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CADTH Reimbursement Review

Luspatercept (Reblozyl)

Sponsor: Celgene Inc., a Bristol Myers Squibb company

Therapeutic area: Beta-thalassemia–associated anemia

Clinical Review

Pharmacoeconomic Review

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

ANCOVA	analysis of covariance
CI	confidence interval
CORD	Canadian Organization for Rare Disorders
HRQoL	health-related quality of life
ITT	intention to treat
MID	minimally important difference
OR	odds ratio
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SF-36	Short Form (36) Health Survey
SOC	system organ class
TFC	Thalassemia Foundation of Canada
TranQoL	Transfusion-Dependent Quality of Life questionnaire

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Introduction

Beta-thalassemia is a congenital condition caused by the reduced (beta+) or absent (beta0) synthesis of the *beta-globin* chains of the hemoglobin tetramer.[1] Within the red blood cell (RBC) precursors, when the *beta-globin* chains are reduced or absent, the unassembled alpha chains precipitate and lead to oxidative damage of the cell membrane, thereby resulting in apoptosis (ineffective erythropoiesis).[2,3] Beta-thalassemia major is a severe transfusion-dependent anemia caused by hemolytic anemia leading to poor growth and skeletal abnormalities during infancy. Clinical presentation of beta-thalassemia major usually occurs between 6 and 24 months of age, with severe microcytic anemia, mild jaundice, and hepatosplenomegaly. The hematological diagnosis is based on reduced hemoglobin level (< 70 g/L). The peripheral blood smear shows severe erythrocyte morphologic changes and numerous erythroblasts.

Currently, in Canada, the standard of care for patients with transfusion-dependent anemia associated with beta-thalassemia is RBC transfusion and managing the iron overload associated with the transfusions via iron chelators. Most patients with beta-thalassemia major will require regular lifelong blood transfusions. The burden of transfusional iron overload is associated with the frequency, volume, and duration of blood transfusion therapy. Patients with transfusional iron overload usually require iron chelation therapy to help decrease the iron burden and to prevent and/or delay long-term complications associated with iron deposition in tissues.

The prevalence of thalassemia in the Canadian population is not known but is likely increasing owing to immigration patterns. Individuals from sub-Saharan Africa, Southeast Asia, Mediterranean countries, the Middle East, and the Indian subcontinent are at particular risk, with prevalence ranging from less than 1% to 40% in some ethnic populations.[4]

The objective of this report is to perform a systematic review of the beneficial and harmful effects of luspatercept (25 mg/vial or 75 mg/vial) powder for solution for subcutaneous injection for the treatment of RBC transfusion-dependent anemia associated with beta-

Table 1: Submitted for Review

Item	Description
Drug product	Luspatercept (Reblozyl), 25 mg/vial, 75 mg/vial, powder for solution for SC injection
Indication	Treatment of adult patients with RBC transfusion-dependent anemia associated with beta-thalassemia
Reimbursement request	As per indication
Health Canada approval status	NOC
Health Canada review pathway	Priority review
NOC date	September 25, 2020
Sponsor	Celgene Inc., a Bristol Myers Squibb company

NOC = Notice of Compliance; RBC = red blood cell; SC = subcutaneous.

thalassemia in adult patients. The recommended starting dose of luspatercept is 1 mg/kg up to a maximum of 1.25 mg/kg administered by subcutaneous injection every 3 weeks.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups that responded to CADTH's call for patient input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

Two patient groups, the Thalassemia Foundation of Canada (TFC) and the Canadian Organization for Rare Disorders (CORD) provided a joint response to CADTH's call for patient input. TFC is a national organization with a mission to support and fund thalassemia scientific research, treatment, patient services, public awareness, and education. CORD is a national network for organizations that represents all those with rare disorders. CORD provides a strong common voice to advocate for health policy and a health care system that works for those with rare disorders. CORD works with governments, researchers, clinicians, and industry to promote research, diagnosis, treatment, and services for all rare disorders in Canada.

TFC and CORD conducted a focus group to gain qualitative feedback on the experience of treating thalassemia and opinions about luspatercept that was used to develop an online survey available on Survey Monkey. The survey took place between December 8 and December 14, 2020. A total of 68 participants responded to the survey. Most survey respondents (69%) had a diagnosis of beta-thalassemia major; 6% were diagnosed with alpha-thalassemia or thalassemia intermedia, and 22% were family members or caregivers for someone with (beta) thalassemia. In total, 49% of the patients diagnosed with thalassemia identified as female, 47% as male, and 3% preferred not to say. All patients (100%) who responded to the survey were receiving blood transfusions.

According to the patient input received for this review, the impact that thalassemia has on patients and their families is reflected in all areas of life, including their health, work, and social contexts. Patients were most concerned with serious complications due to thalassemia or its treatment and noted their experience of "iron overload that was not well managed by chelation." Approximately 30% of patients reported a "life-threatening" or "serious" experience of an enlarged spleen. Other complications experienced by patients included: liver damage (hepatitis, fibrosis), infections, hearing and vision sensitivities or loss, and psychological or emotional effects such as anxiety, depression, and panic attacks.

Overall, patients desire improvement in health-related quality of life (HRQoL), reduced symptoms, and decreased burden of treatment. The cycle of transfusion is time-consuming; it interferes with work and school and is a burden to normal social and home life. Moreover, before scheduled transfusion time, patients experience the fatigue, low-energy toll, and mental challenges of low hemoglobin. Approximately 30% of survey respondents reported knowing about luspatercept, with 7% receiving it through clinical trials. All patients who had received luspatercept spoke very positively about the experience.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH for this review identified the main unmet need for patients as a need for treatments with improved tolerability for patients with beta-

thalassemia. The current treatment burden is associated with the long amount of time required to receive a transfusion, the management of iron overloading, and transfusion reactions. Iron chelation is a medication that patients must take every day. It can have severe side effects, such as on kidney function. Patients are generally required to visit a clinic every 2 to 4 weeks for their transfusions. One of the key problems for these patients is not only disruptive visits for transfusion and chelation monitoring, but also frequent visits, requiring absences from family, school, or work. The experts noted that patients would benefit from a treatment that was easy to administer or could be self-administered at home. Not being transfusion-dependent could make a difference to a patient's quality of life.

There are no treatments that address any of the previously mentioned issues. There are no alternatives to transfusion except for stem cell transplant; however, this treatment is not available to adult populations and is an option that is available only to select patients at specialized medical centres. Hence, luspatercept would be prescribed for the full population of adult patients.

The clinical experts are of the opinion that the place in therapy for luspatercept would be for it to be added to the regular standard therapy of transfusion and iron chelation. Other than stem cell transplant in the very young patient population, luspatercept would be the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy. Among the signals to monitor for would be a thrombosis in splenectomized patients who are at a higher risk.

The clinical experts anticipated that initiating treatment with luspatercept would be based on a discussion with the patient. Patients with advanced kidney disease who have glomerular filtration rates of less than 30 mL/min would not be suitable for treatment with luspatercept; this is also in accordance with the product monograph. The clinical experts identified various patient populations who would derive greater benefit from this treatment, such as patients who do not chelate well and do not tolerate chelation therapy. In these patients, fewer transfusions may lead to less iron overload and more manageable chelation.

Experts agreed that a clinically meaningful response to luspatercept treatment would be fewer transfusions and/or increased intervals between transfusions. A meaningful reduction in transfusion rate would ideally be around 25% to 30% along with transfusions intervals increasing from 4 to 6 weeks. Another aspect of a clinically relevant response would be an improvement in quality of life. The clinical experts stated it would be helpful for the patients if luspatercept could be self-administered but, currently, it is administered at an outpatient clinic or medical day unit. Patients are followed in expert centres and have access to a community centre that can source the blood units for transfusions and administer the injections. They did acknowledge that patient care should occur in a specialty clinic and be provided by a hematologist and other specialists, such as an endocrinologist or obstetrician, when necessary. The clinical experts consider luspatercept to be a novel treatment that is different from currently available treatment; they speculated that if treatment with luspatercept was able to decrease transfusion burden, it would be expected to have a significant impact on patients and the health system.

Clinician Group Input

No clinician group input was received for this review.

Drug Program Input

A question the drug plans asked the clinical experts was whether they could clarify what the maximum dose administered to a patient would be. The clinical experts were not sure what the maximum dose value would be until they use luspatercept. As of now, based on the data in a Canadian clinical setting, it is unlikely that a dose beyond the maximum weight-based dose level (1.25 mg/kg) would be administered. The drug plans also had a question of how a multiple response would be defined. As per the clinical experts, a multiple response in the trial could be referring to some patients who may have had a response and whose transfusion burden dropped, and this may not have been consistent through the study period. Responding to the drug plan's question as to the appropriate setting where luspatercept would be administered, the clinical experts stated it would be helpful for the patients if luspatercept could be self-administered but, currently, it is administered at an outpatient clinic or medical day unit.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

One pivotal trial BELIEVE (N = 336) was included in the CADTH systematic review. BELIEVE is an ongoing phase III, multi-centre, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of luspatercept in adult patients with transfusion-dependent anemia associated with beta-thalassemia. BELIEVE was performed between July 2016 and June 2017 at 65 sites globally. One site in Canada enrolled 13 patients in the trial.

The BELIEVE study had a 12-week screening/run-in period during which the patient's prior 24-week transfusion history was documented to establish baseline assessments. Prior to randomization, patients were stratified based on geographical region (i.e., North America and Europe, Middle East and North Africa, Asia-Pacific). Following the 12-week screening/run-in phase, eligible patients were randomized using interactive response technology (2:1) to receive either luspatercept or placebo along with best supportive care for 48 weeks in a double-blind manner. Patients received a starting dose of 1 mg/kg of the study drug administered by subcutaneous injection every 3 weeks for 48 weeks. During this period, the dose levels were titrated (increased) stepwise up to a maximum of 1.25 mg/kg (Table 10). The maximum total dose per administration was not to exceed 120 mg.

The measure upon which the primary outcome of the study was based was to demonstrate an erythroid response measured as a 33% or greater reduction from baseline in transfusion burden (RBC units/time), with a reduction of at least 2 units in a fixed 12-week period from week 13 to week 24. The measure upon which the 4 key secondary outcomes was based was an erythroid response of 33% or greater in reduction from baseline in transfusion burden, with a reduction of at least 2 units in the fixed 12-week period from week 37 to week 48, an erythroid response of 50% or greater in reduction from baseline in transfusion burden, with a reduction of at least 2 units in the fixed 12-week period from week 13 to week 24 and from week 37 to week 48, and a mean change from baseline in transfusion burden from week 13 to week 24.

Overall, the baseline characteristics of the patients enrolled in the BELIEVE study were well balanced. The mean (standard deviation [SD]) age of the patients was 32.2 (10.67) years and 31.9 (9.89) years in the luspatercept and placebo groups, respectively. A total of 58.9% of the

patients in the luspatercept treatment group and 56.3% of the patients in the placebo group were female.

Efficacy Results

In BELIEVE, the efficacy outcomes identified in the protocol were hematologic response, HRQoL, iron accumulation, health care resource utilization, and serum ferritin levels. The primary and 3 key secondary efficacy outcomes were analyzed using an intention-to-treat (ITT) population.

The primary outcome of the BELIEVE study was to determine the proportion of patients who achieved an erythroid response measured as a 33% or greater in reduction from baseline in transfusion burden (RBC units/time), with a reduction of at least 2 units in a fixed 12-week period from week 13 to week 24. A significantly greater proportion of patients treated with luspatercept exhibited at least a 33% reduction from baseline in transfusion burden during the fixed 12-week period from weeks 13 to 24. In the luspatercept treatment group, 21.4% of the patients responded to the treatment and 4.5% of the patients in the placebo group (difference in proportions = 17.0; 95% confidence interval [CI], 10.4 to 23.6; P < 0.0001) achieved the primary end point.

The first of the 3 key secondary outcomes of the BELIEVE study was to determine the proportion of patients who achieved an erythroid response measured as a 33% or greater in reduction from baseline in transfusion burden (RBC units/time), with a reduction of at least 2 units in a fixed 12-week period from week 37 to week 48. In the luspatercept treatment group, 19.6% of the patients responded to the treatment and 3.6% of the patients in the placebo group (difference in proportions = 16.1; 95% CI, 9.8 to 22.3; P < 0.0001) achieved this secondary end point.

The second of the 3 key secondary outcomes of the BELIEVE study was to determine the proportion of patients who achieved an erythroid response measured as a 50% or greater reduction from baseline in transfusion burden (RBC units/time), with a reduction of at least 2 units in a fixed 12-week period from week 13 to week 24. In the luspatercept treatment group, 7.6% of the patients responded to the treatment and 1.8% of the patients in the placebo group (difference in proportions = 5.8; 95% CI,1.6 to 10.1; P = 0.0303) achieved this secondary end point.

The third key secondary outcome of the BELIEVE study was to determine the proportion of patients who achieved an erythroid response measured as a 50% or greater reduction from baseline in transfusion burden (RBC units/time), with a reduction of at least 2 units in a fixed 12-week period from week 37 to week 48. In the luspatercept treatment group, 10.3% of the patients responded to the treatment and 0.9% of the patients in the placebo group (difference in proportions = 9.4; 95% CI, 5.0 to 13.7; P = 0.0017) achieved this secondary end point.

The fourth key secondary outcome of the BELIEVE study was to determine the mean change from baseline in RBC transfusion burden to the fixed week 13 to week 24 interval. In the luspatercept treatment group, the mean (SD) change from baseline in transfusion burden was –0.67 (1.795) and, in the placebo group it was 0.66 (1.774). This end point was outside the statistical hierarchy; it is at risk of type I error and should be viewed as supportive evidence for the overall effect of luspatercept.

