the assessment of comorbidities, when peripheral blood or bone marrow features associated with MDS are revealed. Differential diagnosis is informed by an assessment of the patient's medication history (ingestion of alcohol or drugs) and exclusion of diseases (including autoimmune disorders, renal failure, malignancies, chronic infections or inflammations, aplastic anaemia, and paroxysmal nocturnal haemoglobinuria).[11] Analysis of bone marrow and blood samples is central to the diagnosis[11, 12] and facilitates the exclusion of non-myelodysplastic syndrome causes of cytopenias.[2, 12, 19] Analysis of somatic mutations and flow cytometry analysis of bone marrow cells can be useful when a diagnosis of myelodysplastic syndrome is uncertain.[11]

Beta-thalassemia

The beta-thalassaemias (or β-thalassaemias) are a group of inherited disorders characterised by absent or reduced production of the beta-globin (or β-globulin) chains of haemoglobin, the oxygen carrying molecule in human red blood cells. Mutations in the β-globin gene can be passed on from each of the 2 carrier parents to affected offspring in a recessive Mendelian manner. As the adult human haemoglobin molecule is made up of 2 alpha-globulin (or α-globulin) and 2 β-globin chains, the reduced synthesis of β-globin in patients with beta-thalassaemia leads to an imbalance in the α/β-globin chain ratio, accumulation of excess unpaired α-globin chains that form haemichromes and inclusion bodies, and premature death of red blood cells or their precursors in the bone marrow and

[14] It is estimated that approximately 30% of all MDS patients have > 15% of bone marrow erythroid precursors that are ring sideroblasts. Ring sideroblasts as defined by the International Working Group on Morphology of Myelodysplastic Syndromes (IWG-MDS) is an erythroblast with at least 5 siderotic granules covering at least a third of the circumference of the nucleus. Patients with ring sideroblasts with splicing factor mutations have been shown to have ineffective erythropoiesis, possibly related to the defects in iron utilization (Conte, 2015; del Rey, 2015; Dolatshad, 2015). In patients with refractory anaemia with ring sideroblasts (RARS), the required number of ring sideroblasts is ≥ 15%; however, RARS definition also includes cases with ring sideroblasts ≥ 5% if the SF3B1 mutation is present (Arber, 2016).

[15] Arber, D. The 2016 revision to the World Health Organisation classification of myeloid neoplasms and acute leukemia, Blood, 2016; 127(20): 2391-2405.

[16] MDS-RS with single lineage dysplasia (MDS-RS-SLD), MDS-RS with multilineage dysplasia (MDS-RS-MLD).

[17] Greenberg, P. Revised international prognostic scoring system for myelodysplastic syndromes, Blood, 2012; 120(12): 2454-2465.

[18] NCCN clinical practice guidelines in oncology; myelodysplastic syndromes, version 2.2019 – October 18, 2018.

[19] Zini, G. Diagnostics and prognostictation of myelodysplastic syndromes, Ann Lab Med, 2017; 37: 465-474.

peripheral circulation. Anaemia in beta-thalassemia arises mainly due to: (i) ineffective erythropoiesis, (ii) red cell haemolysis, and (iii) abnormal red cell morphology. Ineffective erythropoiesis can lead to erythroid expansion in the bone marrow which in turn can lead to bony deformities and osteoporosis, making patients with beta-thalassemia more susceptible to fractures. The acceleration of red blood cell destruction can also result in splenomegaly which is due to extra medullary haematopoiesis, which occurs because of increased red blood cell destruction in the bone marrow.[20] Onset of anaemia in beta-thalassemia generally occurs between 6 and 24 months of age, corresponding to the switch from the gamma (*γ*-)chain of fetal haemoglobin G to the *β*-chains of adult haemoglobin G.

About 80 to 90 million people (around 1.5 % of the global population) are carriers of the beta-thalassaemia gene (also known as beta-thalassaemia minor, or beta-thalassaemia trait) with approximately 60,000 symptomatic individuals born annually.[21] The annual incidence of symptomatic individuals is estimated at 1 in 100,000 worldwide and 1 in 10,000 in the European Union (EU).[22] Incidence is highest in the Mediterranean region, the Middle East, North America and South East Asia (particularly India, China, Thailand and Indonesia; this region accounts for approximately 50% of affected births). In Australia, the frequency of beta-thalassaemia is not well described and the number of affected individuals is unclear.

Patients are classified as having beta-thalassaemia major or beta-thalassaemia intermedia (including haemoglobin E/beta-thalassaemia (HbE/*β*-thalassaemia)), primarily based on the severity of genetic background, anaemia, and clinical presentation at diagnosis. However, no systematic classification criteria exist[23] and in more recent years, there has been increasing acknowledgment of the role of red blood cell transfusion therapy in determining the severity and course of disease; patients are now categorised as having transfusion-dependent beta-thalassemia or nontransfusion dependent beta-thalassemia. Patients with transfusion-dependent beta-thalassaemia (which includes conventional beta-thalassaemia major and severe forms of haemoglobin E/beta-thalassaemia) commonly present to clinical attention in early childhood (before two years of age) with severe anaemia (haemoglobin < 7 g/dL). These patients require life-long, regular blood transfusion therapy. Patients with nontransfusion dependent beta-thalassaemia (which includes conventional beta-thalassaemia intermedia and mild to moderate forms of haemoglobin E/beta-thalassaemia) present later in childhood or adolescence with mild to moderate anaemia and require no or only occasional transfusions in instances of blood loss or worsening anaemia due to periods of physiological stress (for example, during infections, surgery, or pregnancy).

Current treatment options

Myelodysplastic syndromes

As outcomes for patients with myelodysplastic syndromes are heterogeneous, individual risk stratification using tools such as the revised International Prognostic Scoring System (IPSS-R) is important in managing patients—including selecting candidates for allogeneic haematopoietic stem cell transplantation (ASCT), the only potentially curative therapy for MDS.[24] The IPSS-R can be supplemented by molecular genetic testing, since certain gene

[20] Rivella, S. Ineffective erythropoiesis and thalassemias. Curr Opin Hematol, 2009; 16(3): 187–194.
[21] Modell, B. et al. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ, 2008; 86(6) :480-487.
[22] Galanello, R. et al. Beta-thalassemia, Orphanet J Rare Dis, 2010; 5: 11.
[23] Taher, A. et al. Thalassemia. Lancet. 2018; 391: 155-167.
[24] David P. Steensma: Myelodysplastic syndromes current treatment algorithm 2018: *Blood Cancer Journal* volume 8, Article number: 47 (2018).

mutations such as *TP53* influence risk independent of established clinicopathological variables.

The main focus of management in patients with IPSS-R lower-risk myelodysplastic syndrome is the treatment of cytopenias (predominantly anaemia) and the improvement of quality of life.[11] For lower risk patients with symptomatic anaemia, treatment with erythropoiesis-stimulating agents (ESAs) or lenalidomide[25] (for those with deletion of chromosome 5q) can ameliorate symptoms. Some lower risk patients may be candidates for immunosuppressive therapy, thrombopoiesis-stimulating agents, or a DNA hypomethylating agent (HMA; azacitidine or decitabine).

Many patients with MDS who develop anaemia, particularly those with IPSS-R lower-risk myelodysplastic syndrome (40%), become transfusion dependent.[12, 26] Red blood cell-transfusion dependence and lower haemoglobin levels have been associated with a deleterious impact on outcomes and increased mortality in patients with myelodysplastic syndrome.[27, 28, 29] Other clinical consequences of long-term red blood cell-transfusion dependence include a potentially negative impact on quality of life, the development of iron overload and its associated complications, and the development of immune-related disorders and increased risk of infection.[27, 30, 31] Three drugs have been approved by the US Food and Drug Administration (FDA) for use in myelodysplastic syndrome-related indications: the orally administered immunomodulatory drug lenalidomide, and two parenterally administered nucleoside analogues that are DNA hypomethylating agents (HMA), azacitidine and decitabine. In addition to these agents, there is extensive off-label use of the erythropoiesis-stimulating agents (ESA) epoetin and darbepoetin in myelodysplastic syndrome, which is supported by US National Comprehensive Cancer Network (NCCN) guidelines. In Australia, azacitidine may be given for people with intermediate II or high grade myelodysplastic syndrome while lenalidomide is used for treatment of low risk MDS with deletion of chromosome 5q abnormality. There are currently no approved agents for the treatment of anaemia in lower-risk MDS patients without deletion of chromosome 5q in Australia and red blood cell transfusions remain the mainstay of treatment.[32]

Beta-thalassaemia

General care for patients with beta-thalassaemia requires substantial supplemental paediatric care, including careful attention to nutrition and monitoring for signs of infection, red blood cell transfusions to prevent the damage of chronic anaemia, and iron chelation to prevent the damage of iron overload due to ineffective erythropoiesis and regular blood transfusion. In older patients with signs of iron overload, supportive care is typically required to address endocrine insufficiencies, metabolic bone disease and cardiac

[25] Lenalidomide (Revlimid, Celgene) is approved for use in patients with transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with a del(5q) abnormality with or without additional cytogenetic abnormalities (Revlimid AU PI, 2019).
[26] Zeidan, A. et al. Current therapy of myelodysplastic syndromes, Blood Rev, 2013; 27: 243-259.
[27] Platzbecker, U. et al. The clinical, quality of life, and economic consequences of chronic anemia and transfusion support in patients with myelodysplastic syndromes, *Leuk Res* 2012; 36: 525-536.
[28] Fenaux, P. et al. How we treat lower-risk myelodysplastic syndromes. *Blood* 2013; 121: 4280-4286.
[29] Hellström-Lindberg, E. et al. Erythropoiesis stimulating agents and other growth factors in low-risk MDS, *Best Pract Res Clin Haematol*, 2013; 26(4): 401-410.
[30] Fenaux, P. et al. International vidaza high-risk MDS survival study group. efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study, Lancet Oncol, 2009; 10(3): 223-232.
[31] Vamvakas, E. et al. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention, Blood 2009; 113: 3406-3417.
[32] State of the Nation: Blood Cancer in Australia. Available from https://www.leukaemia.org.au/about-us/mylifecounts/stateofthenation/. Accessed 15 April 2020.

failure. Iron-related cardiotoxicity is the most common cause of mortality in patients with beta-thalassaemia.[33]

The clinical guidelines in Australia advise that transfusions given at haemoglobin concentration < 70 g/L are appropriate and may be associated with reduced mortality. The goal is to maintain a pre-transfusion haemoglobin concentration of 90 to 100 g/L, with transfusions at monthly intervals.[34]

In patients with transfusion dependent beta-thalassaemia, transfusion and iron chelation therapy have served patients for decades with a clear patient survival benefit. However, availability and administration of regular and chronic transfusion therapy continue to not only pose challenges for patients' quality of life, but also present a public health burden. The efficacy and safety of current iron chelators are established but not ideal, with persisting challenges in adherence, access, and affordability. Haematopoietic stem cell transplantation is now an established option in patients with transfusion-dependent beta-thalassemia, but its use is limited to small groups of younger patients with available matched donors who can tolerate and afford the procedure. Splenectomy is primarily restricted to patients with splenomegaly or hypersplenism because of the high risk of infections and vascular disease following the procedure. There is no therapy that is approved or widely used to address the underlying ineffective erythropoiesis and anaemia of beta-thalassemia.

Unmet medical need

Myelodysplastic syndromes

The majority (80% to 85%) of patients with myelodysplastic syndrome develop anaemia.[35] Erythropoiesis-stimulating agents are the first-line treatment option for anaemia in lower-risk patients with myelodysplastic syndromes without del(5q); lenalidomide is the recommended treatment for patients with del(5q).[36,37] Despite an initial response to erythropoiesis stimulating agent (ESA) treatment, approximately 70% of patients will become unresponsive to ESAs. In addition, ESAs are less effective in patients with either endogenous epoetin level ≥ 200 U/L or those requiring red blood cell transfusion of ≥ 2 units/month.

Treatment options remain suboptimal in the lower-risk myelodysplastic syndrome patients who are not eligible or no longer respond to ESAs, and many patients will ultimately require long-term red blood cell transfusions.**Error! Bookmark not defined.**[Error! Bookmark not defined.] Red blood cell-transfusion dependence and lower haemoglobin levels have been associated with a deleterious impact on outcomes and increased mortality in patients with myelodysplastic syndrome.[27, 28, 29]

Beta-thalassaemia

There is no available therapy approved or widely used to address the underlying ineffective erythropoiesis and anaemia of beta-thalassaemia, the source of clinical morbidity and diminished quality of life. In patients with transfusion-dependent beta-thalassaemia, transfusion and iron chelation therapy have shown a clear survival benefit. However, administration of regular and chronic transfusion therapy continues to

[33] Cappellini, M. et al. Guidelines for the management of transfusion dependent thalassemia (TDT). Nicosia, Cyprus: Thalassemia International Federation; 2014a.
[34] Module 3 – Medical. National Blood Authority 2012. Available at: https://www.blood.gov.au/system/files/documents/20180426-Module3-QRG.pdf
[35] Steensma, D. et al. The myelodysplastic syndromes: diagnosis and treatment. *Mayo Clin Proc* 2006; 81: 104-130.
[36] Fenaux, P. et al. How we treat lower-risk myelodysplastic syndromes. *Blood* 2013; 121: 4280-4286.
[37] National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology; Myelodysplastic Syndromes, Version 2.2019 – October 18, 2018.

pose challenges for patients' quality of life, also presenting a public health burden. Challenges with access and affordability of transfusion exist especially in resource-constrained countries. Moreover, transfusional iron overload necessitates iron overload monitoring and iron chelation therapy. The efficacy and safety of current iron chelators are not ideal, with persisting challenges in adherence, access, and affordability.

Haematopoietic stem cell transplantation is an established option in patients with transfusion-dependent beta-thalassaemia, but its use is limited to small groups of younger patients with available matched donors who can tolerate the procedure. Splenectomy is primarily restricted to patients with splenomegaly or hypersplenism because of the high risk of infections and vascular disease following the procedure.

Clearly, there is an unmet need for the development of novel therapies that can ameliorate the ineffective erythropoiesis and anaemia of beta-thalassaemia, and subsequently prevent the development of morbidity and poor quality of life.

Luspatercept

Luspatercept is a recombinant fusion protein consisting of a modified form of the extracellular domain of the human activin receptor type IIB (ActRIIB) linked to the human immunoglobin G1 (IgG1) Fc domain. It acts as a ligand trap for select TGF-β superfamily ligands. By binding to certain endogenous ligands that act as negative regulators of erythropoiesis, luspatercept inhibits downstream Smad2/3 signalling, resulting in erythroid maturation through differentiation of late stage erythroid precursors (normoblasts) in the bone marrow. TGF-β superfamily signalling through Smad2/3 is abnormally high in disease models characterised by ineffective erythropoiesis, that is, myelodysplastic syndrome and beta-thalassaemia, and in the bone marrow of myelodysplastic syndrome patients.

Regulatory status

This product is considered a new biological for Australian regulatory purposes.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
United States of America		8 November 2019 (for beta-thalassaemia) 3 April 2020 (for myelodysplastic syndrome)	*Reblozyl is indicated for the treatment of anaemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions* *Reblozyl is indicated for Myelodysplastic Syndromes with Ring Sideroblasts or Myelodysplastic/Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis Associated Anaemia* *Reblozyl is indicated for the treatment of anaemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative*

Region	Submission date	Status	Approved indications
			neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
European Union		26 June 2020 (for beta-thalassemia and myelodysplastic syndromes)	*Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.* *Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia associated with beta-thalassaemia*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2020-01706-1-6

Description	Date
Submission dossier accepted and first round evaluation commenced	2 June 2020
First round evaluation completed	2 November 2020
Sponsor provides responses on questions raised in first round evaluation	4 January 2021
Second round evaluation completed	17 March 2021
Delegate's Overall benefit-risk assessment	17 August 2021
Registration decision (Outcome)	27 August 2021
Completion of administrative activities and registration on the ARTG	30 August 2021
Number of working days from submission dossier acceptance to registration decision*	250

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

Luspatercept is a recombinant fusion protein consisting of two identical chains, each consisting of the modified form of the extracellular domain of human activin receptor type IIB (ActRIIB) linked to the human immunoglobulin G1 (IgG1) Fc domain (including the hinge, CH2 and CH3 domains) through a linker.

Luspatercept is produced in Chinese hamster ovary cells.

Luspatercept for injection is formulated as a single-use, sterile, preservative-free, lyophilized powder intended for subcutaneous administration after reconstitution with sterile water for injection. Luspatercept for injection is formulated with the following excipients: citric acid monohydrate, hydrochloric acid, polysorbate 80, sodium citrate dihydrate, sucrose, sodium hydroxide, and water for injection.

Reblozyl (luspatercept) for injection is a white to off-white lyophilized powder supplied in a single-dose vial. Each carton contains one vial. Reblozyl (luspatercept) is available in two presentations: 25 mg/vial and 75 mg/vial.

The container closure system for Reblozyl (luspatercept) for injection consists of a Type I, borosilicate glass vial with TopLyo film coating, sealed with a bromobutyl rubber stopper and capped with a flip-off seal.

Vials should be stored refrigerated at 2°C to 8°C in original carton to protect from light. Do not freeze. Data supports a shelf life of up to 3 years.

Nonclinical

The sponsor has applied to register a new biological entity, luspatercept (Reblozyl). The product is proposed to be used for the treatment of adult patients with transfusion-dependent anaemia associated with myelodysplastic syndromes with ring sideroblasts or associated with beta thalassaemia. Dosing is to involve subcutaneous administration once every three weeks, at a starting dose of 1 mg/kg, up to a maximum of 1.75 mg/kg.

The submitted nonclinical dossier was of high quality with no major deficiencies. The scope of the nonclinical program was in accordance with the relevant TGA-adopted guideline on the nonclinical evaluation of biotechnology-derived pharmaceuticals.[38] All pivotal safety-related studies were Good Laboratory Practices compliant.

Luspatercept represents a novel pharmacological class. The molecule is a recombinant fusion protein consisting of a modified form of the extracellular domain of the human activin receptor type IIB (ActRIIB) linked to the human IgG1 Fc domain. It binds to certain endogenous ligands for ActRIIB (which are members of the TGF-β (transforming growth factor-beta) superfamily) to inhibit their activity as negative regulators of erythropoiesis.

In vitro, luspatercept was shown to possess nanomolar or subnanomolar affinity for certain human TGF-β superfamily ligands (bone morphogenetic protein 6 (BMP6), activin B, growth differentiation factor 11 and 8 (GDF11; GDF8) and to inhibit activation of the Smad2/3 signalling pathway (which is used by ActRIIB, and overactivated in patients with ineffective erythropoiesis). *In vivo*, luspatercept increased red blood cell count, haemoglobin and haematocrit in normal mice and monkeys, acting via promotion of the

[38] International Conference on Harmonisation guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals.

maturation of late stage erythroblasts. Positive effects on red blood cell parameters by luspatercept or its murine orthologue were also demonstrated in various rodent disease models (of anaemia, myelodysplastic syndrome, and beta-thalassaemia). The submitted primary pharmacology studies offer support for the utility of luspatercept in the proposed indications.

Safety pharmacology endpoints were examined in monkeys. No adverse effects on central nervous system, cardiovascular or respiratory function are predicted in patients.

The pharmacokinetic profile of luspatercept was as expected for a large protein drug, and similar in laboratory animal species and humans. This was characterised by slow SC absorption, a long serum half-life and a low volume of distribution. High bioavailability of luspatercept by the SC route was demonstrated in monkeys.

Luspatercept displayed a low order of acute toxicity by the SC route in rats and cynomolgus monkeys.

Repeat-dose toxicity studies, involving SC administration once every two weeks, were conducted with luspatercept in rats (up to three months duration) and cynomolgus monkeys (up to six months). The kidney was identified as the key target organ for toxicity, with findings of membrano-proliferative glomerulonephritis in both laboratory animal species and additionally renal interstitial fibrosis/fibroplasia in monkeys. Renal injury in the two laboratory animal species occurred at doses yielding systemic exposure similar to that obtained in patients at the maximum recommended clinical dose and is seen to be a direct effect of the drug on the kidney rather than to be related to immune complex deposition secondary to the development of anti-drug antibodies. Other treatment related histopathological changes observed in the pivotal toxicity studies involved the adrenal gland (cortical congestion, necrosis and mineralisation) and liver (hepatocellular vacuolation and necrosis) in rats, and the choroid plexus (vascular degeneration, pigment deposition and mixed inflammatory cell infiltration) in monkeys.

Genotoxicity and formal carcinogenicity studies were not conducted, in line with ICH guidance. Of note, though, haematological malignancies were observed in a juvenile toxicity study in rats. A relationship to treatment is uncertain but cannot be excluded. Clinical concern is reduced given the absence of similar findings elsewhere across the toxicity program (including in the 6-month repeat-dose study in monkeys, and in adult rats).

Luspatercept was found to inhibit ovulation in female rats; male fertility was unaffected. Embryofetal lethality by luspatercept was observed in both animal species examined (rats and rabbits), warranting contraindication in pregnancy, use of contraception in women of childbearing potential and assignment to pregnancy category D.[39] Reduced mean fetal weight and increased fetal skeletal variations were also observed in pregnant rats and rabbits given luspatercept. Maternal administration of luspatercept during pregnancy and lactation in rats was associated with an ongoing reduction in body weight and adverse kidney findings in the offspring. Placental transfer and excretion in milk were demonstrated.

There are no nonclinical objections to the registration of Reblozyl for the proposed indications provided that renal safety is adequately established from the clinical dataset.

[39] Pregnancy category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Clinical

Content of the clinical dossier

In support of clinical pharmacology, the current submission contained one Phase I study, which was undertaken in healthy post-menopausal women and a further four Phase II studies, in populations of patients with either myelodysplastic syndrome or beta-thalassaemia, which provided information on luspatercept pharmacokinetics and pharmacodynamics. In addition, two population pharmacokinetic (popPK) and exposure-response analyses were provided, which examined populations of patients with myelodysplastic syndrome and beta-thalassaemia, respectively. Two further analyses examined the effects of immunogenicity on luspatercept pharmacokinetics and pharmacodynamics and the concentration-QTc relationship in the two target populations.[40]

The following were submitted in support of efficacy and safety:

- In support of the myelodysplastic syndrome indication, a pivotal Phase III, randomised, double-blind, placebo-controlled study (Study ACE-536-MDS-001; also known as the MEDALIST trial) and two supportive Phase II, open-label, single-arm studies (multiple ascending-dose base Study A536-03 and extension Study A536-05) were submitted.
- In support of the beta-thalassaemia indication, a pivotal Phase III, randomised, double-blind, placebo-controlled study (Study ACE-536-β-THAL-002; also known as the BELIEVE trial) and two supportive Phase II, open-label, single-arm studies (multiple ascending-dose base Study A536-04 and extension Study A536-06).

Pharmacology

Pharmacokinetics

The following is an extract of the clinical evaluator's conclusions regarding pharmacokinetics.

- Luspatercept is a novel, first-in-class, recombinant fusion protein that binds to endogenous ligands for the TGF-β superfamily of proteins, which is to be administered by SC injection.
- The conduct of the studies that were provided in support of the current submission was satisfactory, the data analyses undertaken were appropriate and the analytical methods used to measure exposure levels were validated.
- A single Phase I study was provided in support of the current submission, whereas the bulk of the pharmacokinetic/pharmacodynamic data was provided by four Phase II studies undertaken in the two target populations or from population pharmacokinetic/exposure-response analyses.
- Following a single administration of luspatercept to patients with either myelodysplasia syndrome or beta-thalassaemia, the median time to maximum concentration values were approximately 7 days for both patient cohorts and population pharmacokinetic derived K_a (absorption rate constant) values for patients

[40] The QT interval is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation. The corrected QT interval (QTc) estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.

with myelodysplasia syndrome or beta-thalassaemia were 0.456 and 0.409 day^{-1}, respectively.

- The absolute bioavailability of luspatercept following SC administration has not been evaluated.
- *Post hoc* analysis based on the pooled results from 6 clinical studies in the target populations indicated that drug substance manufactured using Processes II and III were bioequivalent as were the Process I/II frozen liquid and Process III lyophilised powder.
- A single dosage form, that is, the lyophilised powder to be made up in citrate buffer to a concentration of 50 mg/mL, is proposed for marketing. This formulation will be available in two vial strengths containing either 25 mg or 75 mg of luspatercept powder.
- Luspatercept exposure increased in an approximately dose-proportional manner in healthy subjects and in patients with either myelodysplasia syndrome or beta-thalassaemia.
- In subjects with MDS or β-thalassemia, dose normalised C_{trough} (trough concentration) increased by approximately 1.47-fold and 1.53-fold, respectively following the first and fourth doses and steady-state occurred around the time of the third dose. In long term Phase II extension studies, luspatercept V/F (volume of distribution/bioavailability) was similar in healthy subjects and in patients with myelodysplasia syndrome or beta-thalassaemia and ranged from 6.93 L to 10.6 L across studies.
- The exact mechanism via which luspatercept is eliminated from the body is unknown; however, like other antibodies it is thought to take place through normal proteolytic pathways.
- Following a single dose of 0.25 mg/kg luspatercept to healthy post-menopausal females the CL/F (apparent clearance) and $t_{1/2}$ (terminal half-life) values were 366.4 mL/day and 14.9 days, respectively. The corresponding values following multiple doses of 1.0 mg/kg to patients with myelodysplastic syndrome were 822 mL/day and 8.96 days, respectively and in beta-thalassaemia patients were 588.9 mL/day and 8.76 days, respectively.

Intra and inter individual variability of pharmacokinetics

- In patients with myelodysplastic syndrome, inter-individual variation on luspatercept area under the concentration-time curve at steady state (AUC_{ss}), apparent clearance (CL/F) and volume of central compartment distribution/bioavailability (V1/F) of 38%, 36.4% and 22.5%, respectively and the residual error was 22.1%. The corresponding inter-individual estimates for the beta-thalassaemia population were 35.9%, 34.7%, 27.6%, respectively and the residual error was 20.8%.

Pharmacokinetics in the target populations

- Following the proposed doses of 1 mg/kg, 1.33 mg/kg and 1.75 mg/kg luspatercept to patients with myelodysplastic syndrome, projected luspatercept exposure increased with dose and ranged from 9.29 to 16.3 μg/mL for maximum concentration (C_{max}) and 148 to 258 μg.day/mL for AUC_{ss}. At the three projected doses, from lowest to highest, the percentages of patients who achieved a target AUC_{ss} of ≥158 μg.day/mL, were 43.8%, 76.2% and 91.5%, respectively.
- In patients with beta-thalassaemia following the proposed doses of 1 mg/kg and 1.25 mg/kg, projected luspatercept exposure increased with dose and the percentages of patients who achieved a target AUC_{ss} of ≥ 131 μg.day/mL were 49.8% and 71.9%, respectively.

Pharmacokinetics in special populations

- As luspatercept is primarily eliminated by protein catabolism and its large size is expected to prevent it from being filtered through the glomeruli of the kidney, no dedicated pharmacokinetic studies examined the effects of hepatic or renal impairment on luspatercept pharmacokinetics.
- For subjects with myelodysplastic syndrome, intrinsic factors, such as sex, baseline total bilirubin, baseline burden, positive ring sideroblasts and baseline epoetin had no clinically meaningful effects on either luspatercept CL/F or V1/F.
- For subjects with beta-thalassaemia, intrinsic factors, including age, sex, race, baseline total bilirubin, baseline epoetin, splenectomy and beta-thalassaemia genotype, had no clinically meaningful effects on either luspatercept CL/F or V1/F.

Population pharmacokinetics

- Population pharmacokinetic analysis indicated that luspatercept serum concentration-time data from doses of 0.125 to 1.75 mg/kg administered every 3 weeks to subjects with myelodysplastic syndrome were adequately described by a one-compartment model with first-order absorption and elimination. Body weight, baseline albumin and age were identified as statistically significant covariates of CL/F while body weight and baseline albumin were identified as statistically significant covariates of V1/F. However, these covariates combined only accounted for a small portion of inter-individual variability for CL/F (-5.1%) and V1/F (-7.3%), indicating their impact on overall pharmacokinetics exposure may be limited.
- Population pharmacokinetic analysis indicated that luspatercept serum concentration-time data from doses of 0.2 to 1.25 mg/kg administered every 3 weeks to subjects with beta-thalassaemia were described adequately by a one-compartment model with first-order absorption and elimination. Body weight, baseline albumin and baseline red blood cell transfusion burden were identified as statistically significant covariates of CL/F while body weight and baseline red blood cell transfusion burden were identified as statistically significant covariate of V1/F. However, these covariates combined only accounted for a small portion of inter-individual variability for CL/F (-6.5%) and V1/F (-5.6%), indicating their impact on overall pharmacokinetic exposure may be limited.
- Subcutaneous injection location was not found to be significant covariate of luspatercept pharmacokinetics in either target population.
- Due to the very small number of subjects who tested positive for treatment emergent anti-drug antibodies, their effects on luspatercept pharmacokinetics were either not formally tested (beta-thalassaemia) or were shown to be negligible (myelodysplastic syndrome), whereas, the specific immunogenicity analysis suggested that luspatercept serum concentration in both myelodysplasia syndrome and beta-thalassaemia patients tended to be lower in the presence of neutralising treatment-emergent anti-drug antibodies.

Pharmacokinetic interactions

- As the elimination of luspatercept is expected to take place through normal proteolytic pathways, the potential for drug-drug interactions between luspatercept and other drugs has not been investigated.
- Population pharmacokinetic analyses indicated that the use of iron chelation therapy during luspatercept treatment had no effect on luspatercept CL/F or V1/F.
- The proposed PI appears to accurately describe the submitted pharmacokinetic data.

- Luspatercept binds to GDF-11 and activin B, which are endogenous ligands for the transforming growth factor beta (TGF-β) superfamily, resulting in erythroid maturation through differentiation of normoblasts in the bone marrow.

Pharmacodynamics

The following is an extract of the clinical evaluator's conclusions on pharmacodynamics

Primary pharmacodynamics

- In healthy subjects, luspatercept increased haemoglobin levels, whereas, it had no effects on biomarkers for hepcidin, PAI-1 (plasminogen activator inhibitor-1), CTX (serum cross-linked C-telopeptide of type I collagen) and BSAP (bone-specific alkaline phosphatase).
- In patients with myelodysplastic syndrome, luspatercept induced a mean end of treatment percentage increase from baseline in epoetin (227.86%) and in reticulocytes (42.94%), whereas in patients with beta-thalassaemia epoetin and nucleated red blood cells increased from baseline to end of treatment, with mean increases of 102.46% and 539.51%, respectively.
- In subjects with a low transfusion burden, the haemoglobin-time profiles for the 0.75 to 1.75 mg/kg treatment group for patients with myelodysplastic syndrome and in the 0.6 to 1.25 mg/kg treatment group for patients with beta-thalassaemia suggest that peak increases in haemoglobin levels occurred around the time of luspatercept time to maximum concentration (T_{max}) (7 days). Moreover, haemoglobin increases were sustained through to the end of treatment following a every 3 week dosing schedule. By contrast, for myelodysplastic syndrome patients with a high transfusion burden, there was little change in haemoglobin levels following treatment with any of the luspatercept doses.
- Following luspatercept treatment at the proposed doses to myelodysplastic syndrome patients, haemolysis parameters of direct bilirubin, total bilirubin and lactate dehydrogenase remained relatively unchanged from baseline. By contrast, in beta-thalassaemia patients, the mean levels of haptoglobin, indirect bilirubin and lactate dehydrogenase increased from baseline to end of treatment.
- Drug substance manufacturing processes or drug product formulations appeared to have no effect on luspatercept pharmacodynamics.

Secondary pharmacodynamics

- Based on an analysis of 875 time-matched pairs of concentration-QTcF[41] records collected from 638 subjects with either myelodysplastic syndrome or beta-thalassemia, the effects of luspatercept at the maximum therapeutic doses on placebo-adjusted QTcF were negligible in both target cohorts and ranged from -3.65 to -2.78 ms.
- Luspatercept had no dose-related effects on bone metabolism markers in either target population.
- Population pharmacokinetic-pharmacodynamic analyses indicated that differences in drug substance manufacturing process or drug product formulations were not significant covariates for occurrence of ≥ Grade 3 treatment-emergent adverse events after accounting for the effect of exposure and baseline risk factors in integrated exposure-safety analyses for subjects with myelodysplastic syndrome.

[41] QTcF = cardiac QT interval corrected by Fridericia's formula.

Immunogenicity

- In contrast to the target populations, no anti-drug antibodies were detected in healthy postmenopausal women.
- For all luspatercept-treated patients (that is, both target populations), around 5% tested positive for treatment-emergent anti-drug antibodies and of these, luspatercept-neutralising treatment-emergent anti-drug antibodies were detected in 2.0% of subjects.
- Treatment-emergent anti-drug antibodies were detected more frequently in myelodysplastic syndrome patients (23/260) than in the subjects with beta-thalassaemia (4/284), whereas, in placebo treated patients, 5 of 183 subjects (2.7%) tested positive for treatment-emergent anti-drug antibodies against luspatercept with neutralising treatment-emergent anti-drug antibodies detected in 2 subjects.
- Across all groups, the incidence of treatment-emergent anti-drug antibodies for the natural extra cellular domain of ActRIIB was low (< 2%) and only one subject (0.38%) with myelodysplastic syndrome was found to have neutralising treatment-emergent anti-drug antibodies against the natural extra cellular domain.
- When anti-drug antibody titre was low (< 100) and/or the presence of anti-drug antibodies was transient no obvious effects on individual luspatercept concentration-time profiles were identified. By contrast, luspatercept could not be detected in serum from 2 subjects who were identified as having persistent high-titre neutralising treatment-emergent anti-drug antibodies.
- Of 7 transfusion-free, treatment-emergent anti-drug antibody-positive, subjects with myelodysplastic syndrome, only one subject had diminished haemoglobin response in parallel with diminished luspatercept concentrations, after detection of high-titre treatment-emergent anti-drug antibodies. By contrast, there was no apparent loss of efficacy for reducing red blood cell transfusions among subjects with treatment-emergent anti-drug antibodies. Of 4 luspatercept-treated, treatment-emergent anti-drug antibodies -positive subjects with beta-thalassaemia, 3 subjects achieved a ≥ 50% reduction in red blood cell transfusions for ≥ 12 consecutive weeks, suggesting little impact on efficacy.
- Drug substance manufacturing processes or drug product formulations did not appear to affect the incidence of treatment-induced immunogenicity.

Relationship between drug concentration and pharmacodynamic effects

- In myelodysplastic syndrome patients requiring red blood cell transfusion, an integrated analysis indicated that after accounting for the effects of baseline red blood cell transfusion burden, epoetin and total bilirubin, multivariate logistic modelling indicated that luspatercept the average area under the concentration-time curve from 0 to 15 weeks ($AUC_{avg,0\text{-}15wk}$) was positively associated with the probability of achieving red blood cell transfusion independence. Moreover, the effect of luspatercept was more pronounced in subjects without a dose escalation (odds ratio = 1.93 per 50 µg.day/mL increase in $AUC_{avg,0\text{-}15wk}$) than when including all subjects (odds ratio = 1.35 per 50 µg.day/mL increase in $AUC_{avg,0\text{-}15wk}$). The results also suggested that the probability of achieving red blood cell transfusion independence was lower in subjects with baseline red blood cell transfusion burden ≥ 6 units/8 weeks or baseline epoetin > 500 U/L, whereas, in subjects with baseline total bilirubin > 1.5 x upper limit of normal the probability of achieving red blood cell transfusion independence was higher.
- In myelodysplastic syndrome patients, after accounting for high baseline epoetin (> 500 U/L), luspatercept $AUC_{avg,0\text{-}15wk}$ was positively associated with the probability of

achieving haematologic improvement (erythropoietic)-like response (odds ratio = 1.46 per 50 µg.day/mL increase in $AUC_{avg,0\text{-}15wk}$) in subjects without dose escalation. In addition, for each quartile of luspatercept exposure, a significant reduction from baseline in red blood cell units transfused during Week 1 to Week 15 was identified.

- Potential covariates such as gender, age, weight, moderate renal impairment IPSS-R risk, positive ring sideroblasts, baseline haemoglobin, anti-drug antibodies, change in drug substance manufacturing process and/or drug product formulation were found to have no statistically significant effect on the luspatercept effect parameters in myelodysplastic syndrome patients.
- For patients with beta-thalassaemia, although the relationships between luspatercept exposure and either a ≥ 33% or ≥ 50% reduction in red blood cell transfusion was not dose-dependent, the proportion of subjects achieving red blood cell transfusion reduction was statistically higher in the luspatercept-treated subjects than in those administered placebo (p-value < 0.05). Similarly, although each of the $AUC_{avg,0\text{-}15wk}$ quartile groups demonstrated significant reduction in red blood cell units transfused during Week 1 to Week 15 compared with the baseline or with the placebo group the overall exposure-response curve was flat.

Efficacy for indication: treatment of myelodysplastic syndrome-related transfusion-dependent anaemia

Full indication:

> *Treatment of patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes with ring sideroblasts.*

Studies providing evaluable efficacy data

- Study ACE-536-MDS-001 (also known as the MEDALIST trial; considered as being the pivotal study for this indication): A Phase III, double-blind, randomised study to compare the efficacy and safety of luspatercept (ACE-536) versus placebo for the treatment of anaemia due to the Revised International Prognostic Scoring System (IPSS-R) very low, low, or intermediate risk myelodysplastic syndromes in subjects with ring sideroblasts who require red blood cell transfusions.
- Study A536-03 (supportive study): A Phase II, open-label, ascending dose study of ACE-536 [luspatercept] for the treatment of anaemia in patients with low or intermediate-1 risk myelodysplastic syndromes (MDS).
- Study A536-05 (supportive study): An open-label extension study to evaluate the long-term effects of ACE-536 [luspatercept] for the treatment of anaemia in patients with low or intermediate-1 risk myelodysplastic syndrome previously enrolled in Study A536-03.

Study ACE-536-MDS-001 (MEDALIST trial)

Study ACE-536-MDS-001 (also known as the MEDALIST trial);[42] is an ongoing Phase III, double-blind, randomised, placebo-controlled, multicentre study to determine the efficacy and safety of luspatercept (ACE-536);[43] versus placebo in subjects with anaemia due to IPSS-R[44] very low, low, or intermediate risk myelodysplastic syndrome with ring sideroblasts who required red blood cell transfusions.

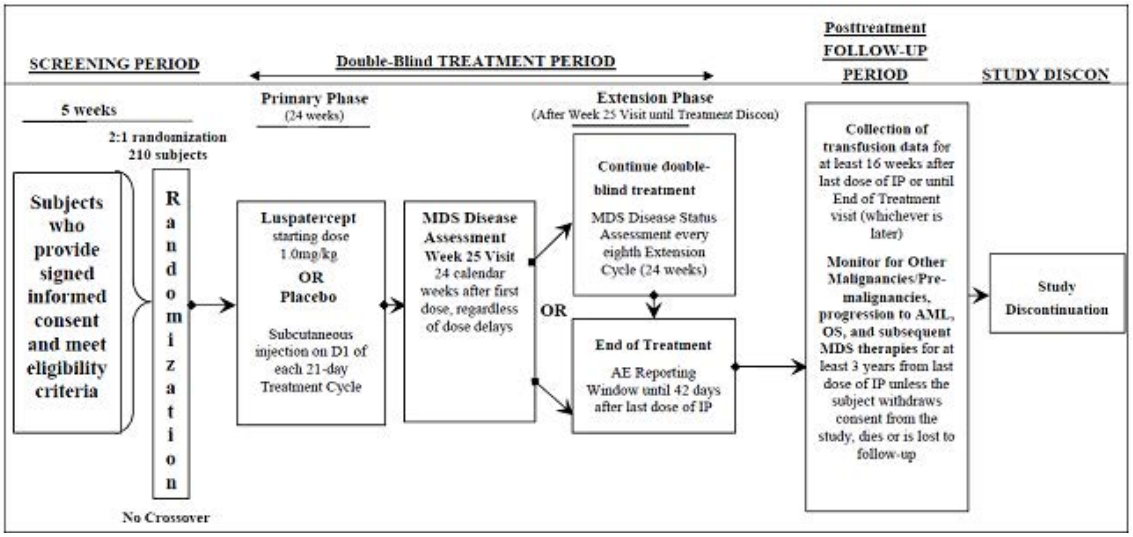
[42] Fenaux et al. Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes NEJM 2020; 382:140-51.
[43] ACE-536 is a drug development code for luspatercept.
[44] Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndromes Risk Assessment Calculator. Developed by the International Working Group for the Prognosis of MDS (IWG-PM) under the aegis of the MDS Foundation, Inc. Available at: https://www.mds-foundation.org/ipss-r/

Study design

The study consists of a screening period, a double-blind treatment period (primary phase and extension phase), and a post treatment follow-up period (see Figure 1, below).

The study was conducted from 9 February 2016 and is currently ongoing (data cut-off date was 8 May 2018). It was conducted at 65 sites in 11 countries as follows: Belgium (6), Canada (4), France (10), Germany (5), Italy (7), the Netherlands (2), Spain (8), Sweden (4), Turkey (2), United Kingdom (6), and United States of America (11).

Figure 1: Study ACE-536-MDS-001 Overall study design



AE = Adverse event; AML = Acute Myeloid leukemia; D1 = Day 1; Discon = Discontinuation; Hgb = Haemoglobin; IP = Investigational product; IWG = International working group; MDS = Myelodysplastic syndromes; OS = Overall survival.

Primary objective

The primary objective of the study was to evaluate red blood cell transfusion independence of luspatercept compared with placebo for the treatment of anaemia due to IPSS-R very low, low, or intermediate risk myelodysplastic syndrome in subjects with ring sideroblasts who required red blood cell transfusions.

Secondary objectives

The secondary objectives of the study were:

- to assess the safety and tolerability of luspatercept compared with placebo;
- to evaluate the effect of luspatercept on reduction in red blood cell transfusions, increase in haemoglobin, duration of red blood cell transfusion independence;
- improvement in health-related quality of life (as scored by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, EORTC QLQ-C30);
- increase in neutrophils;
- increase in platelets;
- decrease in serum ferritin,
- decrease in iron chelation therapy use; and
- time to red blood cell transfusion independence compared with placebo

Study endpoints

Rationale for the efficacy endpoints related to red blood cell transfusion independence: In order to mitigate the potential bias, should subjects in the control group (placebo group) drop out early due to the lack of a rapid response, the primary efficacy analysis in this study was the proportion of subjects achieving red blood cell transfusion independence with a duration of ≥ 8 weeks measured at 24 weeks.

After completion of the myelodysplastic syndrome disease assessment by the investigator at the Week 25 Visit, subjects who exhibited clinical benefit with no evidence of disease progression per IWG-MDS (International Working Group-myelodysplastic syndrome) criteria for altering natural history of myelodysplastic syndrome were to continue the double-blind treatment.[45] The proportion of subjects achieving red blood cell transfusion independence with a duration of ≥ 8 weeks at 48 weeks was assessed as a secondary endpoint to capture potential late responders. In addition, the proportion of subjects achieving red blood cell transfusion independence with a duration of ≥ 12 weeks was assessed as a key secondary endpoint, representing extended duration of benefit achieved with the interventional product.

Study assessments

Myelodysplastic syndrome disease assessment (Week 25 visit): treatment response was assessed locally by the investigator in accordance with IWG 2006 criteria for myelodysplastic syndrome;[45] with modifications for the erythroid response criteria through transfusion assessments, haematology laboratory parameters, peripheral blood smear, bone marrow aspirates and/or biopsies, and cytogenetics.

Central laboratory results from bone marrow and peripheral blood samples (for example, cytomorphology and cytogenetics analysis) were required as part of the myelodysplastic syndrome disease assessment.

In order for the subjects to remain on double-blind treatment beyond the first 24 calendar weeks, the following criteria must have been confirmed upon the completion of the myelodysplastic syndrome disease assessment by the investigator:

- evidence of clinical benefit (For example, decrease in red blood cell transfusion requirement compared with baseline requirement or Hgb increase compared with baseline); and
- absence of disease progression per IWG-MDS criteria for altering natural history of myelodysplastic syndrome.[45]

Inclusion and exclusion criteria

The main inclusion criteria were:

- Subjects aged > 18 years with documented diagnosis of myelodysplastic syndrome according to WHO/FAB classification that met IPSS-R classification of very low, low, or intermediate-risk disease, and the following:
  - ring sideroblasts ≥ 15% of erythroid precursors in bone marrow or ≥ 5% (but < 15%) if SF3B1 mutation was present;
  - less than 5% blasts in bone marrow;
  - peripheral blood white blood cell (WBC) count < 13,000/μL.
- Subject was refractory or intolerant to, or ineligible for, prior erythopoiesis-stimulating agent (ESA) treatment, as defined by any one of the following:

[45] Cheson, B. et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia, *Blood*. 2006; 108(2): 419-425.

  - *Refractory to prior ESA treatment*: Documentation of nonresponse or response that was no longer maintained to prior ESA containing regimen, either as a single agent or in combination (for example, with granulocyte colony stimulating factor (G-CSF)). The ESA regimen must have been either: recombinant human erythropoietin ≥ 40,000 IU/week for at least 8 doses or equivalent; or darbepoetin-α ≥ 500 µg once every three weeks for at least four doses or equivalent.
  - *Intolerant to prior ESA treatment*: Documentation of discontinuation of prior ESA-containing regimen, either as a single agent or in combination (for example, with G-CSF), at any time after introduction due to intolerance or an adverse event.
  - *ESA ineligible*: Low chance of response to ESA based on endogenous serum erythropoietin level > 200 U/L for subjects not previously treated with ESAs.

    Note: Erythropoiesis-stimulating agents are not approved for treatment of anaemia associated with myelodysplastic syndrome in Australia.
- If previously treated with ESAs or G-CSF/granulocyte-macrophage colony-stimulating factor (GM-CSF), both agents must have been discontinued ≥ 4 weeks prior to the date of randomisation
- Required red blood cell transfusions, as documented by the following criteria:
  - average transfusion requirement of ≥ 2 units/8 weeks of packed red blood cells confirmed for a minimum of 16 weeks immediately preceding randomisation.
  - haemoglobin levels at the time of or within 7 days prior to administration of red blood cell transfusion must have been ≤ 10.0 g/dL in order for the transfusion to be counted towards meeting eligibility criteria. Red blood cell transfusions administered when Hgb levels were > 10 g/dL and/or red blood cell transfusions administered for elective surgery did not qualify as a required transfusion for the purpose of meeting eligibility criteria.
  - no consecutive 56-day period that was red blood cell transfusion free during the 16 weeks immediately preceding randomisation.