Other efficacy outcomes were reported descriptively, including, as per the protocol, other hematologic responses (RBC transfusion burden reduction, duration of transfusion

independence, and time to the first erythroid response), iron accumulation, health care resource utilization, and serum ferritin levels. For HRQoL, outcomes of no difference in the treatment groups were observed and no minimally important difference (MID) for patients with transfusion-dependent anemia associated with beta-thalassemia was identified from the literature. The clinical experts consulted by CADTH suggested that serum ferritin levels are not a reliable indicator of iron overload, and that there are frequently large fluctuations with this measurement. The clinical experts suggested that liver iron concentration and myocardial iron concentration were more reliable indicators of iron overload.

The primary efficacy end point and the first 3 key secondary end points were analyzed using a statistical hierarchal testing method. The other efficacy end points were not included in the statistical hierarchy; hence, these end points were not controlled for multiplicity and must be interpreted with consideration of type I error.

Subgroup analyses identified in the CADTH review protocol were splenectomy status (yes versus no) and baseline hematological status. For the primary end point, the effects of luspatercept were consistent in those with and without a spleen. There was a treatment effect in 24% of the splenectomized patients in the luspatercept treatment group versus 3.1% of the splenectomized patients in the placebo group (odds ratio [OR], 9.72; 95% CI, 2.22 to 42.53; P = 0.0003). In the non-splenectomized patients, treatment effect was observed in 17.9% in the luspatercept group and 6.4% in the placebo group (OR, 2.94; 95% CI, 0.81 to 10.69; P = 0.0918). The subgroup analyses were not powered and not controlled for type I error, and imbalances in characteristics may exist, as they were not included in the randomization scheme; therefore, these should be viewed as supportive evidence only for the overall effect of the treatment.

Harms Results

In BELIEVE, 96.0% and 92.7% of the patients in the luspatercept and placebo treatment groups reported at least 1 adverse event, respectively. In the luspatercept treatment group, 4% of the patients, and 0.9% of the patients in the placebo group, reported experiencing at least 1 thromboembolic event. The most commonly occurring adverse events in the luspatercept and placebo treatment groups, respectively, were back pain (27.4% and 29.4%), upper respiratory tract infection (26.5% and 33.0%), headache (26.0% and 23.9%), and bone pain (19.7% and 8.3%).

In BELIEVE, serious adverse events (SAEs) were reported by 15.2% of the patients in the luspatercept treatment group and 5.5% of the patients in the placebo group. The most-reported SAE was infections and infestations, with 5.8% of the patients in the luspatercept group and 2.8% of the patients in the placebo group reporting it.

The proportion of patients who stopped treatment due to an adverse event was 5.4% and 0.9% in the luspatercept and placebo treatment groups, respectively. One patient died in each treatment group. Under the system organ class (SOC) of hepatobiliary disorders, 6.7% of patients in the luspatercept treatment group and 3.7% of patients in the placebo group reported at least 1 associated adverse event. Hypertension was reported as an adverse event in 8.1% of patients in the luspatercept treatment group and 2.8% of the patients in the placebo group.

Critical Appraisal

The BELIEVE study was a randomized, placebo-controlled, double-blind study. Overall, the study was well conducted, and baseline characteristics were generally well balanced. The

Table 2: Summary of Key Results From Pivotal and Protocol-Selected Studies

Key results	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
RBC transfusion burden reduction (≥ 33% reduction) from baseline to the fixed week 13 to 24 interval (ITT population)		
Number of responders, n (%)	48 (21.4)	5 (4.5)
Difference in proportions, % (95% CI)[a]	17.0 (10.4 to 23.6)	
Odds ratio (95% CI)[b]	5.79 (2.24 to 14.97)	
P value	< 0.0001	
RBC transfusion burden reduction (≥ 33% reduction) from baseline to the fixed week 37 to week 48 interval (ITT population)		
Number of responders, n (%)	44 (19.6)	4 (3.6)
Difference in proportions, % (95% CI)[a]	16.1 (9.8 to 22.3)	
Odds ratio (95% CI)[b]	6.44 (2.27 to 18.26)	
P value	< 0.0001	
RBC transfusion burden reduction (≥ 50% reduction) from baseline to the fixed week 13 to week 24 interval (ITT population)		
Number of responders, n (%)	17 (7.6)	2 (1.8)
Difference in proportions, % (95% CI)[a]	5.8 (1.6 to 10.1)	
Odds ratio (95% CI)[b]	4.55 (1.03 to 20.11)	
P value	0.0303	
RBC transfusion burden reduction (≥ 50% reduction) from baseline to the fixed week 37 to week 48 interval (ITT population)		
Number of responders, n (%)	23 (10.3)	1 (0.9)
Difference in proportions, % (95% CI)[a]	9.4 (5.0 to 13.7)	
Odds ratio (95% CI)[b]	11.92 (1.65 to 86.29)	
P value	0.0017	
Harms (safety population), n (%)		
AEs	214 (96.0)	101 (92.7)
SAEs	34 (15.2)	6 (5.5)
WDAEs (from study treatment)	12 (5.4)	1 (0.9)
Deaths	1 (0.4)	1 (0.91)
Notable harms (safety population), n (%)		
Bone pain	44 (19.7)	9 (8.3)
Renal and urinary disorders	20 (9.0)	9 (8.3)
Hypertension	18 (8.1)	3 (2.8)
Hepatobiliary disorders	15 (6.7)	4 (3.7)
Osteoporosis	9 (4.0)	6 (5.5)

Key results	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
Osteopenia	5 (2.2)	5 (4.6)
Hypersensitivity reactions	NR	NR

AE = adverse event; BSC = best supportive care; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intention to treat; NR = not reported; RBC = red blood cell; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a]Difference in proportions (luspatercept minus placebo) and 95% CIs were estimated from the unconditional test.

[b]Odds ratio (luspatercept over placebo), 95% CIs, and P values were estimated from the CMH test stratified by the geographical regions defined at randomization.

Source: Clinical Study Report for BELIEVE.[5]

study population was generally representative of the Canadian population. The proportion of patients who discontinued treatment due to adverse events was higher in the luspatercept group; hence, it is unclear if the blinding of the study was maintained throughout the study. A higher number of patients in the luspatercept treatment group experienced arthralgia, back pain, bone pain, and myalgia, which led to discontinuation of the study drug.

The primary and key secondary end points were appropriately controlled for multiplicity and a hierarchical statistical plan was followed. However, all other outcomes were analyzed using descriptive analyses; hence, the interpretation of the treatment effect is limited. A few preplanned subgroup analyses were completed, but some groups were extremely small, not powered, or not controlled for type I error, and imbalances in characteristics may exist, as they were not included in the randomization scheme; therefore, they should be viewed as supportive evidence only for the overall effect of the treatment.

The primary end point, 33% or greater reduction from baseline in transfusion burden (RBC units/time) with a reduction of at least 2 units from week 13 to week 24, was relevant to clinical practice, as indicated by the clinical expert. The clinical experts also noted that if patients met the 50% or greater reduction from baseline in transfusion burden, it would be more clinically meaningful; however, although in favour of luspatercept, only 8% of luspatercept and 2% of placebo patients achieved this level.

An MID for patients with transfusion-dependent anemia associated with beta-thalassemia could not be identified from the literature for either of the instruments used to assess HRQoL, namely, the Transfusion-Dependent Quality of Life (TranQoL) questionnaire and the Short Form (36) Health Survey (SF-36). The clinical experts were of the opinion that serum ferritin levels are not a reliable indicator of iron overload. The clinical experts suggested that liver iron concentration and myocardial iron concentration were more reliable indicators of iron overload.

Conclusions

One phase III randomized controlled trial (BELIEVE, N = 336) was included in the CADTH systematic review of luspatercept. The study demonstrated that treatment with luspatercept was superior to placebo in terms of reducing transfusion burden by at least 33% during the fixed interval from week 13 to week 24, which was the primary end point. The study also demonstrated that, in the 3 key secondary end points, luspatercept was superior to placebo in reducing transfusion burden by at least 33% during week 37 to 48, and by at least 50% during the fixed interval from week 13 to week 24 and week 37 to week 48 in adult patients with transfusion-dependent anemia associated with beta-thalassemia. The primary and secondary

end points of the study were found to be clinically meaningful by the clinical experts consulted by CADTH. The other end points of the study that were evaluated were transfusion burden reduction, transfusion independence, time to first erythroid response, HRQoL, iron accumulation, health care resource utilization, and serum ferritin. However, due to limitations associated with statistical methodology, the effect of luspatercept on these outcomes is currently unknown. HRQoL was an outcome noted as important to patients, but the effect of luspatercept on HRQoL outcomes was uncertain due to a lack of control for multiplicity and major limitations around the data. Clinical experts have suggested that serum ferritin levels are not a reliable indicator of iron overload and that there are frequently large fluctuations with this measurement.

Key safety issues with luspatercept include thromboembolic events, which were higher in the luspatercept treatment arm compared with the placebo group. A higher number of patients in the luspatercept treatment group experienced arthralgia, back pain, bone pain, and myalgia.

Introduction

Disease Background

Beta-thalassemia is a congenital condition caused by the reduced (beta+) or absent (beta0) synthesis of the beta beta-globin chains of the hemoglobin tetramer.[1] Within the RBC precursors, when the beta-globin chains are reduced or absent, the unassembled alpha chains precipitate and lead to oxidative damage of the cell membrane, thereby resulting in apoptosis (ineffective erythropoiesis).[2,3]

Three clinical and hematological conditions of increasing severity are recognized, i.e., the beta-thalassemia carrier state, thalassemia intermedia, and thalassemia major. The beta-thalassemia carrier state, which results from heterozygosity for beta-thalassemia, is clinically asymptomatic and is defined by specific hematological features. Thalassemia intermedia comprehend a clinically and genotypically heterogeneous group of thalassemia-like disorders ranging in severity from the asymptomatic carrier state to the severe transfusion-dependent type. Beta-thalassemia major is caused by hemolytic anemia, leading to poor growth and skeletal abnormalities during infancy.

Clinical presentation of beta-thalassemia major usually occurs between 6 and 24 months of age, with severe microcytic anemia, mild jaundice, and hepatosplenomegaly. The hematological diagnosis is based on reduced hemoglobin level (< 70 g/L). The peripheral blood smear shows severe erythrocyte morphologic changes and numerous erythroblasts. The number of erythroblasts is related to the degree of ineffective erythropoiesis and is markedly increased after splenectomy.[6] According to the clinical experts consulted by CADTH, in Canada, the diagnosis of anemia is typically made in the first year of life or via prenatal testing if the parent(s) are known carriers.

Most patients with beta-thalassemia major require regular lifelong blood transfusions. The clinical experts consulted for this review indicated that patients with beta-thalassemia often have multiple potential end-organ disease problems and a risk of pulmonary hypertension. They identified osteoporosis as a side effect, particularly in women, and loss of pituitary endocrine access due to iron overloading. They also noted that women may have fertility

problems later in life. Beta-thalassemia intermedia is less severe than beta-thalassemia major and may require episodic blood transfusions. Most transfusion-dependent patients will develop iron overload and require chelation therapy to remove the excess iron.

The prevalence of thalassemia in the Canadian population is not known but is likely increasing owing to immigration patterns. Individuals from sub-Saharan Africa, Southeast Asia, Mediterranean countries, the Middle East, and the Indian subcontinent are at particular risk, with prevalence ranging from less than 1% to 40% in some ethnic populations.[4]

Standards of Therapy

Currently, in Canada, the standard of care for patients with transfusion-dependent anemia associated with beta-thalassemia is RBC transfusion and managing the iron overload associated with the transfusions via iron chelators. The only curative treatment option is allogenic stem cell transplant. However, this treatment is generally offered only to select pediatric patients, depending on their medical comorbidities and the availability of an appropriately matched stem cell donor, as complications associated with performing the transplant increase with age. Another potential treatment is hydroxyurea; however, the clinical experts consulted by CADTH noted that hydroxyurea is seldom effective in this population, although sometimes it has been used to increase hemoglobin or reduce extra-medullary hematopoiesis. It is not a drug that has been shown to reduce transfusions. They also noted that the evidence of the benefit or effectiveness of hydroxyurea is observational. The clinical experts also identified gene therapy as another potential treatment; however, gene therapy is still in the experimental stages and is not yet available in Canada. Blood transfusion plays a very important role in managing the anemia. However, iron overload secondary to transfusions remains a significant problem, as patients who receive multiple transfusions can rapidly become iron-loaded.[7] Patients with transfusional iron overload usually require iron chelation therapy to help decrease the iron burden and to prevent and/or delay long-term complications associated with iron deposition in tissues. The burden of transfusional iron overload is associated with the frequency, volume, and duration of blood transfusion therapy. The complications resulting from untreated transfusional iron overload include hepatic dysfunction and failure, endocrinopathies, and cardiac dysfunction.[8]

The clinical experts consulted by CADTH noted that for beta-thalassemia major, almost all children start transfusions before the age of 1 year, with many starting as early as 4 months. Once patients are transfusion-dependent, it lasts their lifetime. Most patients require RBC transfusions every 2 to 4 weeks. The clinical experts revealed that iron overload occurs with regular RBC transfusions and usually occurs within the first 10 to 20 transfusions, as every unit of blood (250 mL to 300 mL) contains 200 mg of iron, and adults receive nearly 2 to 4 units of blood every month. As patients become transfusion-dependent, they also become iron overloaded. Guidelines recommend that iron chelation therapy be started early.[9] Iron overload is managed using iron chelators, which is either a daily pill or a subcutaneous injection that runs over 8 to 12 hours a night to chelate. In Canada, 3 iron chelators are approved for use, namely, deferasirox, deferiprone, and deferoxamine mesylate. According to the clinical experts consulted by CADTH, the most frequently used iron chelation therapy in Canada is deferasirox.

The clinical experts consulted by CADTH were of the opinion that an ideal situation would be a non–transfusion-dependent state, but realistically identified an ideal medication as one that could reduce the number of RBC transfusions and hence cause less iron overloading. Reduction in the number of blood units required for RBC transfusion and increased intervals

between transfusions would be a preferred goal. Fewer transfusions would equate to less iron loading, less end-organ damage, fewer trips to the hospital environment, less absence from school or work, and less burden on the blood providers who supply antigen-matched blood, which is often stored for almost 14 days. The clinical experts anticipated that fewer transfusions would lead to less iron overloading and less chelation therapy. They also noted that adult patients who lead busy lives with family, work, or higher education would benefit from a greater quality of life. Due to frequent absences from work or school, many patients find it difficult to maintain a job or complete a degree. Fewer absences would lead to an improved contribution to their lives, communities, and workplaces.

Drug

Luspatercept (Reblozyl) is a recombinant fusion protein consisting of 2 identical chains, each consisting of a modified form of the extracellular domain of human activin receptor type IIB, linked to the human immunoglobulin G1 (IgG1) Fc domain, which binds select endogenous-transforming growth factor-beta superfamily ligands to inhibit Smad2/3 signalling.[10]

Luspatercept is indicated for the treatment of adult patients with RBC transfusion-dependent anemia associated with beta-thalassemia. Luspatercept was granted priority review by Health Canada and received a Notice of Compliance on September 25, 2020.

The sponsor's reimbursement request is per the indication under review, which is for the treatment of adult patients with RBC transfusion-dependent anemia associated with beta-thalassemia.

Luspatercept is a lyophilized powder for reconstitution available in 2 strengths: 25 mg/vial and 75 mg/vial. The Health Canada–recommended starting dose is 1 mg/kg every 3 weeks by subcutaneous injection. Prior to each administration, hemoglobin needs to be assessed and reviewed. If an RBC transfusion occurred before dosing, the pre-transfusion hemoglobin needs to be considered for dosing purposes. If the pre-dose hemoglobin is 115 g/L or greater, and the hemoglobin level is not influenced by a recent transfusion, dosing should be delayed until hemoglobin is 110 g/L or less. If a patient does not achieve a response, defined as a reduction in RBC transfusion burden of at least one-third from baseline (≥ 33%) after at least 2 consecutive doses (6 weeks) at the 1.0 mg/kg starting dose, the dose of luspatercept is to be increased to 1.25 mg/kg; this is the maximum dose beyond which the dose should not be increased. If there is an increase in hemoglobin of more than 20 g/L within 3 weeks of the previous dose and, in the absence of transfusion, the dose is to be reduced as per Table 3. Luspatercept is to be discontinued if a patient does not achieve a response after 9 weeks of treatment (administration of 3 doses) at the maximum dose level if no other causes are found, or if unacceptable toxicity occurs at any time. Luspatercept should be reconstituted and administered by a health care professional.[10] Table 4 presents the key characteristics of luspatercept.

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

About the Patient Group and Information Gathered

Two patient groups, TFC and CORD, provided a joint response to CADTH's call for patient input.

TFC is a national organization with a mission to support and fund thalassemia scientific research, treatment, patient services, public awareness, and education. The TFC hosts an annual Valentine's dinner and dance fundraiser. It devotes nearly $100,000 per year to medical grants for research and has established a distinguished medical advisory committee.

CORD is a national network for organizations that represents those with rare disorders. CORD provides a strong common voice to advocate for health policy and a health care system that works for those with rare disorders. CORD works with governments, researchers, clinicians, and industry to promote research, diagnosis, treatment, and services for all rare disorders in Canada.

TFC and CORD conducted a focus group to gain qualitative feedback on the experience of treating thalassemia and opinions about Reblozyl. The focus group responses were used

Table 3: Recommended Dose Titration, Dose Modifications, and Treatment Discontinuation for Luspatercept

Parameter	Luspatercept dosing recommendation
Insufficient response	
No reduction in RBC transfusion burden after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose	Increase dose to 1.25 mg/kg every 3 weeks
No reduction in RBC transfusion burden after 3 consecutive doses (9 weeks) at 1.25 mg/kg	Discontinue luspatercept
Pre-dose hemoglobin ≥ 115 g/L or rapid hemoglobin rise	
Pre-dose hemoglobin is ≥ 115 g/L in the absence of transfusions	Delay dose and restart only when hemoglobin is ≤ 110 g/L
Increase in hemoglobin > 20 g/L within 3 weeks in the absence of transfusion and current dose is:	
1.25 mg/kg	Reduce dose to 1 mg/kg
1 mg/kg	Reduce dose to 0.8 mg/kg
0.8 mg/kg	Reduce dose to 0.6 mg/kg
0.6 mg/kg	Discontinue luspatercept
Adverse events	
Any grade 2 adverse reaction	Delay dose until resolved to ≤ grade 1
Grade 3 or 4 hypersensitivity reactions	Discontinue luspatercept
Grade 3 or 4 leukocytosis (> 100,000 WBC/μL) or hematologic malignancy is suspected	• Delay dose until resolved • Discontinue if hematologic malignancy is confirmed
Other grade 3 or 4 adverse reactions	Delay dose until resolved

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; RBC = red blood cell; WBC = white blood cell.
Note: Grades as per NCI CTCAE or, when not defined, grade 1 is mild, grade 2 is moderate, grade 3 is severe, and grade 4 is life-threatening.
Source: Product monograph for Reblozyl.[10]

to develop an online survey available on Survey Monkey. The identification of focus group members and dissemination of the survey was done by TFC, with outreach to all TFC members through direct email outreach. The interviews and summary of feedback were conducted by CORD. The survey was disseminated to all TFC members across Canada via email. The survey took place between December 8 and 14, 2020. A total of 8 participants informed the focus group and 68 participants responded to the survey. The majority of survey respondents (69%) had a diagnosis of beta-thalassemia major; 6% were diagnosed with alpha-thalassemia or thalassemia intermedia, and 22% were family members or caregivers for someone with (beta) thalassemia. In total, 49% of the patients diagnosed with thalassemia identified as female, 47% as male, and 3% preferred not to say. All respondents who identified their place of residence reported living in Canada. Among these, 73% reside in Ontario, 11% in Alberta, 11% in Quebec, and 5% in Saskatchewan. The disease experience and impact on quality of life were assessed through open-ended questions in the focus group and 1 open-ended question in the survey.

Disease Experience

According to the patient input received for this review, the impact that thalassemia has on patients and their families is reflected in all areas of life, including their health, work, and social contexts. One patient noted that:

> Thalassemia affects me on a daily basis. I am tired all the time. Get sore, back pain. And then eventually depressed. Going on vacation with the family is always a treat, but prior to going it's very stressful. I need to order meds, schedule transfusions, and align everything with my health in order to just go away for 12 days. I have never left the country for more than 15 days. It would be a dream to travel and not have to worry about a transfusion every 2 weeks.

A family member reflected on the experience of their partner: "My wife requires monthly transfusions. It has prevented her from earning a fulltime income in the past and prevented

Table 4: Key Characteristics of Luspatercept

Characteristic	Luspatercept
Mechanism of action	Luspatercept is an r-Fc protein consisting of 2 identical chains, each consisting of a modified form of the ECD of human ActRIIB linked to the human IgG1 Fc domain that binds select endogenous TGF-beta superfamily ligands, to inhibit Smad2/3 signalling
Indication[a]	Treatment of adult patients with red blood cell transfusion-dependent anemia associated with beta-thalassemia
Route of administration	Subcutaneous injection
Recommended dose	Recommended starting dose of 1.0 mg/kg, maximum dose, 1.25 mg/kg
Serious adverse effects or safety issues	• Thrombosis or thromboembolism, hypertension • No dosing recommendations available for patients with severe renal impairments
Other	• Luspatercept is not to be used during pregnancy or breastfeeding • Women had to use contraception during the study and for at least 3 months after their last dose • Could cause fertility problems in women

ActRIIB = activin receptor type IIB; ECD = extracellular domain; IgG1 = immunoglobulin G1; r-Fc = recombinant fusion protein; TGF-beta = transforming growth factor-beta.
[a]Health Canada–approved indication.
Source: Product monograph for Reblozyl.[10]

plans from us moving abroad (for work) due to lack of specialized health care. She has also gone through several emotional issues over the years coping with this disorder."

The most serious and frequently experienced symptoms were related to "fatigue or sleepiness," where 35% of patients reporting these symptoms as "serious, frequent" and 20% as "minor, infrequent" or "not at all." One patient noted, "I don't like it when I get tired because of low hemoglobin — and can't take part in all activities in the school." Approximately half of the survey respondents (47%) reported the experience of "headache, dizziness, difficulty concentrating" as "moderate" or "worse."

Patients were most concerned with serious complications due to thalassemia or its treatment. The occurrence of these serious complications reinforces the continued challenge of thalassemia despite the treatment and care availability. Experience of "iron overload that was not well managed by chelation" was rated as serious by one-fourth (24%) of respondents and moderate by another 30%. About 30% had had a "life-threatening" or "serious" experience of an enlarged spleen and another 15% said their experience was "moderate." Other complications experienced by patients included: liver damage (hepatitis, fibrosis), infections, and hearing and vision sensitivities or loss. One patient expressed, "I worry about reactions during transfusions, and iron build-up over time. COVID-19 is a major added stressor now. The biggest impact is the psychological impact of thalassemia and hearing about friends who have suddenly passed due to complications."

In terms of psychological or emotional effects, approximately 14% of respondents reported the experience of "anxiety, depression, panic attacks" as "serious, frequent" or worse; 29% reported these effects as "moderate," and 24% reporting these were not a problem. The majority of respondents (84%) had no or only minor experience of "confusion and/or memory loss," and the remainder (16%) reported this was a moderate problem.

Experiences With Currently Available Treatments

All patients (100%) who responded to the survey were receiving blood transfusions. The majority (51%) receive transfusion every 4 weeks, while 27% were transfused every 3 weeks, and 13% required transfusion every 2 weeks or more frequently. About 7% of patients reported receiving transfusions at 5- or 6-week intervals, while 1 respondent was transfused "as required." One patient stated:

> I am dependent on monthly transfusions which are not only physically taxing, they are emotionally burdensome, especially for those of us trying to balance the many competing responsibilities with our families and work or school. The transfusions also come with the need to take iron chelation therapy daily. Adherence is a challenge for me, due to a number of factors, which has resulted in my iron liver concentration to increase significantly since starting transfusions over 10 years ago. Annual monitoring of my iron liver concentration includes an MRI of my liver. I also have routine cardiac and spine MRIs, as well as bone mineral density scans, as the impact of thalassemia and iron accumulation are far-reaching.

Respondents reported receiving transfusions for an average of 35 years (range = 3 to 57 years). Overall, this sample represents patients with long-time exposure to blood transfusions and chelation. Most patients have experience with iron chelation by overnight infusion, which is not only onerous but also limiting in terms of mobility. Children are unable to do sleepovers; families are restricted in terms of travel, and adults report limitations in terms of their work, social life, and overall quality of life. One patient stated:

> I started noticing my symptoms as symptoms. How tired I was, the pain I'd feel, the moodiness. I wasn't allowed to go for sleepovers because of my Desferal pump which kept me out of the loop with my friends. Once I switched to Exjade sometime in high school, the stomach pains and the vomiting was too much to handle so I would skip doses for years and didn't tell anyone. I was embarrassed and ashamed of having thalassemia so I pretended I didn't have it. I tried my hardest to fit in at school and had gotten good at pretending to be someone I wasn't, but not taking my Exjade caught up to me and I had extreme iron overload in my liver and my heart. I had a PICC line put in me and was medicated 24/7 for 8 months. It was horrendous and really hard to go through. The site was constantly infected since I was allergic to the tape. It was always itchy and painful and took a toll on my mental health. After that, I was diagnosed with depression and an anxiety disorder. Thalassemia is hard to live with and I wouldn't wish it on anyone; however, I will say I would not be the strong independent individual I am today without it.

Approximately 60% of the patients surveyed required washed (leukocyte-depleted) RBCs to the reduce risk of reactions. Similarly, about half (51%) require special (fully) cross-matched RBCs. These procedures are important for frequently transfused patients and require preplanning to assure access and strict adherence to scheduling to avoid wastage. The majority of respondents (80%) have no or infrequent minor reactions to blood transfusions, although 20% experienced fever, chills, or itching. Nearly half (47%) of patients experienced occasional or frequent complications related to iron overload that is not resolved by chelation.

Improved Outcomes

Overall, patients desire improvement in HRQoL, reduced symptoms, and decreased burden of treatment. The cycle of transfusion is time-consuming; it interferes with work and school and is a burden on normal social and home life. Moreover, before scheduled transfusion time, patients experience the fatigue, low-energy toll, and mental challenges of low hemoglobin. However, more frequent transfusions would take more time away from other responsibilities and would increase the demands on iron chelation, with iron overload already the most impactful complication of thalassemia treatment:

- "Transfusions are very time consuming (8–9 hours/month) which requires time off work/school (add 1–2+ hours if cross-matching the day prior depending how busy the lab is. This affects overall quality of life because a considerable amount of time is spent in hospital."
- "Need to take the day off from work for transfusion, so there is a financial impact (not working, so not paid). Socially less active the week before receiving the transfusion since too tired to do any activity (outside of work, since work already takes all the energy I have)."
- "I have to explain to my employer, forfeiting my right to privacy. Transfusion takes 10–12 hours and leaves me exhausted and short of breath for 24–48 hours after, with an upset stomach and achy. My kids worry for me and are scared for my long-term health. I simply don't have the energy I should due to low hemoglobin and I miss out on activities with my kids if I am a week away from my transfusion because I'm too tired."