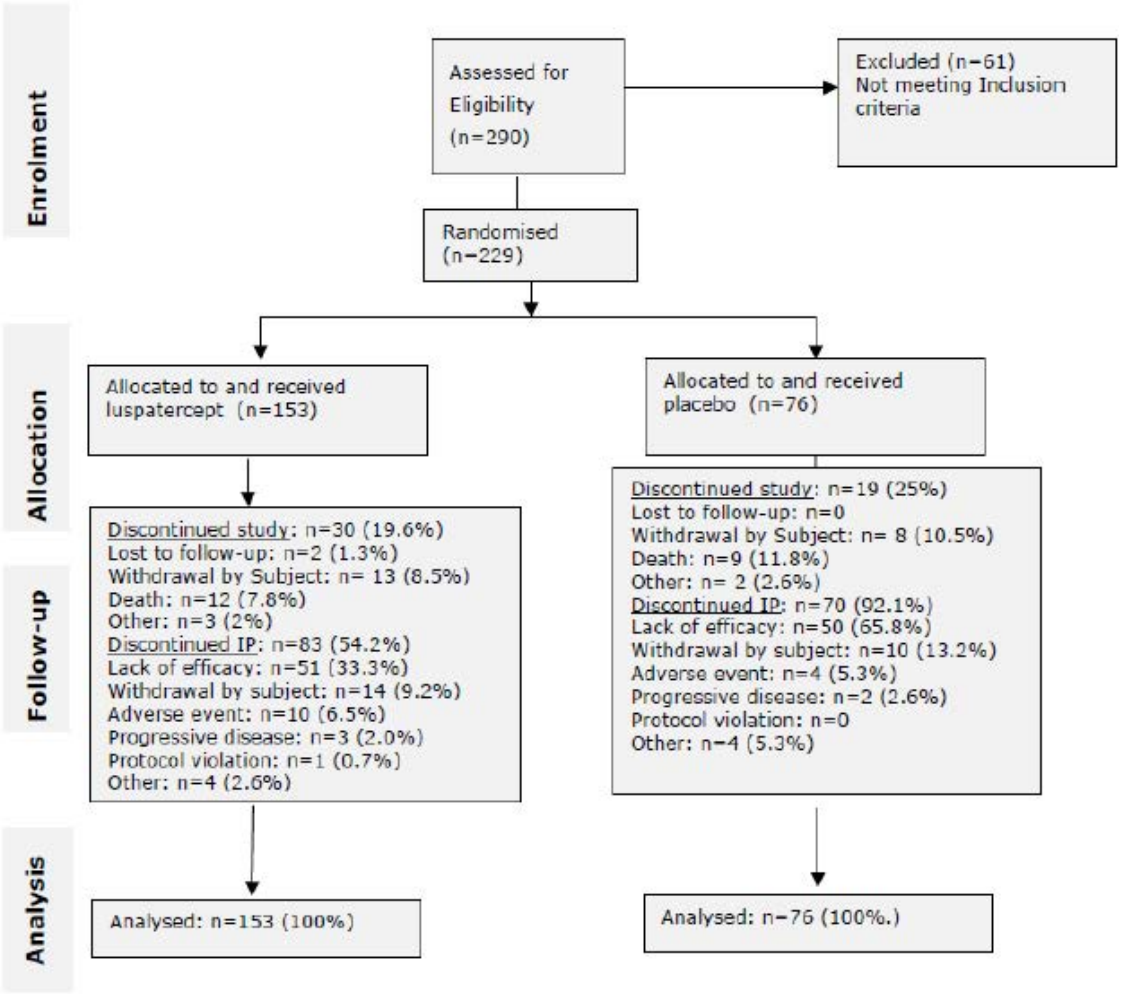
The main exclusion criteria were:

- Prior therapy with disease modifying agents for underlying myelodysplastic syndrome disease for example, immunomodulatory drugs (such as lenalidomide, hypomethylating agents, or immunosuppressive therapy). Subjects who previously received hypomethylating agents or lenalidomide may have been enrolled at the investigator's discretion contingent that the subject received no more than two doses of hypomethylating agents or no more than one calendar week of treatment with lenalidomide. The last dose must have been ≥ 5 weeks from the date of randomisation.
- Previously treated with either luspatercept or sotatercept.
- Myelodysplastic syndrome associated with del(5q) cytogenetic abnormality.
- Secondary myelodysplastic syndrome, that is, myelodysplastic syndrome that was known to have arisen as the result of chemical injury or treatment with chemotherapy and/or radiation for other diseases.
- Known clinically significant anaemia due to iron, vitamin B12, or folate deficiencies, or autoimmune or hereditary haemolytic anaemia, or gastrointestinal bleeding. Iron deficiency to be determined by serum ferritin ≤ 15 µg/L and additional testing if clinically indicated (for example, calculated transferrin saturation (iron/total iron binding capacity ≤ 20%) or bone marrow aspirate stain for iron).
- Prior allogeneic or autologous stem cell transplant.

- Known history of diagnosis of acute myeloid leukaemia.
- Use of any of the following within 5 weeks prior to randomisation:
  - anticancer cytotoxic chemotherapeutic agent or treatment;
  - corticosteroids, except for subjects on a stable or decreasing dose for ≥ 1 week prior to randomisation for medical conditions other than myelodysplastic syndrome;
  - iron chelation therapy, except for subjects on a stable or decreasing dose for at least 8 weeks prior to randomisation;
  - other red blood cell haematopoietic growth factors (for example, interleukin (IL)-3);
  - Investigational drug or device, or approved therapy for investigational use. If the half-life of the previous study drug was known, the use of it within five times the half-life prior to randomisation or within five weeks, whichever is longer, was excluded.

Participant flow for this study is depicted in Figure 2, below.

Figure 2: Study ACE-536-MDS-001 Participant flow



Results for the primary and key secondary efficacy outcomes

Red blood cell transfusion independence for 8 or more weeks: A statistically significantly and clinically meaningfully greater proportion of luspatercept-treated subjects achieved red blood cell transfusion independence ≥ 8 weeks from Week 1 through Week 24 compared

with placebo (37.91% versus 13.16%, p < 0.0001). This benefit was also observed when measured from Week 1 through Week 48 (45.10% versus 15.79%, p < 0.0001) see Table 4.

A rapid onset of effect with luspatercept was observed among the subjects who achieved red blood cell transfusion independence of ≥ 8 weeks during Week 1 to Week 24 in Study ACE-536-MDS-001 (start of the response period occurred in a median of 1.0 and 17 days after the first dose in the luspatercept and placebo groups, respectively).

Among the subjects who achieved red blood cell transfusion independence of ≥ 8 weeks during Week 1 to Week 24, 34.5% (20/58) of subjects in the luspatercept group maintained response at the last evaluation; the Kaplan-Meier estimate of the median duration of red blood cell transfusion independence based on the longest single episode of red blood cell transfusion independence was 30.6 weeks (95% CI: 20.6, 40.6) in the luspatercept group.

Table 3: Study ACE-536-MDS-001 Summary of overall efficacy data

	Reblozyl (N = 153)	Placebo (N = 76)
Primary Endpoint		
RBC-TI ≥ 8 weeks (Weeks 1-24) Number of responders (response rate %)	58 (37.9)	10 (13.2)
Common risk difference on response rate (95% CI)	24.56 (14.48, 34.64)	
Odds ratio (95% CI)	5.065 (2.278, 11.259)	
p-value	< 0.0001	
Secondary Endpoints		
RBC-TI ≥ 12 weeks (Weeks 1-24) Number of responders (response rate %)	43 (28.1)	6 (7.9)
Common risk difference on response rate (95% CI)	20.00 (10.92, 29.08)	
Odds ratio (95% CI)	5.071 (2.002, 12.844)	
p-value	0.0002	
RBC-TI ≥ 12 weeks (Weeks 1-48) Number of responders (response rate %)	51 (33.3)	9 (11.8)
Common risk difference on response rate (95% CI)	21.37 (11.23, 31.51)	
Odds ratio (95% CI)	4.045 (1.827,8.956)	
p-value	0.0003	
RBC-TI ≥ 8 weeks (Weeks 1-48) Number of responders (response rate %)	69 (45.1)	12 (15.8)
Common risk difference on response rate (95% CI)	29.55 (18.73, 40.36)	
Odds ratio (95% CI)[a]	5.306 (2.526, 11.146)	
p-value	< 0.0001	
mHI-E[b] (Weeks 1-24) Number of responders (response rate %) (95% CI)	81 (52.9) (44.72, 61.05)	9 (11.8) (5.56, 21.29)
p-value	<0.0001	
RBC transfusion reduction of 4 units / 8 weeks, n (%)	52/107 (48.6)	8/56 (14.3)
Mean haemoglobin increase of ≥ 15 g/L for 8 weeks, n(%)	29/46 (63.0)	1/20 (5.0)

Red blood cell transfusion independence of 12 or more weeks: A statistically significantly greater proportion of luspatercept-treated subjects achieved red blood cell transfusion independence of ≥ 12 weeks from Week 1 through Week 24 compared with placebo (28.10% versus 7.89%, respectively; p = 0.0002). This benefit was also observed when measured from Week 1 through Week 48 (33.33% versus 11.84%, p = 0.0003).

Modified Haematologic Improvement – Erythroid (mHI-E): For subjects with baseline red blood cell transfusion burden of ≥ 4 units/8 weeks, mHI-E was defined as a reduction in

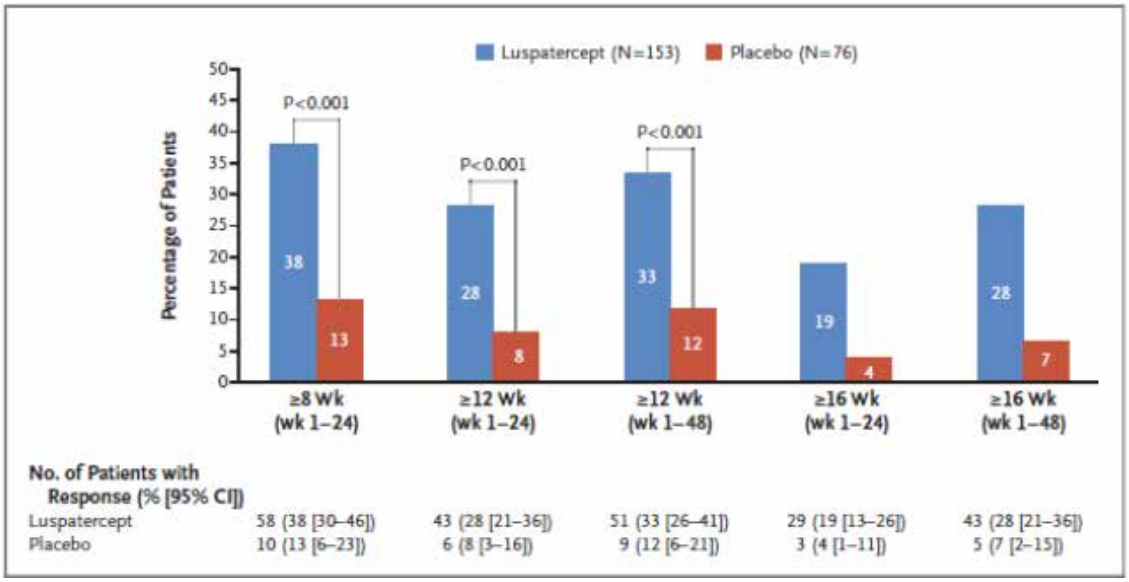
red blood cell transfusion of at least 4 units/8 weeks; for subjects with baseline red blood cell transfusion burden of < 4 units/8 weeks, mHI-E was defined as a mean increase in haemoglobin of ≥ 1.5 g/dL for 8 weeks in the absence of red blood cell transfusions.

A significantly greater proportion of subjects in the luspatercept treatment group than in the placebo group achieved mHI-E between Weeks 1 through 24 (52.9% versus 11.8%, nominal p < 0.0001) and between Weeks 1 through 48 (58.8% versus 17.1%, nominal p < 0.0001). Among subjects who achieved mHI-E during Weeks 1 through 24 or Weeks 1 through 48, the median time to achieve mHI-E was shorter in the luspatercept treatment group (1.0 and 3.0 days, respectively) than the placebo group (22.0 and 81.0 days, respectively).

Serum ferritin levels: A reduction in mean serum ferritin levels was observed from baseline in the luspatercept arm compared to an increase in the placebo at both Weeks 9 through 24 (-2.7 µg/L versus +226.5 µg/L, p = 0.0024) and Weeks 33 through 48 (-72.0 µg/L versus +247.4 µg/L, p = 0.0294) which resulted in a least square mean treatment difference of -229.1 µg/L (95% CI: -375.8, -82.4) and -319.5 µg/L (95% CI: -606.3, -32.7), respectively.

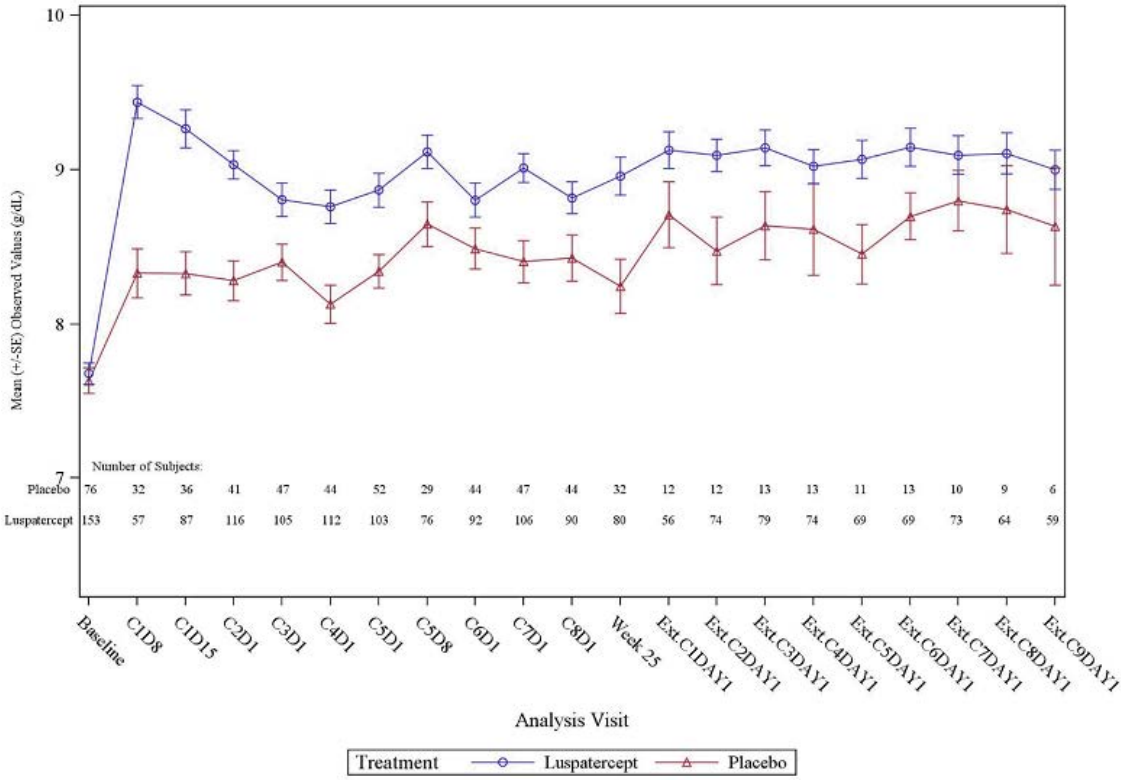
Shown in Figure 3 are the percentages of patients who had independence from red cell transfusion (defined as the absence of a red cell transfusion) for the indicated time periods in each trial group. In the analysis of the primary end point (transfusion independence for ≥ 8 weeks during Weeks 1 through 24), the odds ratio for luspatercept as compared with placebo was 5.07 (95% CI, 2.28 to 11.26). For the key secondary end point of transfusion independence for 12 weeks or longer, the odds ratio was 5.07 (95% CI, 2.00 to 12.84) for the analysis period of Weeks 1 through 24 and 4.05 (95% CI, 1.83 to 8.96) for the analysis period of Weeks 1 through 48. P-values were determined with the use of a Cochran–Mantel–Haenszel test with stratification for average baseline red-cell transfusion burden (≥ 6 units per 8 weeks versus < 6 units per 8 weeks) and baseline revised international prognostic scoring system score (very low or low risk versus intermediate risk). An analysis that applied the new IWG 2018 response criteria 33 with transfusion independence for 16 weeks or longer was also conducted.

Figure 3: Study ACE-536-MDS-001 Independence from red-cell transfusion



In Study ACE-536-MDS-001, a significantly greater proportion of subjects had a mean haemoglobin increase of ≥ 1.0 g/dL sustained for ≥ 8 weeks in the absence of red blood cell transfusion in the luspatercept group than in the placebo group during Week 1 to Week 24 (35.3% (54/153) versus 7.9% (6/76)) and during Week 1 to Week 48 (41.2% (63/153) versus 10.5% (8/76)).

Figure 4: Study ACE-536-MDS-001 Mean (+/- standard error) observed values in haemoglobin by time point from baseline through week 48 (intention to treat population)



C= Cycle; D = Day; Ext = Extension; ITT = Intent-to-treat; SE = Standard error of the mean.

Note: Baseline was defined (after applying the 14/3 day rule) as the lowest of the pretreatment and/or baseline values from the central, local laboratory, or pretransfusion haemoglobin from transfusion records that were within 35 days on or prior to the first dose of investigational product. Haemoglobin values within 14 days after an red blood cell transfusion were excluded from the analysis unless the value was within 3 days prior to another red blood cell transfusion.

Note: As per protocol, entry into the Extension Phase was restricted to subjects who did not progress and demonstrated evidence of clinical benefit at Week 25; thus, the few placebo treated subjects who entered the Extension Phase (That is, beyond Week 25) represented a well performing subset of subjects.

Health-related quality of life and healthcare resource utilisation endpoints

The main health-related quality of life questionnaire used was the EORTC QLQ-C30.[46]

The health-related quality of life-evaluable population consisted of 225 subjects, 149 in the luspatercept group and 76 in the placebo group (only 4 subjects from the luspatercept treatment group were excluded).

Mean scores were comparable at baseline between treatment groups across all domains of the EORTC QLQ-C30. No clinically meaningful changes from baseline were observed for both treatment groups across all the primary domains of interest over the 24 week treatment phase. The distributions of observed change scores across the 5 primary domains of interest (fatigue, dyspnoea, global health status, physical functioning, emotional functioning) and the scheduled visits within the 24 week treatment phase

[46] EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer quality of life questionnaire.

showed that health-related quality of life was maintained over time and comparable between treatment groups (That is, no clinically meaningful changes).

According to the applicant, maintenance of health-related quality of life is a clinically relevant outcome in this population since health-related quality of life is expected to worsen over time in myelodysplastic syndrome patients due to chronic transfusions.[47]

Other supportive studies

The Phase II, open-label, ascending dose study and Study A536-05, an open-label extension study, were evaluated and are considered supportive evidence for the efficacy of luspatercept by the clinical evaluator.

Clinical evaluator's conclusions on efficacy

In the Phase III trial involving patients with lower-risk myelodysplastic syndromes with ring sideroblasts who had been receiving regular red cell transfusions and had disease that was refractory to or unlikely to respond to erythropoiesis stimulating agents or who had discontinued such agents owing to an adverse event, 38% of the patients in the luspatercept group met the primary end point of transfusion independence for 8 weeks or longer, as compared with 13% of those in the placebo group ($p < 0.001$).

The median duration of the longest single continuous period of response to luspatercept was 30.6 weeks.

A significantly greater proportion of subjects in the luspatercept treatment group than in the placebo group achieved modified haematologic improvement – erythroid (mHI-E) between Weeks 1 through 24 (52.9% versus 11.8%, nominal $p < 0.0001$).

In conclusion, the rapid onset of treatment effect, extended duration of transfusion independence, erythroid response, and increased haemoglobin levels suggest that luspatercept had useful clinical effects in these patients.

Indication: Treatment of patients with transfusion dependent anaemia associated with beta-thalassaemia

Studies providing evaluable efficacy data

- Study ACE-536-B-THAL-001 (also known as the BELIEVE trial; considered pivotal for this indication): A Phase III, double-blind, randomised, placebo-controlled, multicentre study to determine the efficacy and safety of luspatercept (ACE-536) versus placebo in adults who require regular red blood cell transfusions due to beta-thalassaemia.[48]
- Study A536-04 (supportive study): A Phase II, Open-label, ascending dose study to evaluate the effects of ACE-536 [luspatercept] in patients with beta-thalassaemia.
- Study -536-06 (supportive study): An open-label extension study to evaluate the long-term effects of ACE-536 [luspatercept] in patients with beta-thalassaemia previously enrolled in Study A536-04.

Study ACE-536-β-THAL-001

Study design

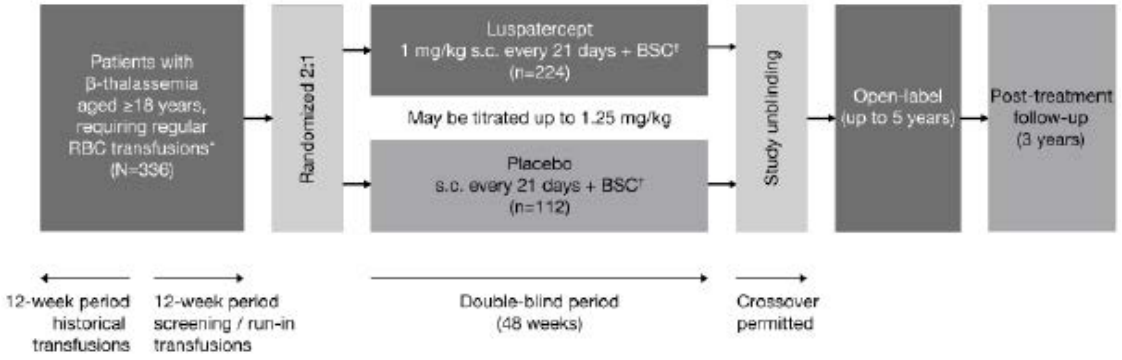
This is an ongoing Phase III, double-blind, randomised, placebo-controlled, multicentre study designed to determine the efficacy and safety of luspatercept + best supportive care

[47] Oliva, E. et al. Quality of life and physicians' perception in myelodysplastic syndromes, *Am J Blood Res*, 2012; 2(2): 136-147.
[48] Cappellini, M. et al. A Phase 3 Trial of Luspatercept in Patients with Transfusion-Dependent *β*-Thalassemia, N Engl J Med, 2020; 382: 1219-1231

versus placebo + best supportive care in approximately 300 subjects aged ≥ 18 years who require regular red blood cell transfusions due to beta-thalassaemia (see Figure 5, below).

The first subject visit was on 2 May 2016 and the last subject completed Week 48 visit on 14 May 2018. The study was conducted at 65 sites in 15 countries (Australia, Malaysia, Taiwan, Thailand, Israel, Lebanon, Tunisia, Turkey, Bulgaria, Canada, France, Greece, Italy, UK and USA).

Figure 5: Study ACE-536-B-THAL-001 Study design



BSC = best supportive care; RBC = red blood cells; s.c. subcutaneously.

* Regular RBC transfusions defined as 6-20 RBC units in the 24 weeks prior to randomisation with no ≥ 35 day transfusion free period during that time.

† RBC transfusions and iron chelation therapy to maintain each patient's baseline haemoglobin level.

Primary objective

The primary objective of the study was to determine the proportion of subjects treated with luspatercept + best supportive care versus placebo + best supportive care who achieved erythroid response, defined as ≥ 33% reduction from Baseline in transfusion burden (red blood cells/time) with a reduction of at least two units, from Week 13 to Week 24.

Note, the following rationale for choosing a 33% or greater reduction in red blood cell transfusion burden as clinically meaningful was provided by the sponsor:

> A 33% or greater reduction in RBC [red blood cell] transfusion burden is considered to be clinically meaningful for patients transfused based on the decrease in transfusional iron accumulation and related complications. It was estimated that a patient who requires 2 RBC units every 4 weeks pretreatment and reduced frequency to 2 RBC units every 6 weeks would benefit from a reduction in transfusional iron intake of approximately 1700 mg/year, based on an estimated 200 mg iron/RBC unit.[49,50]

Secondary objectives

Secondary objectives were:

- to evaluate the proportion of subjects who achieved ≥ 33% reduction from Baseline in transfusion burden from Week 37 to Week 48 versus placebo;
- to evaluate the proportion of subjects who achieved ≥ 50% reduction from Baseline in transfusion burden from Week 13 to Week 24 versus placebo;

[49] Cohen, A. et al. Effect of transfusional iron intake on response to chelation therapy in beta-thalassemia major, *Blood*, 2008; 111(2): 583-587.
[50] Porter, J. et al. Practical management of iron overload, *Br J Haematol*, 2001; 115: 239-252.