Experience With Drug Under Review

Approximately 30% of survey respondents reported knowing about Reblozyl, with 7% receiving it through clinical trials. All patients who had received Reblozyl spoke very positively about the experience:

- "Access to Reblozyl has allowed for less frequent transfusions."

- "The most important benefit…the ability to decrease or not require blood transfusions."
- "Having access to this medication (Reblozyl) would substantially improve my daughter's quality of life because she would spend less time in hospital and it would reduce her exposure to donor blood. My daughter has received approximately 250 blood transfusions (so far) which translates to about 588 units of blood and over 6 months of her life spent in hospital to treat her disease."

Additional Information

When survey respondents were presented with information about how Reblozyl works and the possible benefit to patients, 88% said it would be "very important" to have access.

Clinician Input

All CADTH review teams include at least 1 clinical specialist with expertise in the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). In addition, as part of the luspatercept review, a panel of 4 clinical experts from across Canada was convened to characterize unmet therapeutic needs, assist in identifying and communicating situations where there are gaps in the evidence that could be addressed through the collection of additional data, promote the early identification of potential implementation challenges, gain further insight into the clinical management of patients living with beta-thalassemia, and explore the potential place in therapy for luspatercept (e.g., potential reimbursement conditions). A summary of this panel discussion is presented subsequently.

Unmet Needs

The clinical experts stated there is a need for treatments with improved tolerability for patients with beta-thalassemia. The current treatment burden is associated with the long amount of time required to receive a transfusion, the management of iron overloading, and transfusion reactions. Iron chelation is a medication that patients must take every day and can have severe side effects, such as on kidney function. Patients are generally required to visit a clinic every 3 to 5 weeks for their transfusions. In addition, patients require regular visits to endocrinology for osteoporosis, BMD testing of bone mineral density, cardiology, T2* MRI testing, hepatology follow-up, and eye and audiology exams. One of the key problems for these patients is not only the disruptive visits for transfusion and chelation monitoring, but also their frequency; thus, there are frequent absences from family, school, or work. Not being transfusion-dependent could make a difference to a patient's quality of life.

The experts noted that transfusions may be particularly challenging in patients with poor IV access and patients with complex transfusion needs; this may include patients with alloantibodies for whom it is more difficult to find appropriate units of blood and those with a history of recurrent episodes of severe transfusion reactions. For patients experiencing adverse reactions to transfusions, increasing the interval would be helpful both to blood providers and patients. There are no currently available treatments that address any of the aforementioned issues. There are no alternatives to transfusion except for stem cell transplant. Hence, luspatercept would be prescribed for the full population of adult patients.

Further, the patient's quality of life often fluctuates, as they may experience low energy or recurring back pain, which occurs due to increased erythropoiesis. The experts noted that patients would benefit from a treatment that was easy to administer or could be self-administered at home.

Place in Therapy

The clinical experts consulted by CADTH anticipated that luspatercept could be added to the regular standard therapy of RBC transfusion and iron chelation. Other than stem cell transplant in the very young patient population, luspatercept is the first treatment approved that addresses the underlying disease process rather than managing symptoms. The experts anticipated that luspatercept would be offered to all adult patients with transfusion-dependent beta-thalassemia; this would be in accordance with the product monograph. As previously noted, the evidence for the benefit or effectiveness of hydroxyurea is observational; hence, the clinical experts would not recommend that it be tried before luspatercept.

Patient Population

The clinical experts anticipated that initiating treatment with luspatercept would be based on a discussion with the patient. The clinical experts noted there is no biomarker that can be used to predict a response to luspatercept in beta-thalassemia. In a patient with documented iron overload, cardiac and liver MRIs), this conversation would need to occur as soon as possible. Patients are re-evaluated regularly and, with better access to diagnostics such as T2* MRIs, there are objective measures that can be used to assess response to treatment. Patients are formally monitored every 3 months; however, most physicians are frequently updated regarding their patient's status due to frequent clinic visits. The clinical experts noted there are some patients who are not adherent to their current treatments. However, they would still be considered for luspatercept; these patients would most likely need to be monitored closely. Patients with advanced kidney disease who have glomerular filtration rates of less than 30 mL/minute would not be suitable for treatment with luspatercept; this is also in accordance with the product monograph. Women on certain types of birth control are at an increased risk for thrombosis. Such patients would be closely monitored and may choose an alternative method of contraception with a lower thrombosis risk. Based on the evidence from the trial, it would be difficult to predict which patients would derive the most benefit.

The clinical experts identified various patient populations who would derive greater benefit from this treatment, such as patients who do not chelate well and do not tolerate chelation therapy. In those patients, fewer transfusions may lead to less iron overload and more manageable chelation. In addition, patients who have difficulties with transfusion due to transfusion-induced alloantibodies, which makes it difficult for blood providers to supply the compatible blood, and those who require washed blood due to recurrent transfusion reactions, may benefit from treatment with luspatercept.

Assessing Response to Treatment

Experts agreed that a clinically meaningful response to luspatercept treatment would be fewer transfusions and/or increased intervals between transfusions. A meaningful reduction in transfusion rate would ideally be around 25% to 30% along with transfusions intervals increasing from 4 to 6 weeks. Another aspect of a clinically relevant response would be an improvement in quality of life. If, for example, before their next transfusion, patients could maintain high hemoglobin levels, this would allow them to have more energy and better perform their activities of daily living and would require fewer hospital visits.

Discontinuing Treatment

The clinical experts anticipated that treatment with luspatercept would be discontinued in patients who do not exhibit a meaningful response to treatment as described within the product monograph (summarized in Table 3 of this review).

Appropriate Treatment Setting

The clinical experts stated it would be helpful for the patients if luspatercept could be self-administered but, currently, it is administered at an outpatient clinic or medical day unit. Patients are followed in expert centres and have access to a community centre that can source the blood units for transfusions and administer the injections. The luspatercept product monograph specifies that luspatercept should be reconstituted and administered by a health care professional, but the clinical experts consulted by CADTH speculated that patients could be taught to reconstitute and self-administer luspatercept at home. They did acknowledge, however, that patient care should occur in a specialty clinic and be provided by a hematologist and other specialists, such as an endocrinologist or obstetrician, when necessary.

Additional Information

The clinical experts consulted by CADTH see luspatercept as a novel treatment that is different from currently available treatment. They speculated that if treatment with luspatercept was able to decrease transfusion burden, it would be expected to have a significant impact on patients and the health system. The experts also expressed that, as this is chronic therapy, only patients who have a response would be maintained on the therapy for a longer term.

Clinician Group Input

No clinician group input was identified by CADTH for this review.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 5.

Clinical Evidence

The clinical evidence included in the review of luspatercept is presented in 3 sections. The first section, the systematic review, includes the pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The third section includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review. No indirect evidence met the inclusion criteria for this review.

Systematic Review (Pivotal and Protocol-Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of luspatercept (25 mg/vial or 75 mg/vial) powder for solution for subcutaneous injection for the treatment of RBC transfusion-dependent anemia associated with beta-thalassemia in adult patients.

Table 5: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Despite there being a maximum dose level, is there a ceiling dose? It is weight-based, but is there a certain dose that, once reached, would not be surpassed, even if weight suggested higher? The maximum dosing in the monograph is 1.25 mg/kg but for someone who is heavily obese, would the dose be limited to a ceiling dose or would it still go by the 1.25 mg/kg?	The clinical experts indicated they would not be able to identify what a maximum dose value would be until they used luspatercept. As of now, based on the data in a Canadian clinical setting, it is unlikely that a dose beyond the maximum dose level would be administered. The clinical experts were of the opinion that obese patients are not seen in this disease area.
How is a diagnosis made and are there criteria that require specific documentation to be made?	As per the clinical experts, diagnosis of transfusion-dependent anemia associated with beta-thalassemia is made in the first few years of life. The clinical experts stated that diagnosis is not an issue and can be done using routine blood tests (CBC and Hgb electrophoresis) and then confirmed by genetic testing, which could be done at a provincial hemoglobinopathy laboratory in Hamilton, for example. In Ontario, neonatal screening is done for hemoglobinopathies as part of routine screening for all pregnancies. The screening of the partners of women with hemoglobinopathies or thalassemia is recommended before planning a pregnancy and can be easily done by family physicians.
Studies included the subgroups of the beta0/beta0 gene mutation and the subgroup of patients with a high transfusion burden (> 6 units/12 weeks) at baseline. Will these groups benefit from the drug and be considered eligible?	The clinical experts noted that in the BELIEVE trial, it was shown that both patients with a non–beta0 /beta0 mutation (classically less severe patients) as well as patients with a beta0/beta0 mutation, responded to treatment with luspatercept.
Blood pressure monitoring is also needed before each dose. Will the prescription be dispensed by community pharmacies and, if so, will they be expected to keep a record of the Hgb and blood pressure results?	The clinical experts stated it would be helpful for the patients if luspatercept could be self-administered but, currently, it is administered at an outpatient clinic or medical day unit. Patients are followed in expert centres and have access to a community centre that can source the blood units for transfusions and administer the injections.
Since reconstitution of the drug and administration must be done by an HCP: • Will there be a restriction to a hospital or clinic setting, or would community pharmacies administer the drug (given Hgb and blood pressure need to be monitored)? • Community pharmacies may not have the capacity to administer the drug.	The luspatercept product monograph specifies that luspatercept should be reconstituted and administered by a health care professional, but the clinical experts speculated that patients could be taught to reconstitute and self-administer luspatercept at home.
The submission referenced “Multiple episodes of response,” which is a bit confusing. Please clarify what this means and how this may affect reimbursement.	As per the clinical experts, multiple episodes of response in the trial could be referring to some patients who may have had a response and the transfusion burden dropped, but this may not have been consistent through the study period.

CBC = complete blood count; Hgb = hemoglobin; HCP = health care provider.

Methods

The studies selected for inclusion in the systematic review include the pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 6. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist.[11]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid and Embase (1974–) through Ovid. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Reblozyl (luspatercept) and beta-thalassemia. Clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, and Health Canada's Clinical Trials Database.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

Table 6: Inclusion Criteria for the Systematic Review

Criteria	Description
Patient population	Adult patients with RBC transfusion-dependent anemia associated with beta-thalassemia Subgroups: • patients with or without splenectomy • baseline hematologic status
Intervention	Luspatercept powder for solution for subcutaneous injection: • recommended starting dose: 1 mg/kg every 3 weeks • maximum dose: 1.25 mg/kg every 3 weeks
Comparators	• RBC transfusion plus iron chelation therapy • Placebo
Outcomes	**Efficacy outcomes** • Hematologic response (e.g., erythroid response, RBC transfusion burden, transfusion frequency, RBC units) • HRQoL (e.g., SF-36, TranQoL) • Iron accumulation (e.g., liver iron concentration, myocardial iron) • Health care resource utilization • Serum ferritin **Harms outcomes** AEs, SAEs, WDAEs, mortality, notable harms (e.g., hypertension, thromboembolic events, hepatic and renal events, hypersensitivity reactions, bone health)
Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; HRQoL = health-related quality of life; RBC = red blood cell; RCT = randomized controlled trial; SAE = serious adverse event; SF-36 = Short Form (36) Health Survey; TranQoL = Transfusion-Dependent Quality of Life questionnaire; WDAE = withdrawal due to adverse event.

The initial search was completed on December 22, 2020. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on April 21, 2021.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist.[12] Included in this search were the websites of regulatory agencies (FDA and European Medicines Agency). Google was used to search for additional internet-based materials. See Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 7. A list of excluded studies is presented in Appendix 2.

Description of Studies

One pivotal trial, BELIEVE (N = 336), was included in the CADTH systematic review. Details of BELIEVE are provided in Table 7 and Figure 2.

BELIEVE is an ongoing phase III, multi-centre, randomized, double-blind, placebo-controlled study that aims to evaluate the efficacy and safety of luspatercept in adult patients for the treatment of transfusion-dependent anemia associated with beta-thalassemia. The treatment phase of BELIEVE was performed between July 2016 and June 2017 at 65 sites globally. One site in Canada enrolled 13 patients in the trial.

The BELIEVE trial had a 12-week screening and run-in period where patients were assessed for eligibility into the study. During the 12-week screening and run-in, the patient's prior 24-week transfusion history was documented. This documentation was used to establish baseline assessments. Prior to randomization, patients were stratified based on geographical region (i.e., North America and Europe, Middle East and North Africa, Asia-Pacific).

Following the 12-week screening and run-in phase, eligible patients were randomized (2:1) to receive either luspatercept or placebo along with best supportive care for 48 weeks in a double-blind manner. Patients were randomized by using an interactive response technology. Patients received a starting dose of 1 mg/kg of the study drug administered by subcutaneous injection every 3 weeks for 48 weeks. During this period, the dose levels were titrated (increased) stepwise up to a maximum of 1.25 mg/kg (Table 10) or reduced based on a clinical response. The maximum total dose per administration was not to exceed 120 mg.

Patients completing the 48-week double-blind treatment could continue to receive their assigned study treatment in a long-term double-blind treatment design for up to 48 weeks. Dose titration was allowed during the long-term double-blind treatment. This 48-week

long-term double-blind treatment phase is to be followed by an open-label phase and a post-treatment follow-up period phase of up to 5 years treatment with luspatercept and 156 weeks after last dose, respectively. As the data for the open-label phase and the post-treatment phase were not available for this review, only results of the double-blind treatment phase are presented in this report.