- to evaluate the proportion of subjects who achieved ≥ 50% reduction from Baseline in transfusion burden from Week 37 to Week 48 versus placebo;
- to evaluate the mean change from Baseline in transfusion burden from Week 13 to Week 24;
- to evaluate the mean change from Baseline in liver iron concentration versus placebo;
- to evaluate the mean change from Baseline in mean daily dose of iron chelation therapy used versus placebo; and
- to evaluate the mean change from Baseline in serum ferritin versus placebo.

Inclusion criteria

Key inclusion criteria were:

- male or female, ≥ 18 years of age at the time of signing the informed consent form;
- documented diagnosis of beta-thalassaemia or haemoglobin E beta-thalassaemia (beta-thalassaemia with mutation and/or multiplication of alpha-globin was allowed);
- regularly transfused, defined as 6 to 20 red blood cell units in the 24 weeks prior to randomisation and no transfusion free period for > 35 days during that period; and
- Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1

Exclusion criteria

Key exclusion criteria were:

- a diagnosis of sickle beta-thalassaemia or alpha-thalassaemia (For example, haemoglobin H disease);
- evidence of active hepatitis C virus, hepatitis B virus, or known positive human immunodeficiency virus;
- use of chronic anticoagulant therapy was excluded, unless the treatment stopped at least 28 days prior to randomisation;
- platelet count > 1000 x 109/L;
- treatment with another investigational drug or device ≤ 28 days prior to randomisation;
- prior exposure to sotatercept (ACE-011) or luspatercept (ACE-536)
- used an erythropoietic stimulating agent ≤ 24 weeks prior to randomisation; or
- iron chelation therapy, if initiated ≤ 24 weeks prior to randomisation (allowed if initiated > 24 weeks before or during treatment).

Table 5 lists the baseline characteristics of the Study ACE-536-*β*-THAL-001 study population

Figure 6: Study ACE-536-*β*-THAL-001 Participant flow

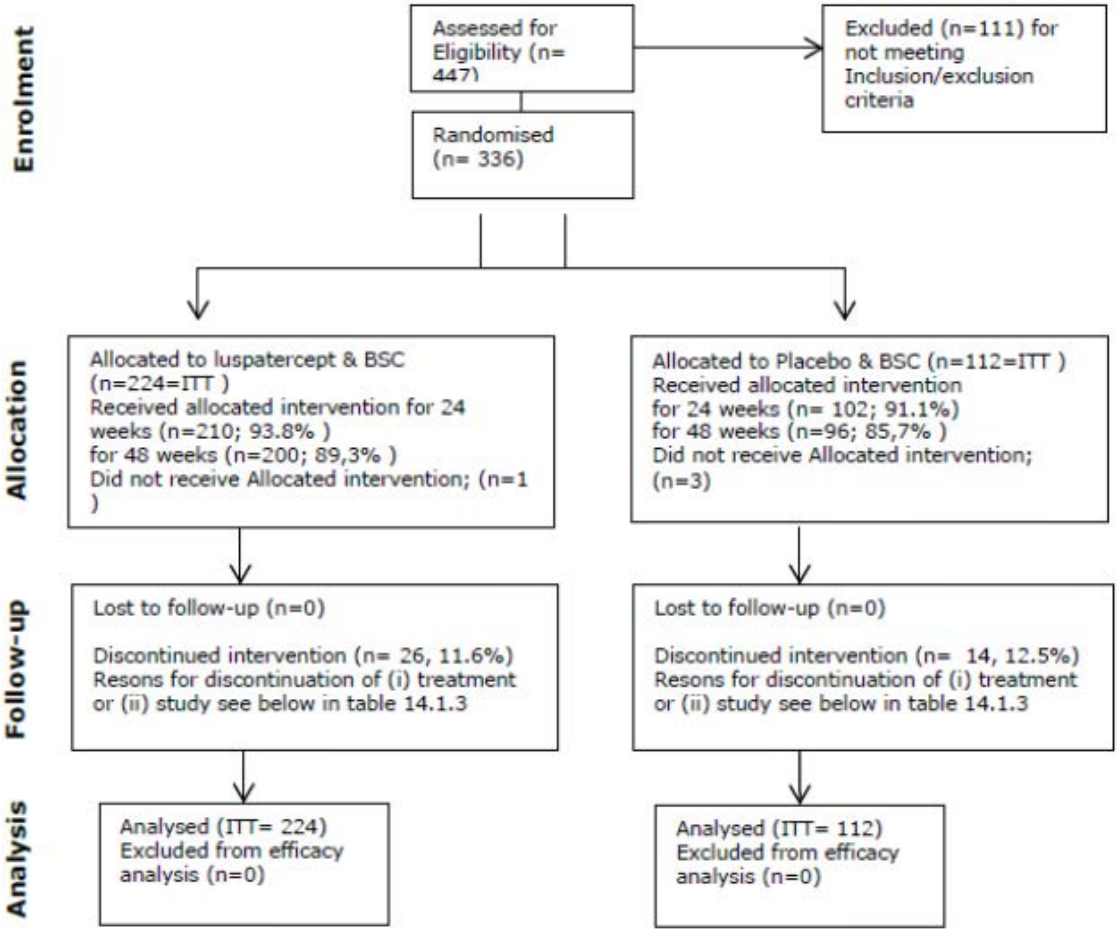


Table 4: Study ACE-536-B-THAL-001 Baseline demographic and disease characteristics

Characteristic	Luspatercept Group (N=224)	Placebo Group (N=112)	Total (N=336)
Median age (range) — yr	30 (18–66)	30 (18–59)	30 (18–66)
Female sex — no. (%)	132 (58.9)	63 (56.3)	195 (58.0)
Geographic region — no. (%)			
North America and Europe	100 (44.6)	51 (45.5)	151 (44.9)
Asia–Pacific	72 (32.1)	35 (31.3)	107 (31.8)
Middle East and North Africa	52 (23.2)	26 (23.2)	78 (23.2)
Diagnosis of hemoglobin E–β-thalassemia — no. (%)	31 (13.8)	21 (18.8)	52 (15.5)
Presence of a β^0/β^0 genotype — no. (%)	68 (30.4)	35 (31.3)	103 (30.7)
Median pretransfusion hemoglobin level (range) — g/dl†	9.3 (4.5–11.4)	9.2 (5.8–11.7)	9.3 (4.5–11.7)
Median transfusion burden (range) — no. of red-cell units in 24 wk‡	14 (6–24)	15 (6–26)	14 (6–26)
Transfusion burden category — no. (%)			
≤10 red-cell units in 24 wk	33 (14.7)	14 (12.5)	47 (14.0)
>10 to ≤15 red-cell units in 24 wk	96 (42.9)	47 (42.0)	143 (42.6)
>15 red-cell units in 24 wk	95 (42.4)	51 (45.5)	146 (43.5)
Previous splenectomy — no. (%)	129 (57.6)	65 (58.0)	194 (57.7)
Mean total bilirubin level — μmol/liter	35.4	35.9	NA
Median liver iron concentration (range) — mg/g of dry liver weight	6.14 (0.8–125.0)	5.05 (0.2–53.2)	5.69 (0.2–125.0)
Liver iron concentration category — no. (%)			
0–3 mg/g of dry liver weight	70 (31.3)	37 (33.0)	107 (31.8)
>3–7 mg/g of dry liver weight	51 (22.8)	30 (26.8)	81 (24.1)
>7–15 mg/g of dry liver weight	38 (17.0)	19 (17.0)	57 (17.0)
>15 mg/g of dry liver weight	65 (29.0)	26 (23.2)	91 (27.1)
Median myocardial iron deposition (range) — msec§	34.7 (3.0–205.9)	36.3 (6.4–57.5)	35.0 (3.0–205.9)
Median serum ferritin level (range) — μg/liter	1441.3 (88.0–6400.0)	1301.5 (136.0–6400.0)	NA
Current iron-chelation therapy — no. (%)¶	222 (99.6)	109 (100.0)	331 (99.7)

* Data on all baseline demographics and disease characteristics, except current iron-chelation therapy, are shown for the intention-to-treat population (all patients who underwent randomisation). Percentages may not total 100 because of rounding. To convert the values for bilirubin to milligrams per deciliter, divide by 17.1. NA denotes not available.

† The baseline pretransfusion haemoglobin level in a patient was defined as the median of all documented pretransfusion haemoglobin levels measured in the 24 weeks (12 weeks of historical information plus 12 weeks of prospectively collected run-in data) before the first dose of luspatercept or placebo.

‡ The baseline transfusion burden was defined as the number of red-cell units transfused in the 24 weeks before the first dose of luspatercept or placebo; red-cell units transfused on the day of the first dose of were considered part of the baseline transfusion burden.

§ Myocardial iron deposition was assessed by means of T2*-weighted magnetic resonance imaging (which allows for distortions in the magnetic field due to haemosiderin or ferritin to quantify effective T2); a value higher than 10 msec indicates minimal risk of heart failure. (Coates TD. Physiology and pathophysiology of iron in hemoglobin-associated diseases. Free Radic Biol Med 2014;72:23-40).

¶ Current iron-chelation therapy was assessed in the safety population (all patients who underwent randomisation and received ≥1 dose of luspatercept or placebo — 223 in the luspatercept group and 109 in the placebo group). Combination iron-chelation therapy was permitted.

Reproduced from Cappellini, M. et al. A Phase 3 Trial of Luspatercept in Patients with Transfusion-Dependent β-Thalassemia, N Engl J Med, 2020; 382: 1219-1231

Results

The study was unblinded for analyses when all patients had received at least 48 weeks of treatment or discontinued treatment.

Efficacy was based on the primary endpoint of red blood cell transfusion burden reduction (≥ 33% reduction from Baseline) with a reduction of at least two units from Week 13 to Week 24. There were significantly more patients taking luspatercept (Reblozyl) who achieved the primary endpoint compared to placebo (21.4% versus 4.5%, respectively; $p < 0.0001$; see Table 6 and Figure 7 below for a summary of efficacy data).

More than 65% of the luspatercept responders who achieved at least a 33% reduction in transfusion burden during any consecutive 12 week interval achieved two or more episodes of response within the treatment exposure period of 64 weeks.

A treatment effect in favour of luspatercept over placebo was observed in all subgroups analysed, including patients with a severe disease condition, such as patients with the $\beta 0/\beta 0$ gene mutation or with a high transfusion burden (> 6 units/12 week) at Baseline.

A reduction in mean serum ferritin levels was observed from Baseline in the luspatercept arm compared to an increase in the placebo arm at Week 48 (-248.02 µg/L versus +106.62 µg/L $p = 0.0024$) which resulted in a least square mean treatment difference of -347.8 µg/L (95% CI: -516.95, -178.65).

The onset of action was rapid with the median time from first dose to first erythroid response ranging from 12 to 25 days in the luspatercept + best supportive care group compared to 43 to 107 days in the placebo group.

No clinically meaningful change in liver iron concentration was observed in beta-thalassaemia patients treated with luspatercept plus best supportive care compared to patients treated with placebo plus best supportive care at 48 weeks.

Table 5: Study ACE-536-B-THAL-001 Summary of overall efficacy data

	Reblozyl (N = 224)	Placebo (N = 112)
≥ 33% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks		
Weeks 13-24 – *Primary Endpoint*	48 (21.4)	5 (4.5)
Risk difference (95% CI)[a]	17.0 (10.4, 23.6)	
p-value[b]	<0.0001	
Weeks 37-48	44 (19.6)	4 (3.6)
Risk difference (95% CI)[a]	16.1 (9.8, 22.4)	
p-value[b]	<0.0001	
Any consecutive 12 weeks[c]	158 (70.5)	33 (29.5)
Risk difference (95% CI)[a]	41.1 (30.7, 51.4)	
p-value[b]	<0.0001	
Any consecutive 24 weeks[c]	92 (41.1)	3 (2.7)
Risk difference (95% CI)[a]	38.4 (31.3, 45.5)	
p-value[b]	< 0.0001	
≥ 50% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks		
Weeks 13-24	17 (7.6)	2 (1.8)
Risk difference (95% CI)[a]	5.8 (1.6, 10.1)	
p-value[b]	0.0303	
Weeks 37-48	23 (10.3)	1 (0.9)
Risk difference (95% CI)[a]	9.4 (5.0, 13.7)	
p-value[b]	0.0017	
Any consecutive 12 weeks[c]	90 (40.2)	7 (6.3)
Risk difference (95% CI)[a]	33.9 (26.1, 41.8)	
p-value[b]	< 0.0001	
Any consecutive 24 weeks[c]	37 (16.5)	1 (0.9)
Risk difference (95% CI)[a]	15.6 (10.5, 20.8)	
p-value[b]	< 0.0001	

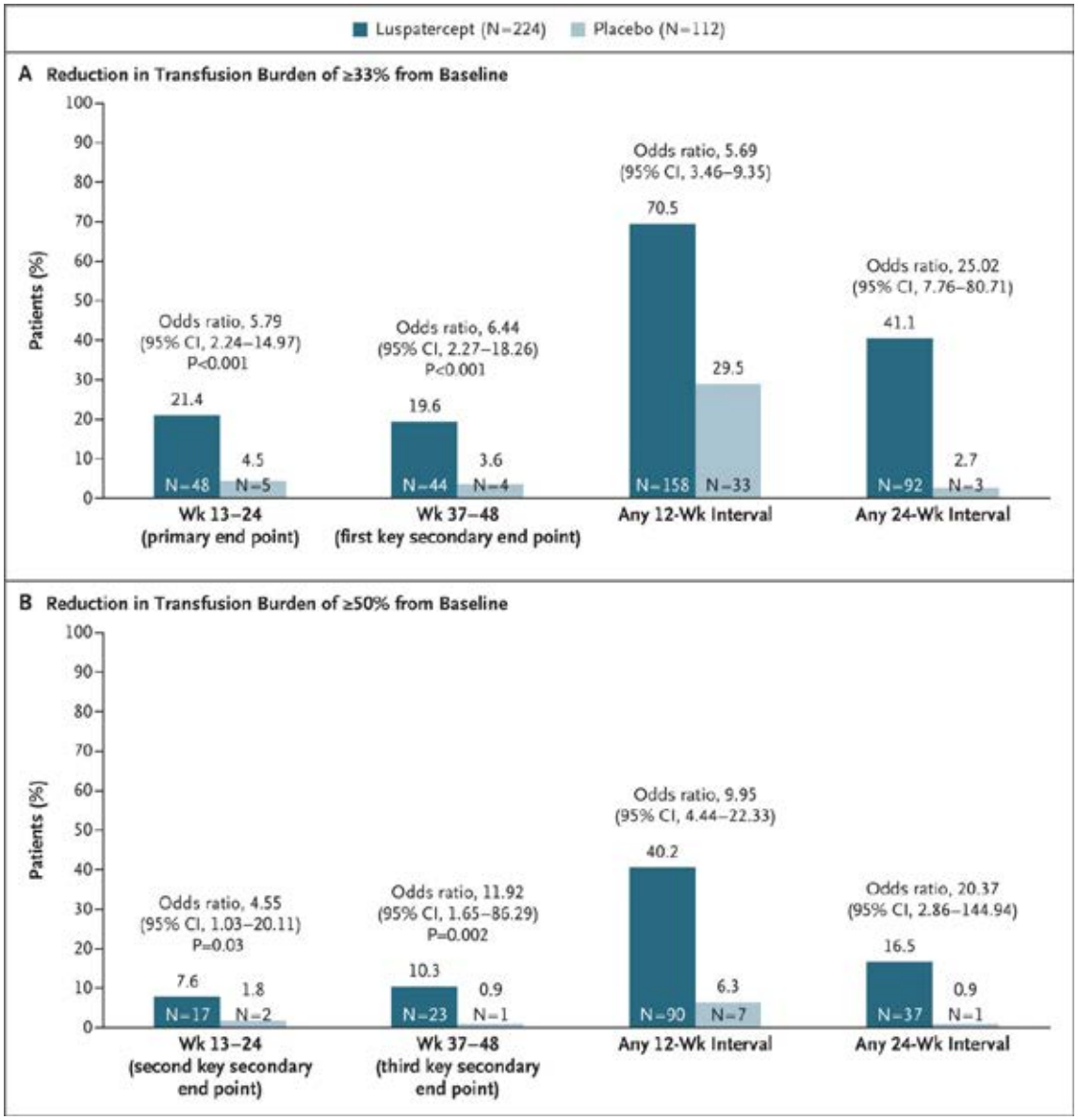
CI = confidence intervals; RBC = red blood cell

[a] Difference in proportions (luspatercept + best supportive care versus placebo + best supportive care) and 95% confidence intervals estimated from the unconditional exact test.

[b] P-value from the Cochran-Mantel-Haenszel test stratified by the geographical region.

[C] Response assessed over any consecutive 12 or 24 week interval showing the proportion of patients achieving treatment benefit at any time.

Figure 7: Study ACE-536-β-THAL-001 Percentage of patients who had a reduction in the transfusion burden of at least 33% or at least 50% from Baseline



CI = confidence interval; Wk = week.

Reductions in the transfusion burden (defined as the total number of red cell units transfused in a specified time interval) were assessed in the intention-to-treat population. Panel A shows the percentages of patients who had a reduction in the transfusion burden of at least 33% from baseline during weeks 13 through 24 (primary end point), during weeks 37 through 48 (first key secondary end point), and during any 12 week or 24 week interval. Panel B shows the percentages of patients who had a reduction in the transfusion burden of at least 50% from baseline during weeks 13 through 24 (second key secondary end point), during weeks 37 through 48 (third key secondary end point), and during any 12 week or 24 week interval. A reduction of at least two red cell units over the fixed and nonfixed 12 week intervals was also required for those end points. To control for multiple comparisons, key secondary end points were evaluated in sequential order once the primary efficacy analysis had shown statistical significance.

Reductions in the transfusion burden of at least 33% and at least 50% from baseline were estimated to avoid the need for approximately 7 and 8 red cell units, respectively, per patient over 6 months. In practice, patients could receive fewer red cell units per visit or have a longer duration between transfusion visits. Either of these outcomes may reduce the iron load, improve patient convenience, and reduce the associated burden of disease.

Supportive studies

The supportive studies, Study A536-04 (a Phase II, open-label, ascending dose study to evaluate the effects of ACE-536 in patients with beta-thalassaemia); and Study ACE-536-06 (an open-label extension study to evaluate the long-term effects of ACE-536 in patients with beta-thalassaemia previously enrolled in Study A536-04) are considered supportive of efficacy by the clinical evaluator.

Clinical evaluator's conclusions on efficacy

In conclusion, available data from the pivotal study (Study ACE-536-B-THAL-001) supports a clinically meaningful effect on reduction in transfusion burden in adult patients with transfusion dependent anaemia associated with beta-thalassaemia in a relatively small number of patients taking luspatercept (21.4%) compared to placebo (4.5%).

Safety

Exposure

The safety of luspatercept was evaluated in a clinical development program consisting of 571 subjects exposed to luspatercept including 260 subjects with myelodysplastic syndrome, 287 subjects with beta-thalassemia, and 24 healthy, postmenopausal females.

Myelodysplastic syndrome

Overall, 260 subjects received at least one dose of luspatercept, representing an overall exposure of 244.13 subject-years. In the Phase III myelodysplastic syndrome study (Study ACE-536-MDS-001) 153 subjects received at least 1 dose of luspatercept for an overall cumulative exposure of 136.7 subject-years, compared with 76 subjects who received at least one dose of placebo for an overall cumulative exposure of 44.5 subject-years. Exposure to study treatment was approximately twice as long in the luspatercept treatment group compared to the placebo treatment group; median treatment duration was 49.0 and 24 weeks, respectively and the median number of doses received was 16.0 and 8.0, respectively.

During the study, compared with placebo, fewer patients in the luspatercept group had their IP dose titrated at least once from 1.0 to 1.33 mg/kg (luspatercept versus placebo: 77.1% versus 93.4%) and from 1.33 to 1.75 mg/kg (58.8% versus 82.9%). A higher proportion of subjects in the luspatercept treatment group than the placebo group remained at the 1.0 mg/kg dose level for the duration of their study participation (primary phase and/or extension phase) through the cutoff date (22.9% versus 6.6%). Overall, 72 subjects (31.4%) had their IP dose delayed at least once during the study: 63/153 subjects (41.2%) in the luspatercept treatment group and 9/76 subjects (11.8%) in the placebo group and most common reasons were Other, predose haemoglobin > 11.5g/dL and suspected related adverse event > Grade 3. A lower proportion of subjects discontinued treatment in the luspatercept compared to placebo group (54.2% versus 92.1%) and lack of efficacy was most common reason for treatment discontinuation (33.3% versus 65.8%). Similarly, proportion of subject who discontinued the study was lower in the luspatercept group (19.6% versus 25%) and most frequent reasons for study discontinuation was death (7.8% versus 11.8%).

In the Phase II myelodysplastic syndrome studies, 107 subjects received at least one dose of luspatercept; 40.2% discontinued study treatment (3.7% due to lack of efficacy) and 17.8% discontinued the study (1.9% due to deaths).

Baseline demographics and disease characteristics were generally similar between luspatercept and placebo groups in the Phase III studies with similar demographics also observed in the Phase II studies. However, the Phase II patient population had more indicators of severe disease such as higher IPSS-R scores, lower rate of *SF3B1* mutation

(indicator of lower risk), 35.5% were ring sideroblast negative (which is not proposed indication). Furthermore, prior erythropoiesis stimulating agent use (46.7%) and iron chelation therapy (28%) use at Baseline in the Phase II studies was lower than in the Phase III study.

Beta-thalassaemia

Overall, 287 subjects received at least one dose of luspatercept, representing an overall exposure of 355.7 subject-years. The median treatment duration and median number of doses received was similar between the luspatercept (63.3 weeks and 21.0 doses, respectively) and the placebo (62.1 weeks and 21.0 doses, respectively) treatment groups.

In the Phase III beta-thalassaemia study (Study ACE-536-β-THAL-001) 223 subjects received at least one dose of luspatercept (overall cumulative exposure of 259.8 subject-years) compared with 109 subjects who received at least 1 dose of placebo (overall cumulative exposure of 123.0 subject-years). A similar proportion of subjects in the luspatercept and placebo groups discontinued treatment (18.8% versus 22%) and discontinued the study (8.5% versus 4.6%); withdrawal by subject was most frequent for treatment/study discontinuation. The proportion of subjects who had at least one dose titration was lower in the luspatercept + best supportive care than in the placebo + best supportive care treatment group (48% versus 67.9%) (dose titration due to < 33% red blood cell transfusion burden reduction (26.9% versus 42.2%), ≥ 33% and < 50% red blood cell transfusion burden reduction (22.4% versus 26.6%)).

In the Phase II studies, a total of 64 subjects received at least one dose of luspatercept and 45.3% of subjects discontinued treatment (most frequently due to protocol deviation and withdrawal by subject). Baseline disease characteristics were similar between the luspatercept and placebo groups in the Phase III study. The Phase II studies had similar baseline characteristics to the Phase III study with similar baseline haemoglobin and liver iron content levels; majority of subjects in both Phase III and II studies had ECOG performance status of 0 (61%) and had a splenectomy (57 to 67%) prior to study.

Summary of safety

Myelodysplastic syndrome

The following is a summary of the clinical evaluator's conclusions on safety for the following proposed indication:

> *Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia (requiring 2 or more RBC units over 8 weeks) due to very low, low and intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.*

The exposure of patients to luspatercept was adequate to assess safety in proposed indications. In the Phase III Study ACE-536-MDS-001 (MEDALIST trial), a slightly higher proportion of patients in the luspatercept group experienced at least one treatment-emergent adverse event compared with placebo group (98% versus 92%). After adjustment for exposure, the incidence per 100 subject-years of any treatment-emergent adverse event, treatment-emergent adverse events leading to dose interruption; and treatment-emergent adverse events leading to dose reduction were higher in the luspatercept group, and serious treatment-emergent adverse events; treatment-emergent adverse events leading to death; and Grade 3 or 4 treatment-emergent adverse events were higher in the placebo group. The most frequently reported treatment-emergent adverse event with higher incidence in the luspatercept compared to placebo group (> 5% higher incidence) were fatigue (26.8% versus 13.2%), diarrhoea (22.2% versus 9.2%), asthenia (20.3% versus 11.8%), nausea (20.3% versus 7.9%), dizziness, back pain, headache, dyspnoea, urinary tract infection, bronchitis, upper respiratory tract infection, influenza, syncope/presyncope, and vertigo/vertigo positional.

In both the luspatercept and placebo treatment groups, the highest incidence of treatment-emergent adverse events generally occurred during Cycles 1 through 4 and decreased thereafter in each successive 4-cycle dosing interval. Similar trends were observed for all Grades 3 or 4 adverse events. The incidence of treatment-emergent adverse events was not related to dose of luspatercept: proportion of subjects with at least one treatment-emergent adverse event was 82.4% (126/153), 70.3% (83/118) and 83.3% (75/90) at the luspatercept 1 mg/kg, 1.33 mg/kg and 1.75 mg/kg dose levels, respectively.

Overall, 24 subjects died: 15 subjects (5.8%) in the pooled luspatercept treatment group and 9 subjects (11.8%) in the placebo treatment group. Approximately half of the deaths occurred while subjects were off study treatment, and the causes of death were as expected in this predominantly elderly myelodysplastic syndrome population. There was no notable association between luspatercept treatment and type or frequency of events with fatal outcomes. All deaths were assessed as not related or unlikely related to luspatercept by the investigators. In the myelodysplasia data pool, serious adverse events were reported for 37.7% of subjects in the luspatercept treatment group, and when adjusted for exposure, the incidence was 51.9/100 subject-years.

There were no notable differences in the incidence of study treatment discontinuation or treatment interruptions. There were no notable clinically significant trends in haematology (other than haemoglobin) or chemistry laboratory values over the course of the studies. There was no evidence of an increased risk for thromboembolic events in luspatercept-treated subjects with myelodysplastic syndrome.

Three subjects progressed to acute myeloid leukaemia (2/153 (1.3%) subjects in the luspatercept treatment group and 1/76 (1.3%) subject in the placebo group). Overall, 7 malignancies were reported in 6 subjects in luspatercept (3.9%, 4.4 exposure adjusted incidence rate) and one subject in the placebo group (1.3%, 2.2 exposure adjusted incidence rate). Although the incidence was numerically greater in the luspatercept group, 95% confidence intervals were overlapping for the luspatercept and placebo treatment groups for the exposure adjusted incidence rates of malignancy events of interest and the rates appear to be within the expected range for an elderly myelodysplastic syndrome population.

In the Phase III myelodysplastic syndrome study, the proportion of patients with kidney injury was higher in the luspatercept compared to placebo group (9.8% versus 5.3%) and the most frequently reported kidney event of interest was renal failure (4.6% versus 2.6%).

Beta-thalassaemia

In the Phase III Study ACE-536-β-THAL-001, treatment-emergent adverse events reported in at least 15% of subjects in the luspatercept group included back pain, bone pain, arthralgia, pyrexia, upper respiratory tract infection, and headache. The most frequently reported all-grade treatment-emergent adverse events (in ≥ 20% of subjects) in the luspatercept + best supportive care treatment group were back pain, upper respiratory tract infection, and headache. Treatment-emergent adverse events (all grades) that were reported by ≥ 5% of subjects in the luspatercept + best supportive care treatment group and at a ≥ 5% higher incidence than in the placebo + best supportive care treatment group were bone pain (19.7% versus 8.3%), arthralgia (19.3% versus 11.9%), hyperuricemia (7.2% versus 0%), dizziness (11.2% versus 4.6%) and hypertension (8.1% versus 2.8%).

The Phase II studies showed a similar distribution of treatment-emergent adverse events with high rates (> 40% as well as an exposure adjusted incidence rate of more than 40/100 subject-years) for the following events: bone pain, arthralgia, myalgia, pyrexia, asthenia, headache.

Overall, 3 subjects in the beta-thalassaemia data pool died: 2 subjects (0.7%) in the pooled luspatercept treatment group and one subject (0.9%) in the placebo treatment group. None of the adverse leading to death were considered related to treatment. The incidence of serious adverse events in the Phase III study was higher with 15.2% (exposure adjusted incidence rate of 14.1/100 subject-years) in the luspatercept treatment group compared to 5.5% (exposure adjusted incidence rate 5.0/100 subject-years) in the placebo group. This difference was evenly distributed amongst System Organ Classes with no particular pattern. The most commonly reported serious adverse events in the luspatercept group was anaemia in 3 (1.3%) subjects, followed by cellulitis, cerebrovascular accident, cholangitis, deep vein thrombosis, pyrexia, and septic shock in 2 (1.8%) subjects each. The incidence of serious adverse events for luspatercept-treated subjects in the Phase II studies (6.3%; exposure adjusted incidence rate of 4.3/100 subject-years) was lower than in Phase III and in the beta-thalassemia data pool (13.2%; exposure adjusted incidence rate of 11.4/100 subject-years). There were no notable differences in incidence of study treatment discontinuation or treatment interruptions. There were no notable clinically significant trends in haematology (other than haemoglobin) or chemistry laboratory values over the course of the studies.

More thromboembolic events were observed in subjects treated with luspatercept compared with placebo in subjects with β-thalassemia. These thromboembolic events were observed in subjects with splenectomy and other recognised risk factors, and the overall incidence and adjusted incidence rates in the luspatercept treatment group. Thromboembolic events were not associated with elevated haemoglobin (haemoglobin above 11.5 g/dL). The risk of thromboembolic events in splenectomised patients with beta-thalassemia is adequately highlighted in PI.

The incidence of Grade 3 or 4 hyperuricemia was higher in the luspatercept group compared to placebo in both the pivotal myelodysplastic syndrome and beta-thalassaemia studies. The sponsors have stated that there does not appear to be any biologic basis for luspatercept treatment to result in increased serum uric acid and that none of the subjects with treatment-emergent adverse event of hyperuricemia or blood uric acid increased had complications such as gout or nephrolithiasis. However, due to consistently higher incidence especially of Grade 3 or 4 adverse events of hyperuricemia observed in both Phase III studies, it is recommended that this adverse event be monitored.

Safety from the US FDA-approved Product Information

The following is extracted from the US FDA-approved PI.

Myelodysplastic syndrome

For the indication of:

> *Myelodysplastic syndromes with ring sideroblasts or myelodysplastic / myeloproliferative neoplasm with ring sideroblasts and thrombocytosis associated anaemia*

The safety of luspatercept at the recommended dose and schedule was evaluated in 242 patients with myelodysplastic syndrome with ring sideroblasts (n = 192) or other myeloid neoplasms (n = 50). The safety population included 63% males and 37% females of median age 72 years (range, 30 to 95 years); of these patients, 81% were White, 0.4% Black, 0.4% Other, and race was not reported in 18.2% of patients. The median time on treatment with luspatercept was 50.4 weeks (range, 3 – 221 weeks); 67% of patients were exposed for 6 months or longer and 49% were exposed for greater than one year.

Among the 242 patients treated with luspatercept, 5 (2.1%) had a fatal adverse event, 11 (4.5%) discontinued due to an adverse event, and 7 (2.9%) had a dose reduction due to an adverse event. The most common (> 10%) all-grade adverse events included fatigue, musculoskeletal pain, dizziness, diarrhoea, nausea, hypersensitivity reactions,

hypertension, headache, upper respiratory tract infection, bronchitis, and urinary tract infection. The most common (> 2%) Grade > 3 adverse events included fatigue, hypertension, syncope and musculoskeletal pain. Selected laboratory abnormalities that changed from Grade 0 or 1 at Baseline to Grade > 2 at any time during the studies in at least 10% of patients included creatinine clearance decreased, total bilirubin increased, and alanine aminotransferase increased.

One patient in each group had progression to higher-risk myelodysplastic syndromes, and acute myeloid leukaemia developed in 4 patients (3 patients (2%) receiving luspatercept and one patient (1%) receiving placebo).

Table 6: Study ACE-536-MDS-001 Adverse events (≥ 5%) in patients receiving Reblozyl (luspatercept) with a difference between arms of > 2% through Cycle 8

Body System /Adverse Reaction	REBLOZYL (N=153)		Placebo (N=76)	
	All Grades n (%)	Grade 3 n (%)	All Grades n (%)	Grade 3 n (%)
General disorders and administration site conditions				
Fatigue [a, b]	63 (41)	11 (7)	17 (22)	2 (3)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain [b]	30 (20)	3 (2)	11 (14)	0 (0)
Nervous system disorders				
Dizziness/vertigo	28 (18)	1 (<1)	5 (7)	1 (1)
Headache [b]	21 (14)	0 (0)	5 (7)	0 (0)
Syncope / presyncope	8 (5)	5 (3)	0 (0)	0 (0)
Gastrointestinal disorders				
Nausea [b]	25 (16)	1 (<1)	8 (11)	0 (0)
Diarrhea [b]	25 (16)	0 (0)	7 (9)	0 (0)
Respiratory, thoracic and mediastinal disorders				
Dyspnea [b]	20 (13)	2 (1)	4 (5)	1 (1)
Immune system disorders				
Hypersensitivity reactions [b]	15 (10)	1 (<1)	5 (7)	0 (0)
Renal and urinary disorders				
Renal impairment [b]	12 (8)	3 (2)	3 (4)	0 (0)
Cardiac disorders				
Tachycardia [b]	12 (8)	0 (0)	1 (1)	0 (0)

Table 7: Study ACE-536-MDS-001 Adverse events (≥ 5%) in patients receiving Reblozyl (luspatercept) with a difference between arms of > 2% through Cycle 8

Body System /Adverse Reaction	REBLOZYL (N=153)		Placebo (N=76)	
	All Grades n (%)	Grade 3 n (%)	All Grades n (%)	Grade 3 n (%)
Injury poisoning and procedural complications				
Injection site reactions	10 (7)	0 (0)	3 (4)	0 (0)
Infections and infestations				
Upper respiratory tract infection	10 (7)	1 (<1)	2 (3)	0 (0)
Influenza / influenza like illness	9 (6)	0 (0)	2 (3)	0 (0)

Table 8: Study ACE-536-MDS-001 Selected Grades 2 to 4 treatment-emergent laboratory abnormalities through Cycle 8

Parameter	REBLOZYL		Placebo	
	N[a]	n (%)	N[a]	n (%)
ALT elevated	151	13 (9)	74	5 (7)
AST elevated	152	6 (4)	76	0 (0)
Total bilirubin elevated	140	17 (12)	66	3 (5)
Creatinine clearance reduced	113	30 (27)	62	13 (21)

[a] Number of patients at Grades 0-1 at baseline.
ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Beta-thalassaemia

The safety of luspatercept in patients with beta thalassemia was evaluated in Study ACE-536-β-THAL-001 (the BELIEVE trial).

Among patients receiving luspatercept, 94% were exposed for 6 months or longer and 72% were exposed for greater than one year.

Serious adverse events occurred in 3.6% of patients on luspatercept. Serious adverse events reported in 1% of patients were cerebrovascular accident and deep vein thrombosis. A fatal adverse event occurred in one patient treated with luspatercept who died due to an unconfirmed case of acute myeloid leukaemia.

Permanent discontinuation due to an adverse event (Grades 1 to 4) occurred in 5.4% of patients who received luspatercept. Most frequent adverse events requiring permanent discontinuation in patients who received luspatercept included arthralgia (1%), back pain (1%), bone pain (<1%), and headache (<1%).

Dosage reductions due to an adverse event occurred in 2.7% of patients who received luspatercept. Most frequent adverse events requiring dosage reduction in > 0.5% of patients who received luspatercept included hypertension and headache.

Dosage interruptions due to an adverse event occurred in 15.2% of patients who received luspatercept. Most frequent adverse reactions requiring dosage interruption in >1% of patients who received luspatercept included upper respiratory tract infection, alanine transaminase increase, and cough.

The most common adverse events (at least 10% for luspatercept and 1% more than placebo) were headache (26%), bone pain (20%), arthralgia (19%), fatigue (14%), cough (14%), abdominal pain (14%), diarrhoea (12%), and dizziness (11%).

Table 9: Study ACE-536-β-THAL-001 Adverse events (> 5%) in patients with beta-thalassaemia receiving luspatercept with a difference between arms of 1%

Body System Adverse Reaction	REBLOZYL (N=223)		Placebo (N=109)	
	All Grades n (%)	Grades ≥3[a] n (%)	All Grades n (%)	Grades ≥3 n (%)
Musculoskeletal and connective tissue disorders				
Bone Pain	44 (20)	3 (1)	9 (8)	0 (0)
Arthralgia	43 (19)	0 (0)	13 (12)	0 (0)
Infections and infestation				
Influenza	19 (9)	0 (0)	6 (6)	0 (0)
Viral Upper Respiratory Infection	14 (6)	1 (0.4)	2 (2)	0 (0)
Nervous system disorders				
Headache	58 (26)	1 (<1)	26 (24)	1 (1)
Dizziness	25 (11)	0 (0)	5 (5)	0 (0)
General disorders and administration site conditions				
Fatigue	30 (14)	0 (0)	14 (13)	0 (0)
Gastrointestinal disorders				
Abdominal Pain [b]	31 (14)	0 (0)	13 (12)	0 (0)
Diarrhea	27 (12)	1 (<1)	11 (10)	0 (0)
Nausea	20 (9)	0 (0)	6 (6)	0 (0)
Vascular disorders				
Hypertension [c]	18 (8)	4 (2)	3 (3)	0 (0)
Metabolism and nutrition disorders				
Hyperuricemia	16 (7)	6 (3)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders				
Cough	32 (14)	0 (0)	12 (11)	0 (0)

Table 10: Study ACE-536-β-THAL-001 Liver function laboratory abnormalities in patients with beta-thalassaemia

	REBLOZYL N = 223 n (%)	Placebo N = 109 n (%)
ALT ≥ 3 × ULN	26 (12)	13 (12)
AST ≥ 3 × ULN	25 (11)	5 (5)
ALP ≥ 2 × ULN	17 (8)	1 (<1)
Total bilirubin ≥ 2 × ULN	143 (64)	51 (47)
Direct bilirubin ≥ 2 × ULN	13 (6)	4 (4)

ALP = alkaline phosphatase; ALT = alanine aminotransferase;
AST = aspartate aminotransferase; ULN = upper limit of normal.

Comments on the Product Information

The Delegate highlighted the following warnings and that they should be included in the Australian PI.

Thrombosis/Thromboembolism

In adult patients with beta thalassaemia, thromboembolic events (TEE) were reported in 8/223 (3.6%) Reblozyl-treated patients. Reported TEEs included deep vein thromboses, pulmonary embolus, portal vein thrombosis, and ischemic strokes. Patients with known risk factors for thromboembolism, for example, splenectomy or concomitant use of hormone replacement therapy, may be at further increased risk of thromboembolic conditions. Consider thrombo-prophylaxis in patients with beta thalassemia at increased risk of TEE. Monitor patients receiving Reblozyl for signs and symptoms of thromboembolic events and institute treatment promptly.

Hypertension

Hypertension was reported in 10.7% (61/571) of Reblozyl-treated patients. Across clinical studies, the incidence of grade 3-4 hypertension ranged from 1.8% to 8.6%. In adult patients with beta thalassemia with normal baseline blood pressure, 13 (6.2%) patients developed systolic blood pressure (SBP) ≥ 130 mmHg and 33 (16.6%) patients developed diastolic blood pressure (DBP) ≥ 80 mmHg. In adult patients with MDS with normal baseline blood pressure, 26 (29.9%) patients developed SBP ≥ 130 mmHg and 23 (16.4%) patients developed DBP ≥ 80 mm Hg.

Monitor blood pressure prior to each administration. Manage new-onset hypertension or exacerbations of pre-existing hypertension using anti-hypertensive agents.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to luspatercept in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Of 284 patients with beta thalassemia who were treated with luspatercept and evaluable for the presence of anti-luspatercept-aamt antibodies, 4 patients (1.4%) tested positive for

treatment emergent anti-luspatercept antibodies, including 2 patients (0.7%) who had neutralising antibodies.

Of 260 patients with MDS who were treated with luspatercept and evaluable for the presence of anti-luspatercept antibodies, 23 patients (8.9%) tested positive for treatment-emergent anti-luspatercept antibodies, including 9 patients (3.5%) who had neutralising antibodies.

Luspatercept serum concentration tended to decrease in the presence of neutralising antibodies. There were no severe acute systemic hypersensitivity reactions reported for patients with anti-luspatercept antibodies in luspatercept clinical trials, and there was no association between hypersensitivity type reaction or injection site reaction and presence of anti-luspatercept antibodies.

Risk management plan

The sponsor has submitted EU-risk management plan (RMP) version 0.3 (dated 24 March 2020; data lock point (DLP) May 2018) and Australian specific annex (ASA) version 1.0 (dated 3 April 2020) in support of this application. At the second round of evaluation, the sponsor provided the approved EU-RMP version 1.0 (dated 12 May 2020; DLP May 2018) and an updated ASA version 2.0 (dated 14 December 2020).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 7.[51]

Table 11: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Thromboembolic events (TEEs; only in the beta-thalassaemia population with splenectomy)	ü*	ü†	ü	-
Important potential risks	Haematologic malignancies (including acute myeloid leukaemia)	ü*	ü†	ü	-
	Off-label use in paediatric patients (developmental toxicity of luspatercept)	ü	-	ü	-
	Use during pregnancy and lactation	ü*	-	ü	ü ‡

[51] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Missing information	Long-term safety	ü	ü†	-	-

* Follow-up questionnaires

† Clinical studies

‡ Healthcare Professional Checklist; Patient Card for women of childbearing potential only

The summary of safety concerns is the same as that recently approved by the European Medicines Agency (EMA).

Routine pharmacovigilance includes follow-up questionnaires; the form(s) for use in pregnancy and lactation require amendment. There is an ongoing (extension) study to obtain further information on long-term safety including haematological malignancy. The paediatric study is currently on hold, as directed by the European regulator.

Routine risk minimisation documents are generally acceptable from RMP perspective. The sponsor will provide additional risk minimisation documents (prescriber checklist; patient card) to address the risks of use during pregnancy. The Consumer Medicines Information (CMI) should be revised to align with the additional risk minimisation documents. The sponsor will conduct a study in Europe on the effectiveness of the prescriber checklist.

Risk-benefit analysis

Delegate's considerations

Myelodysplastic syndromes

In the pivotal trial, (Study ACE-536-MDS-001; MEDALIST trial) luspatercept showed superiority over placebo in all primary and key secondary analyses. The mean reduction in red blood cell units transfused was 5.3 units (95% confidence intervals: 3.6 to 7.1) compared to placebo during Weeks 1 to 24, and the effect was largely maintained in the second period of the study (Weeks 25 to 48). A small proportion of patients achieved a sustained response period of transfusion independence. There is some uncertainty on the long-term treatment effects as a large proportion of patients mainly from the placebo arm discontinued the study after Week 24. Secondary analyses of change in transfusion rates and red blood cell units as well as in serum ferritin using appropriate imputation methods are in support of the primary and key secondary analyses. Although haemoglobin levels did not increase significantly over time, secondary analyses indicate that the reduction in transfused red blood cell units does not come at the expense of a decrease in haemoglobin.

The safety profile of luspatercept shows a manageable adverse event profile. No signal for an increase in progression to/ time to progression to high risk myelodysplastic syndrome or acute myeloid anaemia was identified. However, due to the still limited duration of exposure, uncertainty remains with regard to long-term safety, which has to be addressed by continuing surveillance.

Beta-thalassaemia

Superiority of luspatercept over placebo in all primary and key secondary analyses has been established. Some patients, the so called 'responders' achieved a substantial reduction in red blood cell transfusion needs; the number of responders was only around

20%, however. The effect on red blood cell transfusions is considerably smaller in the average patient, but also robust and clinically relevant. The effect appeared durable over the 96-week treatment period.

Responses favouring luspatercept over placebo were fairly consistent across subgroups. There is some uncertainty on the effect on iron overload, as liver iron content did not drop considerably during 96 weeks of luspatercept treatment. Longer observation might be needed to quantify the effect.

The safety data shows a manageable adverse event profile of luspatercept. However, duration of exposure is still limited to a median treatment duration of about 84 weeks (maximum 231 weeks), while long-term treatment over many years or even decades might be foreseen in a patient population requiring transfusions from a very young age onwards.

The remaining uncertainties with regards to long-term safety and durability of the beneficial effects are especially relevant for this indication considering the rather young population and chronic use and will need to be addressed by continuing surveillance.

Conclusions

The overall benefit versus risk balance of Reblozyl (luspatercept) in adult patients with transfusion dependent myelodysplastic syndrome and beta-thalassaemia is positive.

All clinical experts agree (see section: Independent expert advice, below) that luspatercept has demonstrated clinical benefit in myelodysplastic syndrome and beta-thalassaemia which is relevant in the Australian clinical context.

Proposed action

The Delegate recommends approval of luspatercept for the indications below.

After receiving expert clinical advice and noting that erythropoiesis-stimulating agents (ESAs) are not approved for treatment of anaemia associated with myelodysplastic syndrome in Australia, it is recommended that the indication for myelodysplastic syndrome is modified based on the rationale below.

It is reasonable to extrapolate the clinical trial data to include initial therapy (by making the indication neutral on treatment phase), provided the proposed treatment is for intermediate or lower risk myelodysplastic syndrome with ringed sideroblasts. This would make the indication:

> *Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia (requiring 2 or more RBC units over 8 weeks) due to very low, low and intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS).*
>
> *Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia associated with beta thalassaemia.*

Independent expert advice

The Delegate received the following independent expert advice.

Advice from the first expert:

1. ***Do you think that the pivotal studies in myelodysplastic syndrome and beta-thalassaemia demonstrate clinically meaningful treatment effects of luspatercept which are relevant for the Australian context?***

Study ACE-536-MDS-001 (MEDALIST trial) had the following key characteristics:

Included population: The inclusion criteria required failure of or inappropriate for (defined by high erythropoietin levels) erythropoiesis stimulating agent (ESA) therapy. Patients were required to have at least two units each 8 weeks during screening. Erythropoiesis stimulating agents (erythropoietin analogues) are not approved for use in myelodysplastic syndromes in Australia. This may have precluded consideration of Australian sites. However, in other respects the population is similar to what would be expected for long-term transfusion dependent low risk myelodysplastic syndrome patients in Australia, including age and male predominance. There was a heterogeneity of baseline pretransfusion haemoglobins, which reflects variability in practice likely to be similar in Australia due to the lack of a firm trigger,[52] but the levels were within a range recommended by national guidelines.[53]

Outcomes: Transfusion independence is a clinically relevant outcome. Once transfusion dependent, most patients need transfusions every 3 to 4 weeks. Shorter intervals are occasionally required. Longer intervals rarely exceed 6 weeks, so the endpoint of > 8 weeks transfusion free is reasonable. Anaemia has a significant impact on quality of life and so does having transfusion. The mean increase in haemoglobin in 'responders' was quite significant at 25.5 g/L. While quality of life is not reported, the improvement in haemoglobin is likely to result in improved quality of life as are periods of transfusion independence.[54] Reduction in transfusion has been considered a meaningful endpoint due to the potential adverse effects of transfusion.[56]

Fatigue was higher in treatment group compared with placebo, despite improvements in haemoglobin. Dizziness, back pain were manageable side effects that decreased over time. No signal for serious adverse events was noted, although the treated population is relatively small. This pivotal study therefore demonstrates clinically meaningful data in a population similar to that observed in Australia, with the significant exception that ESA therapy is not standard or common in Australia.

Study ACE-536-β-THAL-001 (BELIEVE trial) had the following characteristics:

The included population of beta-thalassaemia or haemoglobin E beta-thalassaemia (15.5%) matches the requested indication. Beta-thalassaemia is heterogenous, with variable severity and transfusion requirements depending on whether there is any (β^+) or no (β^0) beta globin production. –Alpha-thalassaemia is not included in the study population. Patients had to be having transfusions every 35 days or less. This matches the typical needs of Australian patients. There were four Australian sites included in this study.