The primary objective of the study was to demonstrate the proportion of patients treated with luspatercept versus placebo who achieved an erythroid response measured as a 33% or greater reduction from baseline in transfusion burden (RBC units/time), with a reduction of at least 2 units in a fixed 12-week period from week 13 to week 24. The 4 key secondary outcomes were the proportion of patients with a hematologic improvement measured as a 33% or greater reduction from baseline in transfusion burden, with a reduction of at least 2 units in the fixed 12-week period from week 37 to week 48, the proportion of patients with a 50% or greater reduction from baseline in transfusion burden, with a reduction of at least 2 units in the fixed 12-week period from week 13 to week 24 and from week 37 to week 48, and a mean change from baseline in transfusion burden from week 13 to week 24.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

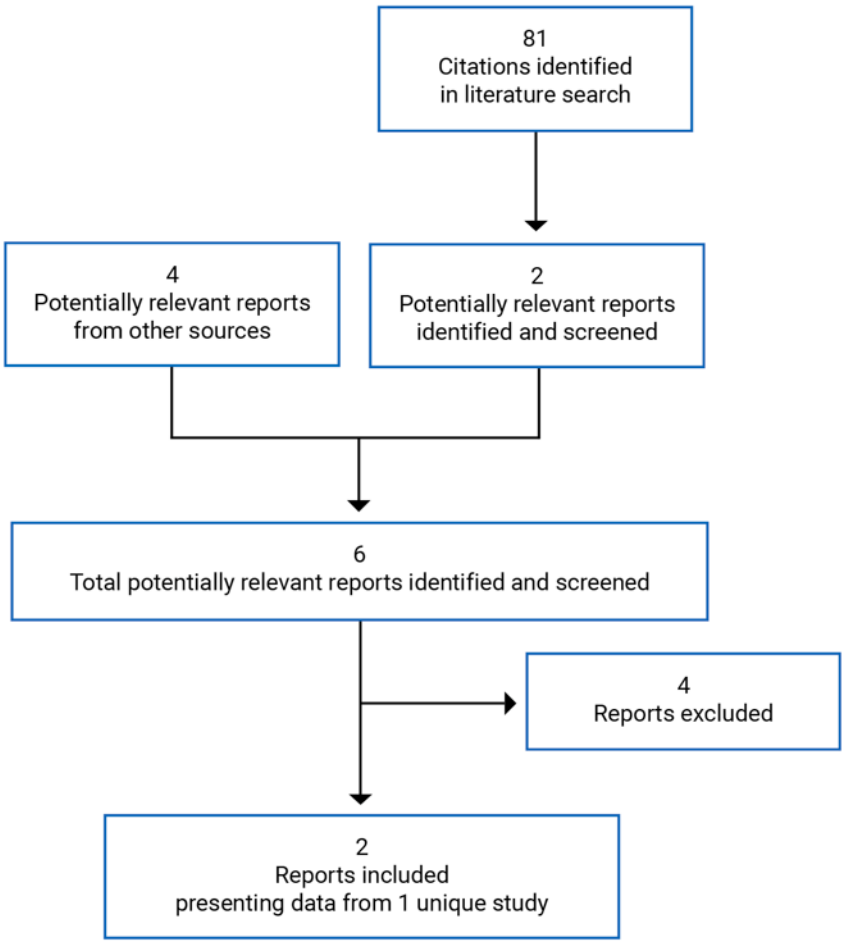


Table 7: Details of the Included Study

Characteristic	BELIEVE
Designs and populations	
Study design	Double-blind RCT, phase III, placebo-controlled
Locations	65 centres: Australia, Malaysia, Taiwan, Thailand, Israel, Lebanon, Tunisia, Turkey, Bulgaria, Canada, France, Greece, Italy, the UK, and the US.
Randomized (N)	336
Inclusion criteria	• ≥ 18 years of age • Documented diagnosis of beta-thalassemia or HbE or beta-thalassemia (beta-thalassemia with mutation and/or multiplication of alpha-globin) • Regularly transfused (6 to 20 RBC units in the 24 weeks before randomization and no transfusion-free period > 35 days during that period) • ECOG score: 0 or 1

Exclusion criteria	• Diagnosis of HbS or beta-thalassemia or alpha-thalassemia (e.g., HbH)
	• Evidence of active HCV infection
	• Deep vein thrombosis or stroke requiring medical intervention ≤ 24 weeks before randomization
	• Use of chronic anticoagulant therapy
	• Platelet count > 1,000 × 10^9/L
	• Uncontrolled diabetes mellitus within 24 weeks before randomization
	• Prior exposure to sotatercept or luspatercept
	• ESA use ≤ 24 weeks before randomization
	• ICT ≤ 24 weeks before randomization
	• Hydroxyurea treatment ≤ 24 weeks before randomization
	• Uncontrolled hypertension (grade > 1)
	• Major organ damage: liver disease, heart disease, lung disease, creatinine clearance < 60 mL/min
	• Proteinuria ≥ grade 3
	• Chronic systemic glucocorticoids ≤ 12 weeks before randomization
	• History of severe allergic or anaphylactic reactions or hypersensitivity
	• Cytotoxic drugs, immunosuppressants ≤ 28 days before randomization
	• History of malignancy, except for:
	  ◦ curatively resected non-melanomatous skin cancer
	  ◦ curatively treated cervical carcinoma
	• other solid tumour with no known active disease

Drugs	
Intervention	Luspatercept starting dose of 1.0 mg/kg SC once every 3 weeks to a maximum dose of 1.25 mg/kg plus BSC
Comparator	Placebo SC once every 3 weeks plus BSC
Duration	
Phase	

Characteristic	BELIEVE
Screening	12 weeks
Treatment period (double blind)	48 weeks
Long-term treatment (double blind)	Maximum 48 weeks after the double-blind treatment period
Open label	Up to 5 years of treatment with luspatercept
Post-treatment follow-up	156 weeks after last dose
Outcomes	
Primary end point	Proportion of patients with hematologic improvement, defined as ≥ 33% reduction from baseline in transfusion burden (RBC units/time) with a reduction of at least 2 units, from week 13 to week 24.
Secondary and exploratory end points	**Secondary** Proportion of patients who achieved ≥ 33% reduction from baseline in transfusion burden from week 37 to 48 with a reduction of at least 2 units Proportion of patients who achieved ≥ 50% reduction from baseline in transfusion burden from week 13 to 24 with a reduction of at least 2 units Proportion of patients who achieved ≥ 50% reduction from baseline in transfusion burden from week 37 to 48 with a reduction of at least 2 units Mean change from baseline in transfusion burden from week 13 to 24 **Other** Mean change from baseline in LIC Mean change from baseline in mean daily dose of ICT Mean change from baseline in serum ferritin Change in osteoporosis or osteopenia, total hip, and lumbar spine measured by BMD Mean change from baseline in myocardial iron Mean change from baseline in QoL assessments, such as the TranQoL and SF-36 Change in HRU Proportion of patients who were transfusion-independent for ≥ 8 weeks Duration of reduction in transfusion burden or transfusion independence Time to erythroid response Post-baseline transfusion events frequency Population PK in patients with beta-thalassemia Safety and immunogenicity **Exploratory** Baseline and change in serum GDF11 and other related biomarkers Change in HbF
Notes	
Publications	Cappellini (2020)

BMD = bone mineral density; BSC = best supportive care; ECOG = Eastern Cooperative Oncology Group; ESA = erythropoiesis-stimulating agent; GDF11 = growth differentiation factor 11; HbE = hemoglobin E; HbF = hemoglobin F; HbH = hemoglobin H; HbS = hemoglobin S; HCV = hepatitis C virus; HRU = health care resource utilization; ICT = iron chelation therapy; LIC = liver iron concentration; PK = pharmacokinetic; QoL = quality of life; RBC = red blood cell; RCT = randomized controlled trial; SC = subcutaneous; SF-36 = Short Form (36) Health Survey; TranQoL = Transfusion-Dependent Quality of Life questionnaire.

Note: 2 additional reports, a CADTH submission[13] and the Health Canada's reviewer's report,[14] were included.
Source: Clinical Study Report for BELIEVE.[5]

Populations

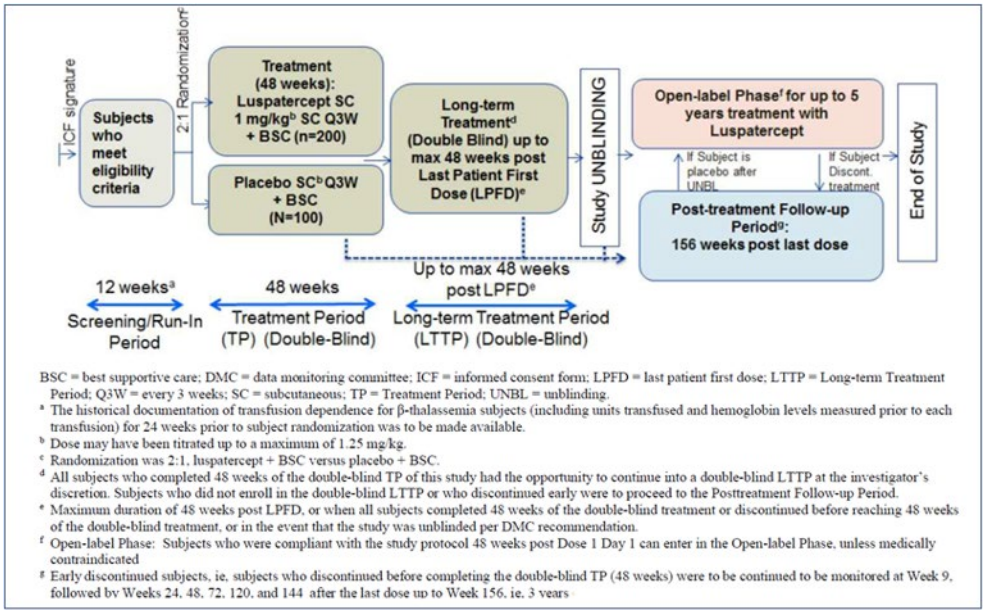
Inclusion and Exclusion Criteria

Detailed inclusion and exclusion criteria for BELIEVE are presented in Table 7. Adult patients 18 years of age and older with a documented diagnosis of hemoglobin E or beta-thalassemia who were being regularly transfused with 6 to 20 RBC units in the 24 weeks before randomization, and who had no transfusion-free period of more than 35 days during that period, were eligible for the study. Patients were excluded from the BELIEVE study if they had a diagnosis of hemoglobin S or beta-thalassemia or alpha-thalassemia, or had a deep vein thrombosis or stroke that required medical intervention 24 weeks before randomization, had uncontrolled diabetes mellitus, had used an erythropoiesis-stimulating agent or hydroxyurea, or had initiated iron chelation therapy within 24 weeks before randomization. Patients with uncontrolled hypertension (defined as a grade greater than 1) or major organ damage were also excluded from the study.

Baseline Characteristics

The baseline characteristics and disease characteristics of patients in the BELIEVE study are summarized in Table 8 and Table 9, respectively. Overall, the treatment groups were well balanced. The mean (SD) age of the patients was 32.2 (10.67) years and 31.9 (9.89) years in the luspatercept and placebo treatment groups, respectively. A total of 58.9% of the patients in the luspatercept group and 56.3% of the patients in the placebo group were female. A total of 54.5% and 53.6% of the patients were White in the luspatercept and placebo groups, respectively. The percentage of patients who had a non–beta0/beta0 gene mutation grouping was 69.2% and 68.8% in the luspatercept and placebo groups, respectively. In the luspatercept group, 57.6% of the patients and, in the placebo group, 58% of the patients, were splenectomized. The mean (SD) baseline transfusion burden assessed during the 12-week

Figure 2: Study Design for BELIEVE



BSC = best supportive care; DMC = data monitoring committee; ICF = informed consent form; LPFD = last patient first dose; LTTP = Long-term Treatment Period; Q3W = every 3 weeks; SC = subcutaneous; TP = Treatment Period; UNBL = unblinding.

[a] The historical documentation of transfusion dependence for β-thalassemia subjects (including units transfused and hemoglobin levels measured prior to each transfusion) for 24 weeks prior to subject randomization was to be made available.

[b] Dose may have been titrated up to a maximum of 1.25 mg/kg.

[c] Randomization was 2:1, luspatercept + BSC versus placebo + BSC.

[d] All subjects who completed 48 weeks of the double-blind TP of this study had the opportunity to continue into a double-blind LTTP at the investigator's discretion. Subjects who did not enroll in the double-blind LTTP or who discontinued early were to proceed to the Posttreatment Follow-up Period.

[e] Maximum duration of 48 weeks post LPFD, or when all subjects completed 48 weeks of the double-blind treatment or discontinued before reaching 48 weeks of the double-blind treatment, or in the event that the study was unblinded per DMC recommendation.

[f] Open-label Phase: Subjects who were compliant with the study protocol 48 weeks post Dose 1 Day 1 can enter in the Open-label Phase, unless medically contraindicated

[g] Early discontinued subjects, ie, subjects who discontinued before completing the double-blind TP (48 weeks) were to be continued to be monitored at Week 9, followed by Weeks 24, 48, 72, 120, and 144 after the last dose up to Week 156, ie, 3 years

run-in period was 6.86 (1.99) and 6.88 (1.82) RBC units per 12 weeks in the luspatercept and placebo treatment groups, respectively.