Outcomes: The primary objective is adequate to (> 33% reduction in transfusion requirements over a 12 week period) to demonstrate efficacy, when compared to placebo, indicating a significant reduction in transfusion requirements, however it could be suggested the magnitude of benefit is best determined over a longer period. The short duration may mean some patients meet the endpoint based on scheduling. For example, a patient with transfusions every 4 weeks would have a 33.3% reduction in the number of red cells transfused if one transfusion was delayed (therefore meeting the primary endpoint in that period). If the therapy was not effective this would lead to an increase in the number of transfusions in the subsequent period as the delayed (rather than reduced) transfusion would be captured in the subsequent period. The converse is also true if a transfusion is brought forward.

A reduction of > 33% over a longer period is clinically meaningful as it would be expected to improve quality of life directly through reduced transfusions and to reduce the additional iron burden. The secondary outcomes were dependent on the primary outcome being met. Having sequential 12 week periods where the benefit was seen in any 12 week period is likely to compound the issue noted above and in the expert's opinion, the expert would consider this a poor indicator of the magnitude of benefit. 29.5% of placebo showed

a 'benefit' over any 12 week period, with this effect largely eliminated over a longer observation period of any 24 week interval (2.7%). This period is likely to be a better indicator of efficacy (41.1%) than either of the shorter periods (including the primary outcome) or the 'any 2 week interval' secondary endpoint. Most secondary endpoints were entirely consistent with the treatment effect found in the primary outcome. While ferritin levels were decreased in the treatment arm, this did not translate to reduced tissue iron stores. However, a longer period is likely to be needed to ascertain this effect.

Safety: An increased risk of thrombotic (arterial and venous) events was seen in this study treatment population not seen in the myelodysplastic syndrome study. The high rate of splenectomy (a known thrombotic risk factor) may be a contributing factor in this group (noting that all patients with thrombotic events were asplenic). This is a known risk with erythropoiesis stimulating agents so the effect may be due to increased haematocrit in the treatment population, however increased peripheral haemolysis (unconjugated bilirubin increased in the treatment group and increased haemolysis would be expected with red cell loss which is delayed from the marrow to the peripheral blood) or other unknown mechanisms may also play a role. This will need to be monitored in the ongoing studies and postmarketing. Despite the potential difficulty with ascertaining the magnitude of effect from the primary outcomes, the thalassaemia study demonstrates consistent improvements in clinical outcomes relevant to Australian populations.

2. Is the proposed second line indication for luspatercept in myelodysplastic syndromes appropriate in Australia where erythropoiesis stimulating agents are not TGA-approved to treat the anaemia associated with myelodysplastic syndromes?

The proposed indications are appropriate for the data available, however as noted above and flagged by the Delegate, do not match clinical practice in Australia.

The second line indication for myelodysplastic syndromes is problematic in Australia as erythropoiesis stimulating agents (ESA) are not approved for use in myelodysplastic syndromes. The acceptance of only a second line indication, subsequent to ESA failure, would have two implications:

- It would essentially endorse therapeutic efficacy of ESAs (as a group, not as individual agents) for this indication without a formal assessment of any ESA for this purpose;
- It would effectively preclude the use of luspatercept for its licenced indication unless an unlicenced therapy is used or it is used 'off-label' as initial therapy. This would also preclude funding, should the sponsor choose to seek Pharmaceutical Benefits Scheme listing.

The data presented for myelodysplastic syndromes shows efficacy in a population that has already failed (or thought unlikely to respond to) ESAs. There seems no reason to suspect that responses are unique to that group. While ESAs enhance erythropoiesis through increased erythroid differentiation, erythropoietin is also required to prevent apoptosis in later erythropoiesis, the stages where luspatercept is active. One would expect (although it is not proven and cannot be assumed) that responses are likely to be equivalent or lower in a group that has failed a prior therapy than in a first line setting. To put this another way, there is no reason to suspect that patients who are ESA responsive are less likely to respond to luspatercept. It is likely that the study design has been informed by international practice and regulation. As there is already effective first line therapy licenced in the USA and Europe, a trial in this setting would have required an active ESA comparator, whereas the current study has shown efficacy against placebo. This is an appropriate comparator in the Australian setting where there is no effective first line therapy. In the expert's opinion, it would be reasonable to extrapolate the data to include initial therapy (by making the indication neutral on treatment phase), provided the

proposed treatment is for intermediate or lower risk myelodysplastic syndromes with ringed sideroblasts. This would make the indication:

> *Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia (requiring 2 or more RBC units over 8 weeks) due to very low, low and intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS).*

Alternatively, ESA's could be assessed, which may increase the therapeutic options available in Australia.

Advice from the second expert:

1. ***Do you think that the pivotal studies in myelodysplastic syndromes and beta-thalassaemia demonstrate clinically meaningful treatment effects of luspatercept which are relevant for the Australian context?***

Myelodysplastic syndrome is a clonal bone marrow disorder that manifests with cytopaenias, the most common of which is anaemia. Supportive care with transfusion is the backbone of therapy. Transfusion carries significant burdens of secondary iron overload and is a burdensome treatment requiring time in hospital and cycles of patient's physical improvement and then deterioration related to time since last transfusion. The only other treatment option currently for myelodysplastic syndromes patients is lenalidomide, for myelodysplastic syndrome patients with transfusion dependent anaemia due to low with 5q- or intermediate-1 risk MDS syndromes. There was not a direct comparison with lenalidomide and luspatercept provided by the sponsor. Erythropoiesis stimulating agents (ESAs) are only available to a select group of patients with MDS who have concomitant renal insufficiency. There is a need for improved treatment in this group of patients.

The pivotal study in myelodysplastic syndromes for luspatercept is presented in the paper by Fenaux et al.,**Error! Bookmark not defined.** provided with the Delegates overview. This paper reports the results of a Phase II clinical trial of low risk myelodysplastic syndromes (Study A536-05) and Study ACE-536-MDS-001 (MEDALIST trial), a Phase III trial evaluating the safety and efficacy of luspatercept in patients with IPSS-R lower risk myelodysplastic syndrome with ring sideroblasts who were requiring regular transfusions and who were refractory or unlikely to respond to erythropoietin based therapy.

In these studies, luspatercept was demonstrated to be superior to placebo in all primary and secondary analyses. The primary endpoint was transfusion independence for 8 weeks or longer during weeks 1 to 24. The secondary endpoint was transfusion independence for 12 weeks or longer assessed during weeks one through 48 and weeks one through 24. Other secondary endpoints were erythroid response as measured by the IWG 2006 criteria, longest duration of primary response, mean increase in haemoglobin levels of at least 1.0 g/dL, progression to acute myeloid leukaemia, mean change in the serum ferritin level and safety analysis.

For patients who are transfusion dependent with myelodysplastic syndrome, achievement of transfusion independence or a clinically significant reduction in transfusion requirement would be an important result. Frequent transfusions not only are a practical burden of treatment but also result in increased iron overload and greater time experiencing fatigue prior to the next transfusion cycle. This reduction of transfusion dependence would need to be sustained to be of a significant clinical benefit.

Fenaux et al.;***Error! Bookmark not defined.*** report that 38% of the treatment group had transfusion independence for 8 weeks or longer as compared with 13% in the placebo group. This response was most pronounced for patients in the group receiving the least transfusions pretrial entry (80% receiving less than four units per 8 weeks, 37% who were receiving 4 to 6 units per 8 weeks and only 9% of patients receiving greater than six units per 8 weeks pretrial entry). There was a mean reduction in the red cell units of 3.6 to

7.1 units compared to placebo during weeks 1 to 24 (mean -5.3 units) and this effect was stable through the second part of the study though to week 48. There was a very small proportion of patients who achieved long term transfusion independence. The significance of the longer term outcomes was unclear due to the lack of a clear comparator with the majority of placebo patients being withdrawn from study after week 24. The secondary analyses supported the primary endpoint.

The measured reduction in transfusion burden if translated to the current clinical environment would reduce transfusion burden most in the group of patients with the least need (those with less than four units per 8 weeks) however the longer term effect of this would be to delay the onset of transfusion dependence and reduce the longer term complications of transfusion such as iron overload and red cell antibody formation, as well as a reduction in use of hospital resources, supply of red blood cell concentrates and a likely improved quality of life due to reduction of both time in hospital and a more stable haemoglobin achieved by the transfusion independence.

This would be a significant improvement for this patient population and allow a proportion independence from transfusion or reduction in transfusion with the associated benefits.

Beta-thalassaemia is an inherited disorder of haemoglobin production resulting in an absence or mutation in the beta-globin gene that causes an inability of the haemoglobin molecule to effectively carry oxygen when inherited in a homozygous pattern. Patients are transfusion dependent from a young age (generally before the second birthday) and remain so lifelong. There is a subgroup of patients with a beta-thalassaemia intermedia who are only transfusion dependent as they age or face physiological challenges such as illness as adults.

The transfusion dependence in beta-thalassaemia results in significant issues with iron overload that are manifest as hepatic and cardiac iron deposition and resultant organ failure, heart, liver and endocrine organs if not actively managed with iron chelation. Patients with beta-thalassaemia major spend significant amounts of time in the hospital receiving transfusions (two or three units of red cells, two or three weekly is typical) and administer iron chelation either orally or subcutaneously daily at home. All iron chelators have known adverse events that require close monitoring. Most patients with beta-thalassaemia major have long term complications of their disease that are directly related to the long-term effects of iron overload.

The pivotal study (Study ACE-536-β-THAL-001; BELIEVE trial) in beta-thalassemia major of luspatercept is presented in Cappellini et al.,[48] which reports a Phase III clinical trial of adults with transfusion-dependent beta-thalassaemia receiving luspatercept versus placebo in combination with best supportive care. The primary end point was the percentage of patients with a reduction in the transfusion burden of at least 33% from baseline during weeks 13 through to week 24 plus a reduction of at least two red cell units over the 12 week interval. Secondary endpoints included the transfusion burden and iron overload parameters.

The patient population was broadly representative of the Australian population with beta-thalassaemia, and transfusion dependence was defined as the receipt of 6 to 20 units of red cells in the 24 weeks prior to randomisation and no transfusion free period during that time of > 35 days.

The primary endpoints of the study were met with more patients receiving luspatercept achieving a reduction in the burden of red cell transfusions (> 33% reduction from baseline) as compared to the placebo (21.4% versus 4.5% respectively). This was both during weeks 13 to 24 and again seen in weeks 37 through 48 with a reduction of at least two red cell units over this 12 week interval. This reduction in transfusion burden was the same in all subgroups including patients with severe disease, with a high transfusion

burden or with β^0/β^0 gene mutation. Additionally, patients had a reduction in the serum ferritin but no reduction in liver iron loading was seen.

For the average patient in this clinical trial, this equates to a reduction of approximately 7 to 8 red cell units over a 6 month period, either giving patients less units with each visit or increasing the duration of time between visits. Considering for most patients with transfusion-dependent beta-thalassaemia would receive 15 to 20 red cell units in this 6 month period this is a clinically significant difference which would improve quality of life, reduce the time in hospital and resource utilisation (including use of red cell units) and equate to less time in hospital for patients with a chronic lifelong burden of disease.

Importantly the ability to manage iron overload is also improved with a reduction in ferritin presumably through the reduction in transfusion which has a direct relationship to iron overload. Ferritin is the standard measure of iron load and is the benchmark by which iron chelation therapy is assessed and adjusted. Reduction of ferritin should result in less risk of cardiac and hepatic iron overload and a reduction in the use of iron chelation therapy. It is not surprising the clinical trial does not demonstrate a reduction in hepatic iron overload as this is a longer term measure of iron deposition and the timeframe of the clinical trial is too short to demonstrate such an outcome. Management of iron overload is one of the biggest challenges in patients with transfusion-dependent beta-thalassaemia and a reduction in this burden is of significant clinical advantage for patients.

2. ***Is the proposed second line indication for luspatercept in myelodysplastic syndromes appropriate in Australia where erythropoiesis stimulating agents are not TGA-approved to treat the anaemia associated with myelodysplastic syndrome?***

In Australia the indications for use of erythropoiesis stimulating agents (ESAs) are restricted by both the listing on by the TGA and the Prescribing Benefits Scheme (PBS) eligibility criteria. Common to both is the listing for patients with chronic renal insufficiency and anaemia. The TGA listing is broader also including the treatment of anaemia and reduction of transfusion requirements in patients with nonmyeloid malignancies where anaemia develops because of concomitantly administered chemotherapy. Effectively neither include patients with myelodysplastic syndromes with the exception of patients who may have concomitant chronic renal impairment.

Hence the listing as 'second line' is inappropriate for the majority of patients with myelodysplastic syndromes who do not have access to an ESA. As the listing is written however it does consider that patients will reach this second line status by being ineligible for use of an ESA as well as having failed an ESA and hence does not exclude any patients. A first line listing would need to consider the efficacy and safety of a potential combination of an ESA and luspatercept or specifically exclude the use in combination.

Advice from the third expert:

1. ***Do you think that the pivotal studies in myelodysplastic syndrome and beta-thalassaemia demonstrate clinically meaningful treatment effects of luspatercept which are relevant for the Australian context?***

Yes, the expert's opinion is based on review of the Delegate's summary, the published literature, and this expert's own clinical and research experience, as outlined and referenced below, along with some comments on the Australian context.

Background: New therapies for myelodysplastic syndromes and beta-thalassaemia major are urgently required. Few curative options exist (such as allogeneic haematopoietic stem cell transplantation (HSCT) for both the myelodysplastic syndromes and thalassaemias, or gene therapy for thalassaemia), and where they do the majority of patients are either not clinically suitable to receive them (for example, due to age or comorbidities), or they have no access for a variety of reasons (such as availability of an HSCT donor, cost, or regulatory

reasons. For example, erythropoiesis stimulating agents (ESAs) are not approved for myelodysplastic syndrome-associated anaemia in Australia). While the outlook for patients with these conditions has improved over recent decades as both diagnosis and supportive care have improved and some new therapies have become available (for example, lenalidomide for myelodysplastic syndrome), health related quality of life remains poor for many people living with these disorders, due to both their underlying disease and the complexities and complications of current therapies, as outlined in the Delegate's overview.

Transfusion supportive care is a mainstay of management for patients with lower risk myelodysplastic syndromes and beta-thalassaemia major and improves some aspects of quality of life. Transfusion support depends on availability of safe blood for transfusion and is readily available in high income countries such as Australia. However, regular red blood cell transfusion every few weeks (typically every 2 to 6 weeks for transfusion dependent patients) over months to years (for myelodysplastic syndrome) or decades (for thalassaemia major) is time consuming and burdensome for patients and families. Many aspects of optimal red blood cell transfusion support remain uncertain and are not evidence based, and complications are relatively common.[52,53,54,55] The financial and other costs of providing long-term transfusion support, and of preventing and managing its complications (especially, in these settings, iron overload and alloimmunisation), are substantial for patients and the community, although poorly documented.[56,57]

Anaemia in myelodysplastic syndromes: Anaemia is very common in patients with myelodysplastic syndromes and occurs due to a combination of bone marrow failure and ineffective erythropoiesis. Haemoglobin concentration is reported to have the greatest single impact on quality of life.[52,58] Both anaemia and transfusion-dependency influence prognosis (progression and survival) in MDS: degree of anaemia likely reflects underlying disease and has been incorporated into prognostic scoring systems. Anaemia itself is associated with worse survival overall, and non-myelodysplastic syndrome/leukaemia and cardiac causes of death, possibly due in part due to cardiac hypertrophy and remodelling from cardiac dysfunction from disease related iron dysregulation and transfusion-related iron overload also contribute.[52,59,60,61]

Definition of transfusion dependency in myelodysplastic syndrome: In Study ACE-536-MDS-001 (MEDALIST trial), patients were eligible if they 'had been receiving regular red cell transfusions (≥ 2 units per 8 weeks during the 16 weeks before randomisation)' and the primary endpoint of the trial was 'transfusion independence for 8 weeks or longer during weeks 1 through 24'

[52] Wood, E. et al. Outpatient transfusions for myelodysplastic syndromes, *Hematology Am Soc Hematol Educ Program*. 2020; 2020(1): 167-174.
[53] Stanworth, S. et al. Red cell transfusion in outpatients with myelodysplastic syndromes: a feasibility and exploratory randomized trial (REDDS), *Br J Haem* 2020; 189(2): 279-290.
[54] Narayan, S. et al. On behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2020 Annual SHOT Report (2021). Available at Shotuk website.
[55] Compernolle, V. et al. International Collaboration for Transfusion Medicine Guidelines. Red blood cell specifications for patients with hemoglobinopathies: a systematic review and guideline, *Transfusion*, 2018; 58(6): 1555-1566.
[56] McQuilten, Z. et al. The cost of blood: a study of the total cost of red cell transfusion in patients with beta thalassaemia using time-driven activity-based costing, *Transfusion* 2019; 59: 3386-3395.
[57] Burns, K. et al. A time-driven, activity-based costing methodology for determining the costs of red blood cell transfusion in patients with beta thalassaemia major, *Transfus Med*, 2019; 29: 33-40.
[58] Stauder, R. et al. Health-related quality of life in lower-risk MDS patients compared with ageand sex-matched reference populations: a European LeukemiaNet study. *Leukemia*, 2018; 32: 1380–1392
[59] De Swart, L. et al. Management of 1000 patients with low- and intermediate-1 risk myelodysplastic syndromes in the European LeukemiaNet MDS Registry, *Leuk Res*, 2011; 35: S3.
[60] Platzbecker, U. Treatment of MDS. *Blood*, 2019; 133(10): 1096-1107.
[61] Germing, U. et al. Treatment of anemia in transfusion-dependent and nontransfusion-dependent lower-risk MDS: current and emerging strategies, *HemaSphere*. 2019; 3(6): e314.

Extracts from the US FDA approved indications for luspatercept note that in myelodysplastic syndromes it is: 'for the treatment of an[a]emia failing an erythropoiesis stimulating agent and requiring two or more red blood cell units over 8 weeks' and in the EU, 'for the treatment of adult patients with transfusion dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy'.

The wording in each case is slightly different from the trial endpoint definition. There is no internationally agreed definition of transfusion dependency in myelodysplastic syndromes. In a recent review of transfusion support for myelodysplastic syndromes,[52] it was noted:

> 'Various definitions of RBC [red blood cell] transfusion dependency in MDS have been proposed, recently reviewed by Germing et al.[62] These include requirements for two RBCs per month, RBC transfusion three or more times in a year, and other variations which include minimum numbers of RBCs or admissions per defined time period – with these definitions being variably applicable either in the routine clinical management setting, in analysis of administrative datasets, or for determining entry or response criteria for clinical trials. Transfusion intensity can be further described as low (3 to 7 RBCs per 16 weeks) or high (≥ 8 RBC per 16 weeks), and patients can be described either as not being transfusion dependent or as having low, medium, or high transfusion burden or dependency. These definitions can be helpful for research purposes but are probably less useful in day-to-day practice, except for the purpose of prognostication'.

And, in the same review:

> 'Management of transfusion dependency in MDS is a real conundrum:
>
> Transfusions are given with the aim of relieving symptoms, and indeed they can do so, but they provide only transient benefits related to the circulating lifespan of the transfused cells. They also carry the risks of both transfusion related adverse effects and MDS associated consequences: If you have MDS, being anaemic or thrombocytopenic makes things worse for you, but being RBC or platelet transfusion dependent has itself been shown to be associated with worse prognosis, regardless of when it develops and even at low dose density.
>
> This association may relate in part to the underlying disease (the worse the ineffective hemopoiesis, the worse the consequences and the worse the prognosis) but also to the transfusion and its sequelae'.

Therefore, treatment of anaemia in myelodysplastic syndromes is a priority, and finding and making available alternatives to transfusion for treatment of transfusion-dependent anaemia in myelodysplastic syndrome are also priorities, with the potential to improve patient quality of life and survival setting of anaemia.[63,64,59]

Anaemia in beta-thalassaemia major: The anaemia in *β*-thalassaemia major is characterised by ineffective erythropoiesis and chronic haemolysis; these lead to extramedullary haematopoiesis followed by development of hepatosplenomegaly and bone marrow expansion, and their diverse consequences. Regular red blood cell transfusion, generally lifelong starting in infancy, serves both to alleviate symptoms of anaemia and to suppress dysfunctional erythropoiesis. Iron accumulation occurs both due

[62] Germing, U. et al. Treatment of anemia in transfusion-dependent and nontransfusion-dependent lower-risk MDS: current and emerging strategies, *HemaSphere*. 2019; 3(6): e314.
[63] Oliva, E. et al. Hemoglobin level threshold for cardiac remodeling and quality of life in myelodysplastic syndrome, *Leuk Res*, 2005; 29(10): 1217-1219.
[64] Oliva, E. et al. A review of anemia as a cardiovascular risk factor in patients with myelodysplastic syndromes, *Am J Blood Res*, 2011; 1(2): 160-166.

to transfusional iron overload, and increased gastrointestinal iron absorption, resulting in multisystem organ dysfunction – especially hepatic, cardiac and endocrine abnormalities.[65]

Compliance with iron chelation has historically been very challenging, so many older patients are living with significant iron overload and end-organ damage. The availability of newer, oral iron chelators has improved compliance, but some iron loading typically still occurs, and although serious adverse effects are rare, they do occur; less serious adverse events are quite common and require monitoring, as outlined in the Delegate's review.

Other complications of transfusion in this setting include alloimmunisation to red blood cell antigens, which cause both acute and delayed haemolytic transfusion reactions.[55,65] Alloimmunisation may result in difficulty in supplying compatible blood and lead to delays in patient care, as reported by international haemovigilance systems; however few haemovigilance data are available in Australia.

Definition of transfusion-dependency in beta-thalassaemia major: The extract from the FDA approved indications for luspatercept notes that it is used in beta-thalassaemia: 'For the treatment of anaemia in adult patients with [beta] *β*-thalassaemia who require regular red blood cell (RBC) transfusions' and in the EU: 'For the treatment of adult patients with transfusion dependent anaemia associated with *β*-thalassaemia'.

As above for myelodysplastic syndromes, there is no internationally agreed definition of transfusion dependency in thalassaemia. In their recently updated guidance on management of transfusion-dependent thalassaemia;[66] the Thalassaemia International Federation (TIF) outline 'Criteria for initiating transfusion therapy' and note that:

> 'for deciding whom to transfuse, the following should be included in the investigations:
>
> – Confirmed diagnosis of thalassaemia.
> – Laboratory criteria: Haemoglobin level (Hb) < 70 g/L on two occasions, > 2 weeks apart (excluding all other contributory causes such as infections) and/or
> – Clinical criteria irrespective of haemoglobin level
> – Significant symptoms of anaemia
> – Poor growth / failure to thrive
> – Complications from excessive intramedullary haematopoiesis such as pathological fractures and facial changes
> – Clinically significant extramedullary haematopoiesis'.

Thalassaemia International Federation recommends to 'transfuse every 2 to 5 weeks, maintaining pretransfusion haemoglobin above 90-105 g/L or up to 110-120 g/L for patients with cardiac complications'; however, no definition of transfusion dependency is provided. Extended red blood cell antigen matching is recommended by TIF and other authorities to reduce alloimmunisation and is now widely practised.

Treatment of anaemia in transfusion-dependent beta-thalassaemia major is therefore a priority and finding and making available alternatives to transfusion for treatment of anaemia are also priorities, with the potential to improve patient quality of life and survival. How transfusion dependency should be defined for the purposes of clinical management and regulatory review in the thalassaemia setting remains uncertain.

[65] Crighton, G. et al. Haemoglobin disorders in Australia: where are we now and where will we be in the future? *Intern Med J*, 2016; 46(7): 770-779.
[66] Capellini, M. et al; Thalassaemia International Federation: Guidelines for the clinical management of transfusion-dependent thalassaemia, 4th edition, 2021.

The Australian context: Myelodysplastic syndromes and beta-thalassaemia major are important issues for Australian patients and the Australian healthcare system; however, few data are available on the epidemiology, clinical management, costs of care, or outcomes for Australian patients with either diagnosis.

For myelodysplastic syndromes, Australian institute of health and welfare (AIHW) and cancer registry numbers are likely underestimates, as definitive studies (for example, bone marrow examination, cytogenetics) are not performed in all patients. In a study of 3149 incident cases of myelodysplastic syndromes from the Victorian admitted episode dataset (VAED), the age standardised incidence rate was higher than reported from local cancer registries (for 2007 9.6 per 100,000 (95% confidence interval (CI), 9.2 to 10.0) versus 4.8). Median age was 79 years and 34.6% were transfusion dependent. Interestingly, transfusion-dependent myelodysplastic syndrome was associated with new diagnoses of congestive heart failure (incident rate ratio 1.92; 95% CI, 1.41 to 2.60), as well as with bacterial and fungal infections, and with leukaemia and sepsis as causes of death.[67]

Furthermore, in a related study linking VAED and Victorian Cancer Registry (VCR) data,[68] it was identified that many patients were missed by each of these data sources: the two source capture-recapture method used here estimated that there were 948 additional cases not captured in one of the two data sources, bringing the total number of incident cases in the population (Victoria) for the period of 2003 through 2010 to 5202. Using both data sources, the age standardised incidence rate was 10.1 per 100,000 (95% CI 9.6 to 10.5). Cases not reported to the VCR were more likely to require red blood cell transfusion (which may explain why they were identified in the VAED data). Overall, 22% of patients were transfusion-dependent.

For beta-thalassaemia, a 2016 review noted that 'Australia has no local data on incidence, prevalence, therapy, healthcare costs or outcomes for people living with haemoglobinopathies'.[65] This remains the case at a national level, although the Australian haemoglobinopathy registry now has pilot data from 10 hospitals on more than 340 patients with beta-thalassaemia major, intermedia with major phenotype, and haemoglobin E disease/beta-thalassaemia compound heterozygotes (data accepted for presentation, BLOOD 2021 conference, September 2021). This does not represent the true national burden of disease from thalassaemia major in Australia, as not all hospitals are on the registry and/or have not yet entered data. Analysis of available registry data in 2018,[69] showed that 97% of beta-thalassaemia patients received regular transfusions, and that adult beta-thalassaemia patients received a median of 3 (interquartile range: 2.5, 3) red blood cells per transfusion, on average every 4 weeks.

Alloantibodies to red blood cell antigens were identified in 32% of beta-thalassaemia patients on the registry.

Review of trial data in the Delegate's summary: In Study ACE-536-MDS-001 (MEDALIST trial in myelodysplastic syndromes), the primary outcome was transfusion independence, and the results were very positive. Furthermore, even where patients did not achieve complete transfusion independence, many achieved haematologic improvement, here defined as mean haemoglobin increase of 1.5 g/dL for 8 weeks in the absence of red blood cell transfusion, which is likely to be meaningful. Not surprisingly, patients with the lowest transfusion burden achieved the best responses: 'When evaluated according to the baseline transfusion burden, transfusion independence for 8 weeks or longer in the

[67] McQuilten, Z. et al. Myelodysplastic syndrome incidence, transfusion dependence, health care use, and complications: an Australian population-based study 1998 to 2008, *Transfusion* 2013; 53(8): 1714-1721.
[68] McQuilten, Z. et al. Underestimation of myelodysplastic syndrome incidence by cancer registries: Results from a population-based data linkage study, *Cancer*, 2014; 120(11): 1686-1694.
[69] Waters, N. et al. The Australian Haemoglobinopathy Registry: 2018 Snapshot. *Blood*, 2018, abstract P243.

luspatercept group occurred in 80% of the patients (37 of 46) who had been receiving less than four units per 8 weeks, in 37% of those (15 of 41) who had been receiving 4 to less than six units per 8 weeks, and in 9% of those (6 of 66) who had been receiving at least six units per 8 weeks'.

While reductions in serum ferritin were modest, they were both statistically and clinically significant and when compared to the increases seen in the patients on placebo.

Although improvements in quality of life were not demonstrated in this trial, reduction in ongoing transfusion requirements and requirement for frequent hospital visits would be welcomed by most patients and hospitals.

In Study ACE-536-B-THAL-001 (BELIEVE trial in beta-thalassaemia major), the primary outcome measure was a ≥ 33% reduction from baseline in transfusion burden (red blood cell/time) with a reduction of at least two units of red blood cells. Again, the results were very positive.

Responses were quite rapid in both trials, and, for responders, were generally sustained for extended periods.

Safety data provided were reviewed and this expert agrees that these are acceptable. However, long term safety data are not yet available and will be important for these patient groups, especially in beta-thalassaemia major, where it could be anticipated that patients may be receiving the therapy for many years or decades outside the setting of clinical trials, and therefore monitoring will be less frequent and less intensive.

Luspatercept is subcutaneously administered every 21 days. This is likely to be manageable for patients and families and provide greater patient autonomy and satisfaction in management of their condition.

2. ***Is the proposed second-line indication for luspatercept in myelodysplastic syndromes appropriate in Australia where erythropoiesis stimulating agents are not TGA-approved to treat the anaemia associated with myelodysplastic syndromes?***

Yes, in Study ACE-536-MDS-001 (MEDALIST trial), participants had disease that was refractory to or unlikely to respond to erythropoiesis stimulating agents (ESAs) or had discontinued treatment due to ESA intolerance. Since ESAs are not approved in Australia, and better therapies are needed to improve outcomes for patients with myelodysplastic syndromes, it is reasonable to consider this alternate therapy.

Advisory Committee considerations[70]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

[70]The ACM provides independent medical and scientific advice to the Minister for Health and the TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre market and post-market functions for medicines. Further information can be found here: https://www.tga.gov.au/committee/advisory-committee-medicines-acm

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Reblozyl (luspatercept) 25 mg and 75 mg, powder for injection, vial, indicated for:

> *Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia (requiring 2 or more RBC units over 8 weeks) due to very low, low and intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS).*
>
> *Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia associated with beta thalassaemia.*

Specific conditions of registration applying to these goods

- Reblozyl (luspatercept) is to be included in the Black Triangle Scheme. The PI and CMI for Reblozyl must include the black triangle symbol and mandatory accompanying text for 5 years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Reblozyl European Union (EU) risk management plan (RMP) (version 1.0, dated 12 May 2020, data lock point May 2018), with Australian specific annex (version 2.0, dated 14 December 2020), included with submission PM-2020-01706-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
- Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.
- The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.
- Laboratory testing & compliance with Certified Product Details (CPD)
  - All batches of 334510 Reblozyl luspatercept 25 mg powder for injection vial and 334511 Reblozyl luspatercept 75 mg powder for injection vial supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the CPD.
  - When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.
- The CPD, as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Attachment 1. Product Information

The PI for REBLOZYL approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

REBLOZYL® (LUSPATERCEPT)

1 NAME OF THE MEDICINE

Australian Approved Name: luspatercept

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

REBLOZYL 25 mg powder for injection

Each vial contains 25 mg of luspatercept. After reconstitution, each mL of solution contains 50 mg luspatercept.

REBLOZYL 75 mg powder for injection

Each vial contains 75 mg of luspatercept. After reconstitution, each mL of solution contains 50 mg luspatercept.

Luspatercept is a protein produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder for injection.

White to off-white lyophilised powder, free of visible foreign matter.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

REBLOZYL is indicated for the treatment of adult patients with transfusion-dependent anaemia (requiring 2 or more RBC units over 8 weeks) due to very low, low and intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS).

REBLOZYL is indicated for the treatment of adult patients with transfusion-dependent anaemia associated with beta thalassaemia.

Limitation of Use

REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anaemia.

4.2 DOSE AND METHOD OF ADMINISTRATION

REBLOZYL treatment should be initiated and monitored under the supervision of a physician experienced in the treatment of haematological diseases.

Treatment with REBLOZYL should be continued or modified based upon clinical and laboratory findings. Treatment should be continued as long as the patient is deriving clinical benefit from treatment.

Patients must have their haemoglobin (Hb) assessed and have results available prior to each administration. If an RBC transfusion occurred prior to dosing, the pre-transfusion Hb must be considered for dosing purposes.

If the pre-dose Hb is ≥ 115 g/L in the absence of transfusion for at least 3 weeks, delay dosing until the Hb is ≤ 110 g/L.

Dosage

Myelodysplastic Syndromes (MDS)

The recommended starting dose of REBLOZYL is 1.0 mg/kg once every 3 weeks by subcutaneous (SC) injection.

In patients who are not RBC transfusion-free after at least 2 consecutive doses at the 1.0 mg/kg starting dose, the REBLOZYL dose should be increased to 1.33 mg/kg. If patients are not RBC transfusion-free after at least 2 consecutive doses at the 1.33 mg/kg dose level, the REBLOZYL dose should be increased to 1.75 mg/kg.

The dose increase should not occur more frequently than every 6 weeks (2 administrations) and should not exceed the maximum dose of 1.75 mg/kg every 3 weeks. The dose should not be increased immediately after a dose delay.

If a patient loses response (transfusion independence) or the Hb concentration reduces by ≥10 g/L within 3 weeks in the absence of transfusion, the REBLOZYL dose should be increased by one dose level.

β -Thalassaemia

The recommended starting dose of REBLOZYL is 1.0 mg/kg once every 3 weeks by subcutaneous (SC) injection.

If a patient does not achieve a reduction in RBC transfusion burden after at least 2 consecutive doses (6 weeks) at the 1.0 mg/kg starting dose, increase the REBLOZYL dose to 1.25 mg/kg.

Do not increase the dose beyond the maximum dose of 1.25 mg/kg.

Dosage Adjustment

Dose Reduction and Dose Delay

Dose reduction and dose delay: In case of Hb increase > 20 g/L within 3 weeks of luspatercept treatment in absence of transfusion, the REBLOZYL dose should be reduced by one dose level.

Dose should not be reduced below 0.8 mg/kg.

If the pre-dose Hb is ≥ 115 g/L in the absence of transfusion for at least 3 weeks, delay dosing until the Hb is ≤ 110 g/L. If there is also a concomitant rapid increase in Hb (> 20 g/L within 3 weeks in absence of transfusion), a dose reduction to one step down (minimum 0.8 mg/kg) should be considered after the dose delay.

After dose delay, patient should restart at previous dose or at reduced dose as dose reduction guidance. Dose reductions during treatment with REBLOZYL are provided below.

Table 1: Dose reductions for MDS

Current Dose	Dose Reduction
1.75 mg/kg	1.33 mg/kg
1.33 mg/kg	1 mg/kg
1 mg/kg	0.8mg/kg

Table 2: Dose reductions for β -Thalassaemia

Current Dose	Dose Reduction
1.25 mg/kg	1 mg/kg
1 mg/kg	0.8 mg/kg

If the dose delay is > 12 consecutive weeks, discontinue treatment.

Dose Modifications for Toxicity

For patients experiencing Grade 3 or higher adverse reactions, modify treatment as follows:

- For related Grade 3 or 4 hypersensitivity reactions, discontinue treatment
- For other related Grade 3 or 4 adverse reactions, interrupt treatment; When the adverse reaction resolved to no more than Grade 1, restart treatment at the next lower dose level.
- For > 2 dose reductions due to suspected related AE, treatment should be discontinued.

Missed Doses

In case of a missed or delayed scheduled injection of REBLOZYL, the patient should be administered REBLOZYL as soon as possible and dosing continued as prescribed with at least 3 weeks between doses.

Patients Experiencing a Loss of Response

If patients experience a clinical response followed by a loss of response to REBLOZYL, causative factors (e.g. a bleeding event) should be investigated. If typical causes for a loss of haematological response are excluded, dose increase should be considered as described above for the respective indication being treated.

Discontinuation

REBLOZYL should be discontinued if patients do not experience a reduction in transfusion burden after 9 weeks of treatment (administration of 3 doses) at the maximum dose level if no other causes are found.

Method of Administration

After Reconstitution

REBLOZYL is administered by SC injection into the upper arm, thigh and/or abdomen. The exact total dosing volume of the reconstituted REBLOZYL solution (50 mg/mL) required for the patient should be calculated and slowly withdrawn from the single-dose vial(s) into a syringe.

The recommended maximum volume of medicinal product per injection site is 1.2 mL. If more than 1.2 mL is required, the total volume of REBLOZYL should be divided into separate similar volume injections and injected into separate sites.

If multiple injections are required, a new syringe and needle must be used for each SC injection. Any unused portion should be discarded. No more than one dose from a vial should be administered.

If the REBLOZYL solution has been refrigerated after reconstitution, it should be removed from the refrigerator 15-30 minutes prior to injection to allow it to reach room temperature. This will allow for a more comfortable injection.

REBLOZYL must be reconstituted gently prior to administration. Aggressive shaking should be avoided. While reconstituting, gentle swirling and inversion should be used to mix as indicated in the reconstitution procedure below.

Reconstitution of the Product

REBLOZYL is supplied as a lyophilised powder for reconstitution before use. Only sterile water for injections (WFI) should be used when reconstituting REBLOZYL.

The appropriate number of REBLOZYL vials should be reconstituted to achieve the desired dose. A syringe with appropriate graduations must be used for reconstitution to ensure accurate dosage.

The following steps should be followed for reconstitution:

1. Remove the coloured cap from the vial and wipe the top with an alcohol wipe.
2. *25 mg vial:* Add 0.68 mL WFI into the vial by means of a syringe with appropriate graduations with a needle directing the flow onto the lyophilised powder. Allow to stand for one minute. Each 25 mg single-dose vial will deliver at least 0.5 mL of 50 mg/mL luspatercept.

   75 mg vial: Add 1.6 mL WFI into the vial by means of a syringe with appropriate graduations with a needle directing the flow onto the lyophilised powder. Allow to stand for one minute. Each 75 mg single-dose vial will deliver at least 1.5 mL of 50 mg/mL luspatercept.
3. Discard the needle and syringe used for reconstitution. Do not use them for subcutaneous injection.
4. Gently swirl the vial in a circular motion for 30 seconds. Stop swirling and let the vial sit in an upright position for 30 seconds.
5. Inspect the vial for undissolved powder in the solution. If undissolved powder is observed, repeat step 4 until the powder is completely dissolved.
6. Invert the vial and gently swirl in an inverted position for 30 seconds. Bring the vial back to the upright position and let it sit for 30 seconds.
7. Repeat Step 6 seven more times to ensure complete reconstitution of material on the sides of the vial.
8. Visually inspect the reconstituted solution prior to administration. REBLOZYL is a colourless to slightly yellow, clear to slightly opalescent solution which is free of visible foreign particulate matter. Do not use if undissolved product or foreign particulate matter are observed.
9. If the reconstituted solution is not used immediately, see Section 6.4 for storage conditions.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.
- Pregnancy (see section 4.6)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified Precautions

Thromboembolic Events

In adult patients with β-thalassaemia, thromboembolic events (TEE) were reported in 8/223 (3.6%) REBLOZYL-treated patients. Reported TEEs included deep vein thromboses, pulmonary embolus, portal vein thrombosis, and ischaemic strokes. Patients with known risk factors for thromboembolism, e.g. splenectomy or concomitant use of hormone replacement therapy, may be at further increased risk of thromboembolic conditions.

Consider thrombo-prophylaxis in patients with β-thalassemia at increased risk of TEE. Monitor patients receiving REBLOZYL for signs and symptoms of thromboembolic events and institute treatment promptly.

Increased Blood Pressure

Hypertension was reported in 10.7% (61/571) of REBLOZYL-treated patients across the following studies: MDS - a Phase 3 study (MEDALIST) and two Phase 2 studies; β-thalassemia - a Phase 3 study (BELIEVE) and two Phase 2 studies; and one Phase 1 study in healthy subjects. Across these clinical studies, the incidence of Grade 3-4 hypertension ranged from 1.8% to 8.6%. In adult patients with β-thalassemia with normal baseline blood pressure, 13 (6.2%) patients developed systolic blood pressure (SBP) ≥130 mm Hg and 33 (16.6%) patients developed diastolic blood pressure (DBP) ≥80 mm Hg. In adult patients with MDS with normal baseline blood pressure, 26 (29.9%) patients developed SBP ≥130 mm Hg and 23 (16.4%) patients developed DBP ≥80 mm Hg.

Monitor blood pressure prior to each administration. Manage new-onset hypertension or exacerbations of pre-existing hypertension using anti-hypertensive agents.

Embryofetal Toxicity

Studies in animals have shown embryofetal toxicity. REBLOZYL may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to use effective contraception during treatment with REBLOZYL and for at least 3 months after the last dose of REBLOZYL. Pregnant women should be informed of the potential risk to the fetus (see Section 4.6).

Use in Hepatic Impairment

No starting dose adjustment is required for patients with total bilirubin (BIL) > upper limit of normal (ULN) and/or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) < 3 x ULN. No specific dose recommendation can be made for patients with ALT or ASL ≥ 3 x ULN or liver injury CTCAE Grade ≥ 3 due to lack of data.

Use in Renal Impairment

No starting dose adjustment is required for patients with mild to moderate renal impairment (eGFR < 90 and ≥ 30 mL/min/1.73 m^2). No dose recommendation can be made for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) due to the lack of clinical data.

Use in the Elderly

No starting dose adjustment is required for REBLOZYL.

Paediatric Use

The safety and efficacy of REBLOZYL in paediatric or adolescent patients (under 18 years of age) has not been established.

Effects on Laboratory Tests

See Section 4.2 (Dose and Method of Administration).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal clinical interaction studies have been performed. Concurrent use of iron-chelating agents had no effect on luspatercept pharmacokinetics.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

The effect of REBLOZYL on fertility in humans is unknown. Luspatercept inhibited ovulation in female rats, (evident as a reduction in the number of corpora lutea), and resulted in decreased numbers of implantations and viable embryos with subcutaneous administration at 15 mg/kg every two weeks (yielding 7 times the exposure in patients at the maximum recommended human dose of 1.75 mg/kg every 3 weeks, based on serum AUC). There was no effect on fertility in male rats up to the same dose level. Effects on fertility in female rats were reversible after a 14-week recovery period. Based on findings in animals, REBLOZYL may compromise female fertility.

Use in Pregnancy – Pregnancy Category D

There are no data from the use of REBLOZYL in pregnant women. Embryofetal lethality was observed with luspatercept in animal studies. REBLOZYL is contraindicated in pregnancy.

Luspatercept was shown to cross the placenta in rats and rabbits. In both rats and rabbits, administration of luspatercept during pregnancy caused increased resorptions and post-implantation loss, and decreased litter size. This was observed at a subcutaneous dose of 30 mg/kg/week in the rat (yielding 15 times the exposure in patients at the maximum recommended human dose, based on serum AUC) and at 40 mg/kg/week in the rabbit (relative

exposure, 30). There was also an increased incidence of skeletal variations and a reduction in mean fetal weight in both species (at ≥15 mg/kg/week in rats and at ≥20 mg/kg/week in rabbits; relative exposure, 8-14). Adverse effects on embryofetal development occurred in the absence of maternotoxicity in rats, and at maternotoxic doses in rabbits.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with REBLOZYL. Consider obtaining a pregnancy test in females of child-bearing potential prior to initiating treatment with REBLOZYL. Advise females of reproductive potential to use effective contraception during treatment with REBLOZYL and for at least 3 months after the last dose. If REBLOZYL is used during pregnancy, or if the patient becomes pregnant while receiving REBLOZYL, the patient should be informed of the potential hazard to the fetus.

Use in Lactation

Luspatercept was detected in the milk of lactating rats. Maternal administration of luspatercept during pregnancy and lactation in rats was associated with reduced postnatal body weight gain and adverse effects on the kidney in the offspring. The safe use of REBLOZYL during lactation has not been established.

It is not known whether luspatercept is excreted into human milk or absorbed systemically after ingestion by a nursing infant. As many drugs are excreted in human milk, and because of the unknown effects of luspatercept in infants, taking into account the importance of the drug to the mother, a decision should be made whether to discontinue nursing during treatment with REBLOZYL and for 3 months after the final dose or to discontinue REBLOZYL treatment.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

REBLOZYL may have a minor influence on the ability to drive and use machines due to risks of fatigue, dizziness or syncope; the ability to react may be impaired. Therefore, patients should be advised to exercise caution until they know of any impact on their ability to perform such tasks.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the Safety Profile

The safety evaluation of REBLOZYL is based on the double-blind, randomised, placebo-controlled Phase 3 studies MEDALIST (ACE-536-MDS-001) in MDS patients (with 153 patients treated with REBLOZYL and 76 patients receiving placebo) and BELIEVE (ACE-536-B-THAL-001) in β-thalassaemia patients (with 223 patients treated with REBLOZYL and 109 patients receiving placebo).

At the time of analysis, the median duration of REBLOZYL treatment in MDS patients was approximately twice that in the placebo arm (49.0 weeks versus 24.0 weeks, respectively) and 46% of patients remained on REBLOZYL. The median duration of treatment and median number of doses received in β-thalassaemia patients between the luspatercept arm and placebo arm was similar (63.3 weeks versus 62.1 weeks).

In the MEDALIST study, 6.5% of patients treated with REBLOZYL and 5.3% of patients treated with placebo discontinued treatment due to an adverse event. The adverse reactions

leading to study drug discontinuation in the REBLOZYL treatment group for MDS patients were fatigue (1%) and headache (1%). Asthenia, fatigue, dizziness and headache occurred more frequently during the first 3 months of treatment. Other adverse reactions reported in less than 5% of patients with MDS on REBLOZYL included injection site reactions and hypersensitivity.

In the BELIEVE study, 5.4% of patients treated with REBLOZYL and 0.9% of patients treated with placebo discontinued treatment due to an adverse event. The adverse reactions leading to study drug discontinuation in the REBLOZYL treatment group for β-thalassemia patients were arthralgia (1%), back pain (1%), bone pain (less than 1 %), and headache (less than 1%). Bone pain, asthenia, fatigue, dizziness and headache occurred more frequently during the first 3 months of treatment. Other adverse reactions reported in less than 5% of patients with β-thalassemia on REBLOZYL included vertigo/vertigo positional, syncope/presyncope, injection site reactions and hypersensitivity.

Myelodysplastic Syndromes (MDS)

Tabulated Summary of Adverse Events

A list of the treatment-emergent adverse events (TEAEs) that occurred at a frequency ≥ 10% in any arm are provided in **Table 3** below.

Table 3: Most Frequently Reported TEAEs in ACE-536-MDS-001 (≥ 10%)

Adverse Events	**% occurrence in REBLOZYL arm (N = 153)**	**% occurrence in Placebo arm (N = 76)**
Infections and Infestations		
Bronchitis	11	1
Urinary tract infection	11	5
Upper respiratory tract infection	10	4
Nervous System Disorders		
Dizziness	20	5
Headache	16	7
Respiratory, Thoracic and Mediastinal Disorders		
Cough	18	13
Dyspnoea	15	7
Gastrointestinal Disorders		
Diarrhoea	22	9
Nausea	20	8
Constipation	11	9

Musculoskeletal and Connective Tissue Disorders		
Back pain	19	7
Arthralgia	5	12
General Disorders and Administration Site Conditions		
Fatigue	27	13
Asthenia	20	12
Peripheral oedema	16	17
Injury, Poisoning and Procedural Complications		
Fall	10	12

Tabulated List of Adverse Drug Reactions

The adverse drug reactions (ADRs) listed below have been assessed as being at least possibly related to treatment. The relatedness to treatment has been determined by: biological/pharmacological plausibility for a drug-event relationship, known morbidities of target population and disease being treated, adverse reactions suspected with medicines of this class, weight of evidence (e.g., positive rechallenge, positive dechallenge, time to onset, lack of confounding factors) and medical judgment.

Frequencies are defined in accordance with current guidance, as: very common (≥ 1/10), common (≥ 1/100 to <1/10); and uncommon (≥ 1/1,000 to <1/100).