Table 8: Summary of Baseline Characteristics (ITT Population)

Characteristics	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
Age, years		
Mean (SD)	32.2 (10.67)	31.9 (9.89)
Median (minimum, maximum)	30.0 (18, 66)	30.0 (18, 59)
Gender, n (%)		
Male	92 (41.1)	49 (43.8)
Female	132 (58.9)	63 (56.3)
Childbearing potential	118 (89.4)	57 (90.5)
No childbearing potential	14 (10.6)	6 (9.5)
Race, n (%)		
Asian	81 (36.2)	36 (32.1)
Black or African American	1 (0.4)	0
White	122 (54.5)	60 (53.6)
Not collected or reported	5 (2.2)	5 (4.5)
Other	15 (6.7)	11 (9.8)
Weight, kg		
n	224	112
Mean (SD)	57.1 (10.25)	59.1 (12.49)
Median (minimum, maximum)	56.0 (34, 91)	56.9 (37, 94)
BMI,[a] kg/m^2		
n (%)	223 (99.5)	112 (100)
Mean (SD)	22.11 (3.424)	22.56 (3.604)
Median (minimum, maximum)	21.72 (15.6, 38.3)	22.33 (13.9, 33.2)
Region, n (%)		
North America and Europe	100 (44.6)	51 (45.5)
Middle East and North Africa	52 (23.2)	26 (23.2)
Asia-Pacific	72 (32.1)	35 (31.3)

BMI = body mass index; BSC = best supportive care; ITT = intention to treat; SD = standard deviation.

[a]BMI = weight in kg divided by height in m^2.

Source: Clinical Study Report for BELIEVE.[5]

Table 9: Summary of Baseline Disease Characteristics in the BELIEVE Trial (ITT Population)

Characteristics	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
Beta-thalassemia diagnosis, n (%)		
Beta-thalassemia	174 (77.7)	83 (74.1)
HbE beta-thalassemia	31 (13.8)	21 (18.8)
Beta-thalassemia combined with alpha-thalassemia	18 (8.0)	8 (7.1)
Missing[a]	1 (0.4)	0
Age of starting transfusions (years)		
n (%)	169 (75.4)	85 (75.8)
Mean (SD)	5.9 (11.02)	5.7 (9.67)
Median (minimum, maximum)	2.0 (0, 52)	2.0 (0, 51)
Baseline transfusion burden, 12-week run-in data (RBC units/12 weeks) (week −12 to day 1)		
Mean (SD)	6.86 (1.998)	6.88 (1.83)
Median (minimum, maximum)	6.12 (3.0, 14.0)	6.27 (3.0, 12.0)
Pre-transfusion hemoglobin threshold[b] (g/L) 12-week run-in (g/L)		
Mean (SD)	9.11 (1.117)	9.08 (1.052)
Median (minimum, maximum)	9.30 (4.6, 11.4)	91.6 (6.2, 11.5)
Beta-thalassemia gene mutation, n (%)		
Beta-zero/beta-zero	68 (30.4)	35 (31.3)
Non–beta-zero/beta-zero	155 (69.2)	77 (68.8)
Missing[a]	1 (0.4)	0
ECOG performance status at screening,[c] n (%)		
0	176 (78.6)	91 (81.3)
1	48 (21.4)	20 (17.9)
Missing[a]	0	1 (0.9)
Splenectomy, n (%)		
Yes	129 (57.6)	65 (58.0)
No	95 (42.4)	47 (42.0)
LIC mg/g dw[d]		
Mean (SD)	12.04 (14.847)	10.09 (11.499)
Median (minimum, maximum)	6.14 (0.8, 125.0)	5.05 (0.2, 53.2)
LIC (mg/g dw) category, n (%)		
≤ 3	70 (31.3)	37 (33.0)

Characteristics	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
> 3	154 (68.8)	75 (67.0)
> 3 to ≤ 7	51 (22.8)	30 (26.8)
> 7 to ≤ 15	38 (17.0)	19 (17.0)
> 15	65 (29.0)	26 (23.2)
Myocardial T2* (ms)		
Mean (SD)	33.52 (16.170)	34.76 (10.665)
Median (minimum, maximum)	34.65 (3.0, 205.9)	36.30 (6.4, 57.5)
Myocardial iron content (mg/g dw)		
Mean (SD)	0.9 (1.07)	0.8 (0.64)
Median (minimum, maximum)	0.6 (0, 12)	0.6 (0, 5)
Hip DXA		
Total hip BMD (g/cm^2)		
n (%)	212 (94.6)	106 (94.6)
Mean (SD)	0.80 (0.149)	0.82 (0.141)
Median (minimum, maximum)	0.79 (0.4, 1.3)	0.81 (0.5, 1.2)
T-score		
n (%)	198 (88.3)	98 (87.5)
Mean (SD)	−1.45 (1.139)	−1.34 (1.099)
Median (minimum, maximum)	−1.50 (−4.1, 2.2)	−1.40 (−3.6, 2.6)
Spine DXA		
Lumbar spine BMD (g/cm^2)		
n (%)	210 (93.7)	108 (96.4)
Mean (SD)	0.85 (0.137)	0.88 (0.150)
Median (minimum, maximum)	0.85 (0.5, 1.3)	0.89 (0.4, 1.3)
T-score		
n (%)	199 (88.8)	101 (90.1)
Mean (SD)	−2.15 (1.177)	−1.99 (1.197)
Median (minimum, maximum)	−2.20 (−5.7, 1.9)	−1.90 (−7.3, 0.8)

BMD = bone mineral density; BSC = best supportive care; dw = dry weight; DXA = dual-energy absorptiometry; ECOG = Eastern Cooperative Oncology Group; HbE = hemoglobin E; ITT = intention to treat; LIC = liver iron concentration; RBC = red blood cell; SD = standard deviation.

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

[b]The 24-week pre-transfusion hemoglobin threshold was defined as the mean of all documented pre-transfusion hemoglobin values for a patient during the 24 weeks before dose 1 day 1. The 12-week pre-transfusion hemoglobin threshold was defined as the mean of all documented pre-transfusion hemoglobin values for a patient during the 12 weeks before dose 1 day 1.

[c]ECOG grade: 0 = fully active, able to carry on all pre-disease performance without restriction; 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work).

[d]The value of LIC was either the value collected from the electronic case report form or the value derived from the T2*, R2*, or R2 parameter, depending on which techniques and software were used for the MRI LIC acquisition.

Source: Clinical Study Report for BELIEVE.[5]

Interventions

Patients eligible for the BELIEVE study were randomized in a 2:1 ratio to receive either luspatercept or placebo along with best supportive care every 3 weeks for 48 weeks. Both treatments were administered as a subcutaneous injection in the patient's upper arm, thigh, or abdomen. Doses were administered by the study staff at the clinical site and treatment administrations were documented. Patients in the luspatercept arm received the study drug once every 3 weeks at a starting dose of 1 mg/kg up to a maximum dose of 1.25 mg/kg. Best supportive care included RBC transfusions; iron chelation therapies; antibiotic, antiviral, and antifungal therapies; and/or nutritional support, as needed.

Luspatercept was prepackaged in 3 mL glass vials at 25 mg/vial and 75 mg/vial. The placebo used in the study was sterile normal saline (0.9% sodium chloride for injection) administered as a subcutaneous injection once every 3 weeks. Sterile, normal saline was prepared in syringes by the investigational site's designated individuals to match the active syringe. The investigator and patient were blinded.

The study drug was to be administered according to the following criteria: pre-treatment or pre-transfusion hemoglobin value was to be less than 115 g/L and the increase of hemoglobin was to be 20 g/L or less compared with the pre-dose hemoglobin on day 1 of the previous treatment dose cycle; any related adverse event had to be less than grade 2 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria,[15] and the white blood cell count had to be less than 3 times the count at baseline. Patients had to have had their hemoglobin assessed, and the results had to be available before each administration of the study drug. Hemoglobin not influenced by a transfusion was to be considered for dosing, delays, and reduction actions related to luspatercept. Hemoglobin not influenced by a transfusion was considered a valid hemoglobin measurement within 14 days after transfusion. If a patient was experiencing a dose delay due to hemoglobin increase, hemoglobin measurement was to be performed every week.

The dose titration criteria are presented in Table 10. Dose delay of luspatercept was allowed due to increased hemoglobin or adverse events. If the dose delay was 15 weeks or longer after the administration of the previous dose treatment, treatment was to be discontinued. Dose delays due to an adverse event were at the discretion of the investigator.

During the double-blind treatment phase, treatment with hydroxyurea and anagrelide was not allowed. The use of hematopoietic growth factors was also not allowed. The use of any anticoagulant therapy used for prophylaxis, as well as ASA and low-molecular-weight heparin and platelet aggregation inhibitors, was permitted.

Table 10: Starting Dose Level With Dose Reductions and Dose Titration

Third dose reduction (~ 25%)	Second dose reduction (~ 25%)	First dose reduction (~ 25%)	Starting dose level	First dose titration
0.45 mg/kg	0.6 mg/kg	0.8 mg/kg	1 mg/kg	1.25 mg/kg

Source: Clinical Study Report for BELIEVE.[5]

A total of 97.3% of patients received at least 1 prior iron chelation therapy. The most frequently used iron chelation therapy was deferasirox, with 62.3% of patients in the luspatercept treatment group and 57.8% of patients in the placebo group receiving this therapy. The other prior medications most frequently used in the overall population included vitamin D and analogues (49.4%), folic acid and derivatives (45.2%), calcium (25%), and platelet aggregation inhibitors, excluding heparin (15.7%).

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 11. These end points are further summarized subsequently. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4.

Hematologic Response

Hematologic response was assessed through an erythroid response, RBC transfusion burden, transfusion frequency, and RBC units. The efficacy of luspatercept was assessed using various time intervals for an erythroid response. The primary outcome of BELIEVE was based on an erythroid response measured as a 33% or greater reduction from baseline in transfusion burden (RBC units/time), with a reduction of at least 2 units in the fixed 12-week period from week 13 to week 24. Three of the 4 secondary outcomes assessed an erythroid response of 33% or greater reduction from baseline, with a reduction of at least 2 units in the fixed 12-week period from week 37 to week 48, and a reduction of 50% or greater with a reduction of at least 2 units in the fixed 12-week period from week 13 to week 24 and from week 37 to week 48.

Hematologic response was also assessed using duration of RBC transfusion burden reduction, duration of transfusion independence, and time to the first erythroid response (defined as days to a reduction in RBC transfusion burden of 33% or greater, or 50% or greater). Transfusion reduction was also measured using a consecutive rolling 12-week or 24-week time interval within the entire study period. This end point was not included in either the primary or secondary analyses defined by the protocol.

Transfusion independence was defined as the absence of any transfusion during any consecutive rolling 6-week or 8-week or 12-week interval within the entire study period.

Table 11: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	BELIEVE
Hematologic response (≥ 33% reduction from baseline in transfusion burden [RBC units/time] with a reduction of at least 2 units from week 13 to week 24)	Primary
Hematologic response	Secondary
HRQoL	Other
Iron accumulation	Other
Health care resource utilization	Other
Serum ferritin	Other

HRQoL = health-related quality of life; RBC = red blood cell.

Health-Related Quality of Life

HRQoL was assessed using the SF-36 and TranQoL instruments to determine the effects of luspatercept and placebo on mean change in HRQoL from baseline to week 24 and week 48. The TranQoL domains assessed were total score and physical health. The domains assessed in the SF-36 questionnaire were physical functioning, general health, and Physical Component Score (PCS).

The TranQoL is a disease-specific questionnaire for adults and children with thalassemia major that focuses on quality-of-life issues related to transfusion burden.[16] The TranQoL has 4 versions: a child self-report, an adult self-report, a parent self-report (measuring the impact of the disease on the parent), and a parent proxy report (measuring the child's quality of life). The length of the questionnaire ranges from 29 to 39 items for the child and parent versions, respectively. The TranQoL assesses the following 4 domains: physical health, emotional health, family functioning, and school and career functioning. The total score and domain scores range from 0 (worst) to 100 (best). Internal consistency, test-retest reliability, and the reliability of individual TranQoL domains were acceptable. The ability of the TranQoL to detect a meaningful change in quality of life was determined, as patients who rated their quality of life as better had a 4.0-point (SD = 9.0) improvement in TranQoL scores, from a baseline of 67.1 points to 71.1 points 1 week later (P = 0.008).[16] An MID for the TranQoL in patients with transfusion-dependent thalassemia was not identified in the literature.

The SF-36 is a 36-item, generic, self-reported questionnaire that is scored from 0 to 100 and has been used extensively in clinical trials in many disease areas.[17-20] The SF-36 consists of 8 domains: physical functioning, role — physical, bodily pain, general health, vitality, social functioning, role — emotional, and mental health. For each of the 8 domains, a subscale score can be calculated. The SF-36 also yields 2 summary measures of physical health (the PCS) and mental health (the Mental Component Score [MCS]) derived from scale aggregates. Higher global scores are associated with better quality of life. The scores can also be standardized to the general US population, where an average score is 50. Validity, reliability, and responsiveness for patients with transfusion-dependent thalassemia were not identified in the literature for the English version of the scale. Appendix 4 provides a description and appraisal of these outcome measures.

Iron Accumulation

Iron accumulation was assessed using liver iron concentration and myocardial iron concentration using T2* MRI and were included in the CADTH review. The liver iron concentration was measured at 3 time periods: baseline, 24 weeks, and 48 weeks. Myocardial iron concentration was measured at 2 time points: baseline and 48 weeks.

Health Care Resource Utilization

Health care resource utilization was assessed as number of patients who had a doctor office visit or emergency room visit, or a hospitalization and the number of patients by type of hospitalization (intensive care unit, coronary care unit, other, missing). Number of days of hospitalization was defined as hospitalization end date minus hospitalization start date plus 1. If hospitalization had an unknown start or end date, it was counted as missing.

Serum Ferritin

Serum ferritin was assessed as mean change from baseline. The change was calculated as the difference between the baseline and post-baseline mean serum ferritin levels.

Statistical Analysis

In the BELIEVE study, an estimated sample size of 300 patients (200 in the luspatercept treatment arm and 100 in the placebo treatment arm) was required to achieve at least 90% power to detect the difference between the treatment groups with a 2-sided 0.05 level of significance and assumed a 10% dropout rate for each treatment group. The assumed targeted response rate for the primary end point was 40% in the luspatercept treatment group and 20% in the placebo group.

All efficacy outcomes were to be evaluated using the ITT population except for the HRQoL analyses, which used the HRQoL evaluable population (defined subsequently). For the statistical plan, the sponsor defined the primary outcome as the number of responders (patients who achieve an erythroid response during the 12-week interval from week 13 to week 24 compared with baseline) divided by the number of patients in the ITT population within each treatment group. The erythroid response was defined as patients with a 33% or greater reduction from baseline in RBC transfusion burden, with a reduction of at least 2 units, where the 12-week interval on or before first dose and day 1 is used as the baseline value. The 12-week RBC transfusion burden (units per 12 weeks) is calculated as the number of RBC units transfused during the 12-week interval.

Luspatercept was compared with placebo using the Cochran-Mantel-Haenszel test, where stratification was done by geographical region as defined at randomization. The OR, with a corresponding 2-sided (at 0.05 alpha level) 95% CI and P value, was evaluated. The number and percentage of responders was summarized by treatment group and the difference in proportions (luspatercept minus placebo) and corresponding 95% CI were calculated by unconditional test.

The secondary efficacy outcomes were tested in the following hierarchy:

- Proportion of patients with a hematological response defined as a 33% or greater reduction from baseline in RBC transfusion burden, with a reduction of at least 2 units from week 37 to week 48.
- Proportion of patients with a hematological response defined as a 50% or greater reduction from baseline in RBC transfusion burden, with a reduction of at least 2 units from week 13 to week 24.
- Proportion of patients with a hematological response defined as a 50% or greater reduction from baseline in RBC transfusion burden, with a reduction of at least 2 units from week 37 to week 48.

The analysis of the 3 secondary end points that were followed was similar to the analysis of the primary efficacy end point, which was conducted by using a Cochran-Mantel-Haenszel method, where stratification was done by geographical region, as defined at randomization. To control the overall type I error rate of 0.05 due to multiplicity, the secondary end points were tested using gate-keeping methods. If the result from the primary efficacy analysis in the ITT population showed statistical significance, secondary end point 1 was tested next. Secondary end point 2 was tested only if the test results for both the primary end point and secondary end point 1 were significant. Secondary end point 3 was tested only if the test results for the primary end point and secondary end points 1 and 2 were all significant.

No other end points analyzed in the study were included in the gate-keeping procedures and did not control for type I errors (i.e., fourth key secondary end point, rolling period analyses, HRQoL, iron accumulation, health care resource utilization, serum ferritin).

The additional end points analyzed in the study that were not included in the gate-keeping procedures were: the fourth secondary end point, the duration of transfusion burden, time to the first erythroid response, transfusion independence and duration of transfusion independence, HRQoL, iron accumulation, health care resource utilization, and serum ferritin levels.

The fourth secondary end point was the mean change in RBC transfusion burden at the 12-week interval of week 13 to week 24 from the baseline 12-week interval. This end point was analyzed using an analysis of covariance (ANCOVA) with the baseline values and geographical regions defined at randomization taken as covariates for the ITT population.

The duration of transfusion burden, time to first erythroid response, and transfusion independence and duration of transfusion independence, were measured by using a consecutive "rolling" 12-week or 24-week time interval. The treatment comparison was conducted using a Cochran-Mantel-Haenszel test stratified by the geographical regions defined at randomization as a stratification factor. The difference in proportions (luspatercept minus placebo) and corresponding 95% CI was calculated by exact unconditional test.

The duration of the longest continuous 12 week–based erythroid response (based on 33% and 50% criteria) was analyzed using the Kaplan-Meier method (log-log transformation was used). The median duration of response and 25th and 75th quartiles were associated with 2-sided (at 0.05 alpha level) 95% CIs for each treatment group. The duration of the individual continuous response is defined as the last day of response minus the first day of response plus 1. For patients with a response and who continued to respond at the efficacy cut-off date, the end day of the response was censored.

Time from the first dosing date to the first erythroid response was analyzed and presented using descriptive statistics by treatment group. The difference in time from the first dosing date to the first erythroid response (luspatercept minus placebo) and corresponding 95% CI and P value was estimated by a t-test.

Transfusion independence was defined as the absence of any transfusion during any consecutive rolling 6-week or 8-week or 12-week time interval within the entire study period, up to the efficacy cut-off date. The duration of transfusion independence was summarized using the Kaplan-Meier method. The duration of transfusion independence was defined as the last day of response minus the first day of response plus 1. For patients who continued to respond at the efficacy cut-off date, the end day of the response was censored at the date of efficacy cut-off.

Continuous variables were summarized using mean and SD, while categorical variables were summarized using frequency and percentage. Other efficacy outcomes in the BELIEVE study were analyzed using descriptive statistics. For continuous variables, the ANCOVA method used was analyzed and was presented as the least squares means with corresponding standard errors for each treatment group, along with the least squares mean of treatment difference (luspatercept versus placebo) with corresponding 95% CI and P value, unless otherwise noted previously. Wherever the ANCOVA method was used, the statistical assumption was validated first, and a log transformation was applied, as needed. The iron accumulation was analyzed using an ANCOVA method, with the geographical regions defined at randomization, with both liver iron concentration and myocardial iron concentration at baseline as covariates. The serum ferritin levels were analyzed using the ANCOVA method to

compare the treatment difference between groups, with the geographical regions defined at randomization and baseline serum ferritin level as covariates.

For the HRQoL analyses, the planned analyses included descriptive tests for significance only in the HRQoL evaluable population (i.e., complete-case analysis).

Handling of Missing Data or Dropout

For patients who did not complete 24 weeks or 48 weeks of double-blind treatment, the transfusion records were collected up to 48 weeks or 9 weeks after the last dose, whichever was the later date. The efficacy cut-off date was defined as the minimum date among death date, study discontinuation date, last dose date plus 20, and May 11, 2018. For the imputation for RBC transfusion units, if a patient's efficacy cut-off date was before the end of the 12-week interval, or a patient had any invalid transfusion records (i.e., transfusion unit not available) during the specified 12-week interval, the patient would be included in the analysis as a nonresponder. No other imputation techniques were completed for any other end points in the study (i.e., HRQoL, iron accumulation data). The MRI-derived liver iron concentration value was based on the data-collection technique and software used.

Subgroups

Although a number of subgroups were identified by the sponsor, only those subgroups identified in the protocol are presented (i.e., splenectomy status and baseline hematologic status). The baseline hematologic status was not part of the preplanned subgroup analyses. The subgroup analyses by splenectomy status did not account for multiplicity of testing.

Analysis Populations

The randomized ITT population consisted of all randomized patients regardless of whether or not the patient received luspatercept. The ITT population was the primary analysis population for efficacy.

The safety population consisted of all patients who were randomized and received at least 1 dose of luspatercept.

The HRQoL evaluable population comprised all patients in the ITT population who completed the HRQoL assessment at baseline (screening) and at least 1 post-baseline assessment visit. The completion of an HRQoL assessment was defined for the 2 instruments used for assessment (namely, the SF-36 and TranQoL) as follows:

- SF-36: Completion was defined as answering 50% or more of the items (i.e., 18 or more items answered out of the 36 items or a non-missing total score).
- TranQoL: Completion was defined as answering 75% or more of the items (i.e., 27 or more items answered out of the 36 items or a non-missing total score).

Results

Patient Disposition

In BELIEVE, a total of 336 patients were randomized: 224 patients were randomized to the luspatercept treatment group and 112 patients were randomized to the placebo group. The proportion of patients who completed 24 and 48 weeks of treatment was similar in both treatment groups. The percentage of patients who withdrew from the treatment due to lack of efficacy was 7.1% in the placebo treatment group, and 0.9% in the luspatercept treatment

group. The percentage of patients who withdrew from the treatment due to an adverse event was 4.5% in the luspatercept treatment group and 0.9% in the placebo treatment group. Two deaths were reported, 1 in each treatment group. Table 12 presents the patient disposition of the BELIEVE study.

Exposure to Study Treatments

The summary of exposure to study treatment was conducted in the safety population. In the luspatercept and placebo treatment groups, 99.5% and 97.3% of the patients received at least 1 dose of the study drug, respectively. The mean (SD) treatment duration, in weeks, was

Table 12: Patient Disposition

Characteristic	BELIEVE	
	Luspatercept + BSC	Placebo + BSC
Screened, N	447	
Randomized, N	224	112
Patients who received treatment, N (%)	223 (99.6)	109 (97.3)
Completed 24 weeks of treatment	210 (93.8)	102 (91.1)
Completed 48 weeks of treatment	200 (89.3)	96 (85.7)
Treatment discontinued	42 (18.8)	24 (21.4)
Reason for treatment discontinuation, N (%)		
Withdrawal by patient	26 (11.6)	12 (10.7)
Adverse event	10 (4.5)	1 (0.9)
Lack of efficacy	2 (0.9)	8 (7.1)
Other[a]	3 (1.3)	3 (2.7)
Protocol violation	1 (0.4)	0
Discontinued from study, N (%)	26 (11.6)	14 (12.5)
Reason for study discontinuation, N (%)		
Withdrawal by patient	13 (5.8)	6 (5.4)
Adverse event	4 (1.8)	0
Other[b]	2 (0.9)	1 (0.9)
Death	1 (0.4)	1 (0.9)
ITT, N (%)	224 (100)	112 (100)
Safety, N (%)	223 (99.5)	109 (97.3)
HRQoL evaluable population, N (%)	211 (94.1)	103 (92)

BSC = best supportive care; HRQoL = health-related quality of life; ITT = intention to treat.

[a]Other reasons for treatment discontinuation in the luspatercept plus BSC treatment group were interested in other clinical studies, planning to get pregnant, transferred residence, and personal reasons. Reasons for treatment discontinuation in the placebo plus BSC treatment group were personal reasons (n = 2) and not wishing to enter into the long-term treatment period.

[b]Reasons for study discontinuation in the luspatercept plus BSC treatment group were personal reasons and moved to another city. The reason for study discontinuation in the placebo plus BSC treatment group was personal reasons.

Source: Clinical Study Report for BELIEVE.[5]

62 (16.83) and 60.1 (16.83) in the luspatercept and placebo treatment group, respectively. The mean (SD) number of doses (each dose was administered every 3 weeks) received per patient was 19.8 (5.51) and 19.6 (5.58) in the luspatercept and placebo treatment groups, respectively. In the luspatercept and placebo treatment groups, 64.6% and 64.2% received between 17 and 24 doses per patient, respectively. In the luspatercept treatment group, 46.2% of the patients had their dose of the study drug titrated to the maximum dose of 1.25 mg/kg compared with 66.1% of patients in the placebo treatment group. In the luspatercept treatment group, 11.2% of the patients had their dose reduced to 0.80 mg/kg compared with 2.8% of patients in the placebo treatment group. A total of 1.8% and 0.9% of the patients had a second dose reduction (i.e., reduction of the dose from 0.80 mg/kg to 0.60 mg/kg) in the luspatercept treatment group and placebo treatment group, respectively. In the luspatercept and placebo treatment groups, 61.4% and 41.3% of the patients had at least 1 dose delay, respectively; 13% and 7.3% of the patients had 4 or more dose delays, respectively.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported subsequently. See Appendix 3 for detailed efficacy data on the rolling period.

These efficacy outcomes were RBC transfusion–related and were defined over fixed 12-week intervals. The fixed 12-week intervals were defined as:

- baseline 12-week interval: from day −83 to day 1
- week 1 to week 12 interval: from day 2 to day 85
- week 13 to week 24 interval: from day 86 to day 169
- week 25 to week 37 interval: from day 170 to day 253
- week 37 to week 48 interval: from day 254 to day 337.

Hematologic Response

Reduction in RBC Transfusion Burden

The primary outcome of the BELIEVE study was to determine the proportion of patients who achieved an erythroid response measured as a 33% or greater reduction from baseline in transfusion burden (RBC units/time), with a reduction of at least 2 units in the fixed 12-week period from week 13 to week 24. In the luspatercept treatment group, 21.4% of the patients responded to the treatment and 4.5% of the patients in the placebo group achieved the primary end point, with the difference in proportions being 17.0 (95% CI, 10.4 to 23.6). The OR of 5.79 (95% CI, 2.24 to 14.97; P < 0.0001) favoured luspatercept over placebo. The results of the primary efficacy end point are presented in Table 13.

The first of the 4 secondary outcomes of the BELIEVE study was to determine the proportion of patients who achieved an erythroid response measured as a 33% or greater reduction from baseline in transfusion burden (RBC units/time), with a reduction of at least 2 units in a fixed 12-week period from week 37 to week 48. In the luspatercept treatment group, 19.6% of the patients responded to the treatment and 3.6% of the patients in the placebo group achieved this secondary end point, with the difference in proportions being 16.1 (95% CI, 9.8 to 22.3). The OR of 6.44 (95% CI, 2.27 to 18.26; P < 0.0001) favoured the luspatercept treatment over placebo. The results of this secondary efficacy end point are presented in Table 14.

The second of the 4 secondary outcomes of the BELIEVE study was the proportion of patients who achieved an erythroid response measured as a 50% or greater reduction from

baseline in transfusion burden (RBC units/time), with a reduction of at least 2 units in a fixed 12-week period from week 13 to week 24. In the luspatercept treatment group, 7.6% of the patients responded to the treatment and 1.8% of the patients in the placebo group achieved this secondary end point, with the difference in proportions being 5.8 (95% CI, 1.6 to 10.1). The OR of 4.55 (95% CI, 1.03 to 20.11; P = 0.0303) favoured the luspatercept treatment over placebo. The results of this secondary efficacy end point are presented in Table 15.