Table 4: Adverse Drug Reactions Reported in Patients Treated with REBLOZYL in the ACE-536-MDS-001 Study

	All ADRs	**Grade 3/4 ADRs[a]**
Infections and Infestations		
Very Common	Bronchitis Urinary tract infection Upper respiratory tract infection	
Common	Influenza	Bronchitis Urinary tract infection Upper respiratory tract infection
Nervous System Disorders		
Very Common	Dizziness Headache	
Common	Syncope/presyncope	Headache Syncope/presyncope

Ear and Labyrinth Disorders		
Common	Vertigo + vertigo positional	
Vascular Disorders		
Common	Hypertension	Hypertension
Respiratory, Thoracic and Mediastinal Disorders		
Very Common	Dyspnoea	
Common		Dyspnoea
Gastrointestinal Disorders		
Very Common	Diarrhea Nausea	
Common		Nausea
Musculoskeletal and Connective Tissue Disorders		
Very Common	Back pain	
Common		Back pain
General Disorders and Administration Site Conditions		
Very Common	Fatigue Asthenia	
Common		Fatigue Asthenia

[a] All data included are for Grade 3 events. There were no Grade 4 events.

β-Thalassaemia

Tabulated Summary of Adverse Events

A list of the treatment-emergent adverse events (TEAEs) that occurred at a frequency ≥ 10% in any arm are provided in **Table 5** below.

Table 5: Most Frequently Reported TEAEs in ACE-536-B-THAL-001 (≥ 10.0%)

Adverse Events	% occurrence in REBLOZYL arm (N = 223)	% occurrence in Placebo arm (N = 109)
Infections and Infestations		
Upper respiratory tract infection	27	33
Pharyngitis	9	12
Nervous System Disorders		
Headache	26	24
Dizziness	11	5
Respiratory, Thoracic and Mediastinal Disorders		
Cough	14	11
Oropharyngeal pain	13	11
Gastrointestinal Disorders		
Diarrhea	12	10
Musculoskeletal and Connective Tissue Disorders		
Back pain	27	29
Bone pain	20	8
Arthralgia	19	12
Myalgia	10	10
General Disorders and Administration Site Conditions		
Pyrexia	16	21
Fatigue	14	13
Asthenia	10	10

Tabulated List of Adverse Drug Reactions

The adverse drug reactions (ADRs) listed below have been assessed as being at least possibly related to treatment. The relatedness to treatment has been determined by: biological/pharmacological plausibility for a drug-event relationship, known morbidities of target population and disease being treated, adverse reactions suspected with medicines of this

class, weight of evidence (e.g., positive rechallenge, positive dechallenge, time to onset, lack of confounding factors) and medical judgment.

Frequencies are defined in accordance with current guidance, as: very common (≥ 1/10), common (≥ 1/100 to <1/10); and uncommon (≥ 1/1,000 to <1/100).

Table 6: Adverse Drug Reactions Reported in Patients Treated with REBLOZYL in the ACE-536-B-THAL-001 Study

	All ADRs	Grade 3/4 ADRs
Infections and Infestations		
Common	Influenza	
Metabolism and Nutrition Disorders		
Common	Hyperuricemia	Hyperuricemia
Nervous System Disorders		
Very Common	Headache Dizziness	
Uncommon		Headache
Vascular Disorders		
Common	Hypertension	Hypertension
Gastrointestinal Disorders		
Very Common	Diarrhea Nausea	
Uncommon		Diarrhea
Musculoskeletal and Connective Tissue Disorders		
Very Common	Bone pain Arthralgia	Bone pain
General Disorders and Administration Site Conditions		
Very Common	Fatigue Asthenia	

Description of Selected Adverse Reactions (MDS and β-Thalassaemia)

Hypersensitivity Reactions

Hypersensitivity reactions (including eyelid oedema, drug sensitivity, swelling face, periorbital oedema, hypersensitivity, face oedema, angioedema, lip swelling and drug eruption) occurred in

4.6% of MDS patients and 4.5% of β-thalassaemia patients treated with REBLOZYL. In clinical studies, all events were Grade 1/2 and non-serious. Hypersensitivity led to treatment discontinuation in 1 β-thalassaemia patient (0.4%).

Injection Site Reactions

Injection site reactions (including injection site erythema, injection site pruritus, injection site swelling and injection site rash) occurred in 3.9% of MDS patients and 2.2% of β-thalassaemia patients receiving REBLOZYL and 1.1% of patients treated with placebo. In clinical studies, all events were Grade 1 and non-serious.

Immunogenicity

In clinical studies in MDS, an analysis of 260 MDS patients who were treated with luspatercept and who were evaluable for the presence of anti-luspatercept antibodies showed that 23 (8.8%) MDS patients tested positive for treatment-emergent anti-luspatercept antibodies, including 9 (3.5%) MDS patients who had neutralising antibodies against luspatercept.

In clinical studies in β-thalassaemia, an analysis of 284 β-thalassaemia patients who were treated with luspatercept and who were evaluable for the presence of anti-luspatercept antibodies showed that 4 (1.4%) β-thalassaemia patients tested positive for treatment-emergent anti-luspatercept antibodies, including 2 (0.7%) β-thalassaemia patients who had neutralising antibodies against luspatercept.

Luspatercept serum concentration tended to decrease in the presence of neutralising antibodies. There were no systemic hypersensitivity reactions reported for patients with anti-luspatercept antibodies in luspatercept clinical trials, and there was no association between hypersensitivity type or injection site reactions and presence of anti-luspatercept antibodies.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdosage may cause haemoglobin levels above the desired level. In the event of an overdose, treatment should be delayed until Hb ≤ 110 g/L.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Anti-anaemic preparations, other anti-anaemic preparations, ATC code: B03XA06

Mechanism of Action

Luspatercept is a recombinant fusion protein consisting of a modified form of the extracellular domain of the human activin receptor type IIB (ActRIIB) linked to the human immunoglobin G1 (IgG1) Fc domain. It acts as a ligand trap for select TGF-β superfamily ligands. By binding to certain endogenous ligands that act as negative regulators of erythropoiesis, luspatercept inhibits downstream Smad2/3 signalling, resulting in erythroid maturation through differentiation of late-stage erythroid precursors (normoblasts) in the bone marrow. TGF-β superfamily signalling through Smad2/3 is abnormally high in disease models characterised by ineffective erythropoiesis, i.e., MDS and β-thalassaemia, and in the bone marrow of MDS patients.

Pharmacodynamic Effects

Haemoglobin Response

Haemoglobin increase in patients treated with REBLOZYL was evident within 7 days of therapy initiation and temporally correlated with the time for luspatercept C_{max}. The most pronounced Hb increase was observed after the first dose, with additional increases at subsequent doses for the Q3W dosing schedule. At therapeutic dose levels (0.6 – 1.75 mg/kg), the time for the increased Hb to return to its baseline value appeared to be approximately 6 to 8 weeks from the last dose.

Increasing luspatercept serum exposure (AUC) was associated with greater Hb increase in patients with MDS or β-thalassaemia.

Clinical Trials

Myelodysplastic Syndromes (MDS)

The efficacy and safety of REBLOZYL were evaluated in a Phase 3 multicentre, randomised, double-blind, placebo-controlled study MEDALIST (ACE-536-MDS-001) in adult patients with anaemia requiring RBC transfusions due to IPSS-R very low-, low- or intermediate-risk MDS who have ring sideroblasts.

Patients in both arms were treated for 24 weeks, then continued treatment if they had demonstrated clinical benefit and absence of disease progression.

A total of 229 patients were randomised to receive REBLOZYL 1.0 mg/kg (n=153) or placebo (n=76) subcutaneously every 3 weeks. Dose titration up to 1.75 mg/kg was allowed. All patients were eligible to receive best supportive care (BSC), which included RBC transfusions, iron-chelating agents, use of antibiotic, antiviral and antifungal therapy, and nutritional support, as needed. Patients were required to have received prior treatment with ESA, determined to be unlikely to respond to ESA treatment with serum erythropoietin (EPO) (>200 U/L), or intolerant. Patients with deletion 5q (del5q) MDS, white blood cell count > 13 Gi/L, neutrophils <0.5 Gi/L, platelets < 50 Gi/L, or with prior use of a disease modifying agent for treatment of MDS were excluded from the study. The median age of the 229 study participants was 71 years (range: 26, 95 years). Majority of patients were white (69%) and male (63%).

Table 7 summarises the baseline disease characteristics in patients with MDS in the MEDALIST study.

Table 7: Baseline Disease Characteristics for MDS Patients in ACE-536-MDS-001

	REBLOZYL (N = 153)	Placebo (N = 76)
Time Since Original MDS Diagnosis[a] (months)		
Mean (SD)	57.8 (56.59)	52.7 (42.29)
Median (Min, Max)	44.0 (3, 421)	36.1 (4, 193)
MDS Classification, n (%)		
MDS RARS	7 (4.6)	2 (2.6)
MDS RCMD-RS	145 (94.8)	74 (97.4)
Other	1 (0.7)	0
Serum EPO (U/L) categories[b], n (%)		
< 200	88 (57.5)	50 (65.8)
200 to 500	43 (28.1)	15 (19.7)
> 500	21 (13.7)	11 (14.5)
Missing	1 (0.7)	0
IPSS-R classification risk category, n (%)		
Very low	18 (11.8)	6 (7.9)
Low	109 (71.2)	57 (75.0)
Intermediate	25 (16.3)	13(17.1)
Other	1 (0.7)	0
Baseline RBC transfusion burden / 8 weeks categories, n (%)		
≥ 6 units	78(51.0)	46(60.5)
< 6 units	75 (49.0)	30(39.5)
≥ 4 and < 6 units	47(30.7)	19(25.0)
< 4 units	28(18.3)	11(14.5)

EPO = erythropoietin; IPSS-R = International Prognostic Scoring System-Revised

[a] Time since original MDS diagnosis was defined as the number of years from the date of original diagnosis to the date of informed consent.

[b] Baseline EPO was defined as the highest EPO value within 35 days of the first dose of study drug.

A summary of the overall efficacy results are presented below in **Table 8**.

Table 8: Summary of Overall Efficacy Data – ACE-536-MDS-001

	REBLOZYL (N = 153)	**Placebo (N = 76)**
Primary Endpoint		
RBC-TI ≥ 8 weeks (Weeks 1-24) Number of responders (response rate %)	58 (37.9)	10 (13.2)
Common risk difference on response rate (95% CI)	24.56 (14.48, 34.64)	
Odds ratio (95% CI)[a]	5.065 (2.278, 11.259)	
p-value	< 0.0001	
Secondary Endpoints		
RBC-TI ≥ 12 weeks (Weeks 1-24) Number of responders (response rate %)	43 (28.1)	6 (7.9)
Common risk difference on response rate (95% CI)	20.00 (10.92, 29.08)	
Odds ratio (95% CI)[a]	5.071 (2.002, 12.844)	
p-value	0.0002	
RBC-TI ≥ 12 weeks (Weeks 1-48) Number of responders (response rate %)	51 (33.3)	9 (11.8)
Common risk difference on response rate (95% CI)	21.37 (11.23, 31.51)	
Odds ratio (95% CI)[a]	4.045 (1.827, 8.956)	
p-value	0.0003	
RBC-TI ≥ 8 weeks (Weeks 1-48) Number of responders (response rate %)	69 (45.1)	12 (15.8)
Common risk difference on response rate (95% CI)	29.55 (18.73, 40.36)	
Odds ratio (95% CI)[a]	5.306 (2.526, 11.146)	
p-value	< 0.0001	
mHI-E[b] (Weeks 1-24) Number of responders (response rate %) (95% CI)	81 (52.9) (44.72, 61.05)	9 (11.8) (5.56, 21.29)
p-value[c]	<0.0001	

RBC transfusion reduction of 4 units / 8 weeks, n (%)[d]	52/107 (48.6)	8/56 (14.3)
Mean haemoglobin increase of ≥ 15 g/L for 8 weeks, n(%)[e]	29/46 (63.0)	1/20 (5.0)
mHI-E[b] (Weeks 1-48) Number of responders (response rate %) (95% CI)	90 (58.8) (50.59, 66.71)	13 (17.1) (9.43, 27.47)
p-value[c]	< 0.0001	
RBC transfusion reduction of 4 units / 8 weeks, n (%)[d]	58/107 (54.2)	12/56 (21.4)
Mean haemoglobin increase of ≥ 15 g/L for 8 weeks, n (%)[e]	32/46 (69.6)	1/20 (5.0)

RBC-TI = RBC transfusion independent; CI = confidence interval; mHI-E = modified haematological improvement - erythroid

[a] Cochran-Mantel-Haenszel test stratified for average baseline transfusion burden (≥ 6 units versus < 6 units per 8 weeks), and baseline IPSS-R score (very low or low versus intermediate).

[b] Proportion of patients meeting the HI-E criteria as per International Working Group (IWG) 2006 criteria (Cheson et al., 2006) sustained over a consecutive 56-day period during the indicated treatment period.

[c] p-value from Cochran-Mantel-Haenszel test to compare luspatercept treatment arm to placebo arm.

[d] For patients with baseline RBC transfusion burden of ≥ 4 units/8 weeks, mHI-E was defined as a reduction in RBC transfusion of at least 4 units/8 weeks.

[e] For patients with baseline RBC transfusion burden of < 4 units/8 weeks, mHI-E was defined as a mean increase in Hb of ≥ 15 g/L for 8 weeks in the absence of RBC transfusions.

The median duration of the longest RBC-TI period among responders in the REBLOZYL treatment arm was 30.6 weeks.

More than 62% (36/58) of the REBLOZYL responders who achieved RBC-TI ≥ 8 weeks from Weeks 1-24 had 2 or more episodes of RBC-TI at the time of analysis.

A treatment effect in favour of REBLOZYL over placebo was observed in all subgroups analysed including patients with high baseline endogenous EPO level (≥ 200 U/L) and high RBC transfusion burden (≥ 4 units / 8 weeks).

A reduction in mean serum ferritin levels was observed from baseline in the luspatercept arm compared to an increase in the placebo at both Week 9-24 (-2.7 µg/L *versus* +226.5 µg/L, p=0.0024) and Week 33-48 (-72.0 µg/L *versus* +247.4 µg/L, p=0.0294) which resulted in a least square mean treatment difference of -229.1 µg/L (95% CI: -375.8, -82.4) and -319.5 µg/L (95% CI: -606.3, -32.7), respectively.

In open-label Phase 2 studies, the safety and efficacy of REBLOZYL were evaluated in 23 adult patients with lower-risk MDS without ring sideroblasts who had a median baseline transfusion burden of 4 units (range: 2-8 units), and median EPO levels of 429 IU/L (range: 0.3-1960 IU/L) with 48% of patients having an EPO level above 500 IU/L. Of these patients, 30.4% (7/23, 95% CI: 13.2 to 52.9) of patients achieved RBC-TI ≥ 8 weeks. The median duration of longest RBC-TI (min, max) was 196 days (70, 378). The safety profile in patients with MDS without ring sideroblasts was generally consistent with that of the Phase 3 population.

β-Thalassaemia

The efficacy and safety of REBLOZYL were evaluated in a Phase III multi-centre, randomised, double-blind, placebo-controlled study BELIEVE (ACE-536-B-THAL-001) in patients with β-thalassaemia requiring regular red blood cell transfusions (6-20 RBC units per 24 weeks) with no transfusion-free period greater than 35 days during that period.

Patients in both the luspatercept and placebo arms were treated for at least 48 weeks. After unblinding, placebo patients were able to cross-over to luspatercept.

A total of 336 patients with β-thalassaemia were randomised to receive REBLOZYL (n=224) or placebo (n=112) subcutaneously once every 3 weeks. All patients were eligible to receive best supportive care, which included RBC transfusions; iron-chelating agents; use of antibiotic, antiviral, and antifungal therapy; and/or nutritional support, as needed.

The study excluded patients with haemoglobin S/β-thalassaemia or alpha-thalassaemia or who had major organ damage (liver disease, heart disease, lung disease, renal insufficiency). Patients with recent deep vein thrombosis or stroke or recent use of erythropoiesis-stimulating agent (ESA), immunosuppressant, or hydroxyurea therapy were also excluded.

The median age was 30 years (range: 18-66). The trial was comprised of patients who were 42% male, 54.2% White, 34.8% Asian, and 0.3% Black or African American. The percent of patients reporting their race as “other” was 7.7%, and race was not collected or reported for 3% of patients.

Table 9 summarises the baseline disease characteristics in patients with β-thalassaemia in the BELIEVE study.

Table 9: Baseline Disease Characteristics for β-thalassaemia Patients in ACE-536-B-THAL-001

	REBLOZYL (N = 224)	**Placebo (N = 112)**
Baseline transfusion burden 12 weeks prior to randomisation		
Median (min, max)	6.12 (3.0, 14.0)	6.27 (3.0, 12.0)
β-thalassaemia gene mutation grouping, n (%)		
β0/β0	68 (30.4)	35 (31.3)
Non-β0/β0	155 (69.2)	77 (68.8)
Missing[a]	1 (0.4)	0

[a] “Missing" category includes patients in the population who had no result for the parameter listed.

The study was unblinded for analyses when all patients had received at least 48 weeks of treatment or discontinued treatment.

Efficacy was based on the primary endpoint of RBC transfusion burden reduction (≥33% reduction from baseline) with a reduction of at least 2 units from Week 13 to Week 24. There were significantly more patients taking Reblozyl who achieved the primary endpoint compared to placebo (21.4% vs. 4.5%, respectively; p <0.0001).

A summary of the overall efficacy results are presented below in **Table 10**.

Table 10: Summary of Overall Efficacy Data – ACE-536-B-THAL-001

	REBLOZYL (N = 224)	**Placebo (N = 112)**
≥ 33% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks		
Weeks 13-24 – *Primary Endpoint*	48 (21.4)	5 (4.5)
Risk difference (95% CI)[a]	17.0 (10.4, 23.6)	
p-value[b]	<0.0001	
Weeks 37-48	44 (19.6)	4 (3.6)
Risk difference (95% CI) [a]	16.1 (9.8, 22.4)	
p-value[b]	<0.0001	
Any consecutive 12 weeks[c]	158 (70.5)	33 (29.5)
Risk difference (95% CI) [a]	41.1 (30.7, 51.4)	
p-value[b]	<0.0001	
Any consecutive 24 weeks[c]	92 (41.1)	3 (2.7)
Risk difference (95% CI) [a]	38.4 (31.3, 45.5)	
p-value[b]	< 0.0001	
≥ 50% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks		
Weeks 13-24	17 (7.6)	2 (1.8)
Risk difference (95% CI) [a]	5.8 (1.6, 10.1)	
p-value[b]	0.0303	
Weeks 37-48	23 (10.3)	1 (0.9)
Risk difference (95% CI) [a]	9.4 (5.0, 13.7)	
p-value[b]	0.0017	
Any consecutive 12 weeks[c]	90 (40.2)	7 (6.3)
Risk difference (95% CI) [a]	33.9 (26.1, 41.8)	
p-value[b]	< 0.0001	

Any consecutive 24 weeks[c]	37 (16.5)	1 (0.9)
Risk difference (95% CI) [a]	15.6 (10.5, 20.8)	
p-value[b]	< 0.0001	

CI =confidence interval

[a] Difference in proportions (luspatercept + BSC – placebo + BSC) and 95% CIs estimated from the unconditional exact test.

[b] P-value from the CMH test stratified by the geographical region.

[c] Response assessed over any consecutive 12- or 24-week interval showing the proportion of patients achieving treatment benefit at any time.

More than 65% of the REBLOZYL responders who achieved at least a 33% reduction in transfusion burden during any consecutive 12-week interval achieved 2 or more episodes of response within the treatment exposure period of 64 weeks.

A treatment effect in favour of REBLOZYL over placebo was observed in all subgroups analysed, including patients with a severe disease condition, such as patients with the β0/β0 gene mutation or with a high transfusion burden (> 6 units/12 week) at baseline.

A reduction in mean serum ferritin levels was observed from baseline in the luspatercept arm compared to an increase in the placebo arm at Week 48 (-248.02 µg/L *versus* +106.62 µg/L p=0.0024) which resulted in a least square mean treatment difference of -347.8 µg/L (95% CI: -516.95, -178.65).

The onset of action was rapid with the median time from first dose to first erythroid response ranging from 12 to 25 days in the luspatercept+BSC group compared to 43-107 days in the placebo group.

No clinically meaningful change in liver iron concentration was observed in β-thalassemia patients treated with REBLOZYL plus best supportive care (BSC) compared to patients treated with placebo plus BSC at 48 weeks.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In healthy volunteers and patients, luspatercept is slowly absorbed following SC administration, with the C_{max} in serum often observed approximately 7 days post-dose across all dose levels. Population pharmacokinetic (PK) analysis suggests that the absorption of luspatercept into circulation is linear over the range of studied doses, and the absorption is not significantly affected by the location of SC (upper arm, thigh, or abdomen). Interindividual variability in AUC was approximately 38% in MDS patients and 36% in β-thalassaemia patients.

Distribution

At the recommended doses, the mean apparent volume of distribution was 9.68 L for MDS patients and 7.08 L for β-thalassaemia patients. The small volume of distribution indicates that luspatercept is confined primarily in extracellular fluids, consistent with its large molecular mass.

Metabolism

Luspatercept is expected to be catabolised into amino acids by general protein degradation process.

Excretion

Luspatercept is not expected to be excreted into urine due to its large molecular mass that is above the glomerular filtration size exclusion threshold. At the recommended doses, the mean apparent total clearance was 0.516 L/day for MDS patients and 0.437 L/day for β-thalassaemia patients. The clearance was independent of dose or time. The mean half-life in serum was approximately 13 days for MDS patients and 11 days for β-thalassaemia patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies have not been conducted. As a large protein molecule, luspatercept is not expected to interact with DNA or other chromosomal material.

Carcinogenicity

No formal carcinogenicity studies have been conducted with luspatercept. Haematological malignancies (granulocytic leukaemia, lymphocytic leukaemia and malignant lymphoma) were observed in 3 out of 44 rats given luspatercept at 10 mg/kg every two weeks from postnatal day 7 to 91 in a juvenile toxicity study. This dose yielded 5 times the systemic exposure in patients at the maximum recommended human dose (based on serum AUC). The occurrence of these tumours in such young animals is unusual. A relationship to luspatercept treatment is uncertain but cannot be excluded. No other proliferative or pre-neoplastic lesions attributable to luspatercept were observed in other toxicity studies conducted with luspatercept, including a 6-month study in monkeys where there was equivalent exposure.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Citric acid monohydrate
Sodium citrate dihydrate
Polysorbate 80
Sucrose
Hydrochloric acid
Sodium hydroxide

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened Powder Vial

Luspatercept lyophilised powder supplied in single-use vials should be stored at 2 - 8°C.

Do not freeze. Store in the original package in order to protect from light.

After Reconstitution

When stored in the original container, chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated for up to 8 hours at room temperature (≤ 25°C) or for up to 24 hours at 2 - 8°C.

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, the reconstituted product should not be stored longer than 24 hours at 2 - 8°C.

Do not freeze the reconstituted solution.

6.5 NATURE AND CONTENTS OF CONTAINER

REBLOZYL 25 mg powder for injection

3 mL Type I glass vial with a hydrophobic inner coating closed with a bromobutyl rubber stopper and an aluminium flip-off seal with yellow polypropylene button.

REBLOZYL 75 mg powder for injection

3 mL Type I glass vial with a hydrophobic inner coating closed with a bromobutyl rubber stopper and an aluminium flip-off seal with orange polypropylene button.

Pack size: 1 vial

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Each vial of REBLOZYL is for single use in one patient only. Discard any residue.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Name

Recombinant fusion protein consisting of two identical chains, each consisting of the modified form of the extracellular domain (ECD) of human activin receptor type IIB (ActRIIB), linked to the human IgG1 Fc domain (including the hinge, CH2 and CH3 domains) through a glycylglycylglycine linker.

CAS Number

1373715-00-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

Sponsored in Australia by:

Celgene Pty Limited
Level 15, 60 City Road
Southbank VIC 3006
Australia
Telephone: 1800 CELGENE (1800 235 4363)

9 DATE OF FIRST APPROVAL

30 August 2021

10 DATE OF REVISION

N/A

Summary Table of Changes

Section Changed	Summary of New Information

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au