The third of the 4 secondary outcomes of the BELIEVE study was to determine the proportion of patients who achieved an erythroid response measured as a 50% or greater reduction from baseline in transfusion burden (RBC units/time), with a reduction of at least 2 units in a fixed 12-week period from week 37 to week 48. In the luspatercept treatment group, 10.3% of the patients responded to the treatment and 0.9% of the patients in the placebo group achieved this secondary end point, with the difference in proportions being 9.4 (95% CI, 5.0 to 13.7). The OR of 11.92 (95% CI, 1.65 to 86.29; P = 0.0017) favoured the luspatercept treatment over placebo. The results of this secondary efficacy end point are presented in Table 16.

Table 13: RBC Transfusion Burden Reduction (≥ 33% Reduction) From Baseline to the Fixed Week 13 to Week 24 Interval (ITT Population)

Characteristics	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
Number of responders, n (%)	48 (21.4)	5 (4.5)
Difference in proportions, % (95% CI)[a]	17.0 (10.4 to 23.6)	
Odds ratio (95% CI)[b]	5.79 (2.24 to 14.97)	
P value	< 0.0001	

BSC = best supportive care; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; RBC = red blood cell.

[a]Difference in proportions (luspatercept minus placebo) and 95% CIs were estimated from the unconditional test.

[b]The odds ratio (luspatercept over placebo), 95% CIs, and P value were estimated from the CMH test stratified by the geographical regions defined at randomization.

Source: Clinical Study Report for BELIEVE.[5]

Table 14: RBC Transfusion Burden Reduction (≥ 33% Reduction) From Baseline to the Fixed Week 37 to Week 48 Interval (ITT Population)

Characteristics	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
Number of responders, n (%)	44 (19.6)	4 (3.6)
Difference in proportions, % (95% CI)[a]	16.1 (9.8 to 22.3)	
Odds ratio (95% CI)[b]	6.44 (2.27 to 18.26)	
P value	< 0.0001	

BSC = best supportive care; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; RBC = red blood cell.

[a]Difference in proportions (luspatercept minus placebo) and 95% CIs were estimated from the unconditional test.

[b]The odds ratio (luspatercept over placebo), 95% CIs, and P value were estimated from the CMH test stratified by the geographical regions defined at randomization.

Source: Clinical Study Report for BELIEVE.[5]

The fourth secondary outcome of the BELIEVE study was to determine the mean change in RBC transfusion burden from baseline to the fixed week 13 to week 24 interval. In the luspatercept treatment group, the mean (SD) change from baseline in transfusion burden was −0.67 (1.795) and, in the placebo group, it was 0.66 (1.774). The least squares mean difference was −1.35 (95% CI, −1.77 to −0.93; P < 0.0001). The results of this secondary efficacy end point are presented in Table 17.

Duration of Transfusion Burden Reduction

For patients with a 33% or greater reduction in RBC transfusion burden during any rolling 12-week interval, the median longest duration of RBC transfusion burden reduction was 104.0 (95% CI, 98.0 to 113.0) days in the luspatercept treatment group and 90.0 (95% CI, 86.0 to 94.0) days in the placebo treatment group. For patients with a 50% or greater reduction in RBC transfusion burden during any rolling 12-week interval, the median longest duration of RBC transfusion burden reduction was 97.5 (95% CI, 93.0 to 104.0) days in the luspatercept treatment group and 86.0 (95% CI, 84.0 to 103.0) days in the placebo treatment group. The results are presented in Table 18.

Table 15: RBC Transfusion Burden Reduction (≥ 50% Reduction) From Baseline to the Fixed Week 13 to Week 24 Interval (ITT Population)

Characteristics	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
Number of responders, n (%)	17 (7.6)	2 (1.8)
Difference in proportions, % (95% CI)[a]	5.8 (1.6 to 10.1)	
Odds ratio (95% CI)[b]	4.55 (1.03 to 20.11)	
P value	0.0303	

BSC = best supportive care; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; RBC = red blood cell.

[a]Difference in proportions (luspatercept minus placebo) and 95% CIs were estimated from the unconditional test.

[b]Odds ratio (luspatercept over placebo), 95% CIs, and P value were estimated from the CMH test stratified by the geographical regions defined at randomization.

Source: Clinical Study Report for BELIEVE.[5]

Table 16: RBC Transfusion Burden Reduction (≥ 50% Reduction) From Baseline to the Fixed Week 37 to Week 48 Interval (ITT Population)

Characteristics	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
Number of responders, n (%)	23 (10.3)	1 (0.9)
Difference in proportions, % (95% CI)[a]	9.4 (5.0 to 13.7)	
Odds ratio (95% CI)[b]	11.92 (1.65 to 86.29)	
P value	0.0017	

BSC = best supportive care; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; RBC = red blood cell.

[a]Difference in proportions (luspatercept minus placebo) and 95% CIs were estimated from the unconditional test.

[b]The odds ratio (luspatercept over placebo), 95% CIs, and P value were estimated from the CMH test stratified by the geographical regions defined at randomization.

Source: Clinical Study Report for BELIEVE.[5]

Frequency of Response

In the luspatercept treatment group, 70.5% of patients exhibited a 33% or greater response

Table 17: Mean Change in Transfusion Burden (RBC Units/12 Weeks) From Baseline to the Fixed Week 13 to Week 24 Interval (ITT Population)

Characteristics	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
Baseline		
Mean (SD)	6.86 (1.998)	6.88 (1.829)
Median (minimum, maximum)	6.12 (3.0, 14.0)	6.27 (3.0, 12.0)
Week 13 to 24		
n (%)	210 (93.75)	102 (91.07)
Mean (SD)	6.15 (2.434)	7.55 (2.228)
Median (minimum, maximum)	6.00 (0.0, 15.0)	8.00 (1.0, 13.0)
Mean change from baseline (week 13 to week 24)		
n (%)	210 (93.75)	102 (91.07)
Mean (SD)	−0.67 (1.795)	0.66 (1.774)
Median (minimum, maximum)	0.00 (−6.0, 5.0)	0.00 (−6.0, 4.4)
LS mean difference (95% CI)[a]	−1.35 (−1.77 to −0.93)	
P value[a]	< 0.0001	

ANCOVA = analysis of covariance; BSC = best supportive care; CI = confidence interval; ITT = intention to treat; LS = least squares; RBC = red blood cell; SD = standard deviation.

Note: Missing data were excluded from this analysis.

[a]Estimates were based on an ANCOVA model with geographical regions defined at randomization and baseline transfusion burden as covariates.

Source: Clinical Study Report for BELIEVE.[5]

Table 18: Longest Duration of RBC Transfusion Burden Reduction During Any Rolling 12-Week Interval (ITT Population)

Characteristics	BELIEVE	
	Luspatercept plus BSC (N = 224)	Placebo plus BSC (N = 112)
Number of patients with ≥ 33% RBC transfusion burden reduction during any rolling 12-week interval, n (%)	158 (70.5)	33 (29.5)
Median days (minimum, maximum)[a]	104.0 (84, 588+)	90.0 (84, 342)
Number of patients with ≥ 50% RBC transfusion burden reduction during any rolling 12-week interval, n (%)	90 (40.2)	7 (6.3)
Median days (minimum, maximum)[a]	97.5 (84, 588+)	86.0 (84, 342)

BSC = best supportive care; CI = confidence interval; ITT = intention to treat; RBC = red blood cell.

[a]The plus sign (+) indicates the maximum value was from censored observation.

Source: Clinical Study Report for BELIEVE.[5]

during any rolling 12-week period compared with 29.5% of the patients in the placebo treatment group. In the luspatercept treatment group, 40.2% of the patients had a 50% or greater response during any rolling 12-week period compared with the 6.3% of the patients in the placebo treatment group (Table 19).

Transfusion Independence

The median longest duration of RBC transfusion independence (Table 20) for 6 or more, 8 or more, and 12 or more weeks, was 60.5 days, 65.0 days, and 270.5 days, respectively, in the luspatercept treatment group, and 44.0 days, 71.5 days, and 0 days, respectively, in the placebo group. The difference in proportions between the luspatercept treatment group and the placebo group was 10.7 (95% CI, 4.1 to 17.4), 8.9 (95% CI, 4.2 to 13.7), and 4.0 (95% CI, 1.4 to 6.6) for 6 or more, 8 or more, and 12 or more weeks, respectively. The OR was 3.18 (95% CI, 1.36 to 7.44; P = 0.0055), 6.76 (95% CI, 1.56 to 29.28; P = 0.0036), and infinity (P = 0.0317) for 6 or more, 8 or more, and 12 or more weeks, respectively.

Table 19: Patients Who Achieved a Single or Multiple Responses (≥ 33% and ≥ 50% RBC Transfusion Burden Reduction From Baseline) During Any Rolling 12-Week Interval (ITT Population)

Patients with ≥ 33% or ≥ 50% response during any rolling 12-week interval	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
Number of patients with ≥ 33% response		
Number of patients with at least 1 response, n (%)	158 (70.5)	33 (29.5)
Mean (SD)[a]	4.3 (3.20)	3.6 (3.15)
Number of patients with 1 response, n (%)[b]	31 (19.6)	8 (24.2)
Number of patients with 2 or more responses, n (%)[b]	127 (80.4)	25 (75.8)
Number of patients with 3 or more responses, n (%)[b]	102 (64.6)	17 (51.5)
Number of patients with 4 or more responses, n (%)[b]	81 (51.3)	12 (36.4)
Number of patients with ≥ 50% response		
Number of patients with at least 1 response, n (%)	90 (40.2)	7 (6.3)
Mean (SD)[a]	3.3 (2.69)	2.3 (1.38)
Number of patients with 1 response, n (%)[b]	28 (31.1)	2 (28.6)
Number of patients with 2 or more responses, n (%)[b]	62 (68.9)	5 (71.4)
Number of patients with 3 or more responses, n (%)[b]	41 (45.6)	2 (28.6)
Number of patients with 4 or more responses, n (%)[b]	30 (33.3)	1 (14.3)

BSC = best supportive care; CI = confidence interval; ITT = intention to treat; RBC = red blood cell; SD = standard deviation.

[a]Mean and median of multiple time periods (response periods may have overlapped).

[b]Percentages are based on number of responders. (A response period was defined as a continuous period in which a patient had an erythroid response during any 12-week interval within the period.)

Source: Clinical Study Report for BELIEVE.[5]

Time to Erythroid Response

For patients exhibiting a reduction in RBC transfusion burden of 33% or more during any rolling 12-week interval, the mean (SD) time from the first dose of the study drug to first erythroid response was 56.1 (82.21) days in the luspatercept treatment group and 119.2 (112.21) days in the placebo treatment group. Between the luspatercept treatment group and the placebo group, the difference in the mean time from the first dose of the study drug to the first erythroid response was −63.1 days (95% CI, −96.3 to −29.9; P = 0.0002). For patients with a reduction in RBC transfusion burden of 50% or more during any rolling 12-week interval, the mean (SD) time from the first dose of the study drug to the first erythroid response was 80.5 (103.81) days in the luspatercept treatment group and 90.3 (89.27) days in the placebo treatment group.

Change in Number of RBC Units

During the fixed week 13 to week 24 interval (among the patients in the luspatercept group who exhibited a reduction in RBC transfusion units of 33% or greater and 50% and greater), a 33% or greater reduction per patient from baseline was 3.02 RBC units per 12 weeks; a 50% or greater reduction was 3.17 units per 12 weeks. Results were not reported for the placebo group.

During the fixed week 1 to week 24 interval, patients exhibited a reduction in RBC transfusion units of 33% or greater and 50% or greater. In the luspatercept treatment group, a 33% or greater reduction per patient from baseline was a reduction of 6.05 RBC units per 24 weeks and a 50% or greater reduction was a reduction of 7 RBC units per 24 weeks. Results were not reported for the placebo group.

Table 20: RBC Transfusion Independence (ITT Population)

Characteristic	RBC transfusion independence for any 6-week interval		RBC transfusion independence for any 8-week interval		RBC transfusion independence for any 12-week interval	
	Luspatercept plus BSC (N = 224)	Placebo plus BSC (N = 112)	Luspatercept plus BSC (N = 224)	Placebo plus BSC (N = 112)	Luspatercept plus BSC (N = 224)	Placebo plus BSC (N = 112)
Number of responders, n (%)	38 (17.0)	7 (6.3)	24 (10.7)	2 (1.8)	9 (4.0)	0
Difference in proportions, % (95% CI),[a] luspatercept minus placebo	10.7 (4.1 to 17.4)		8.9 (4.2 to 13.7)		4.0 (1.4 to 6.6)	
Odds ratio (95% CI)[b]	3.18 (1.36 to 7.44)		6.76 (1.56 to 29.28)		Infinity	
P value	0.0055		0.0036		0.0317	
Longest duration of transfusion independence[c] (days)						
Median (minimum, maximum)	60.5 (42, 507+)	44.0 (42, 81)	65.0 (56, 507+)	71.5 (62, 81)	270.5 (90, 507+)	NR

BSC = best supportive care; CI = confidence interval; ITT = intention to treat; NR = not reported; RBC = red blood cell.

[a]The difference in proportions (luspatercept minus placebo) and 95% CIs were estimated from the exact unconditional test.

[b]The odds ratio (luspatercept over placebo), 95% CIs, and P value were estimated from the Cochran Mantel-Haenszel test stratified by the geographical regions defined at randomization.

[c]The plus sign (+) indicates the maximum value was from censored observation.

Source: Clinical Study Report for BELIEVE.[5]

Health-Related Quality of Life

In the BELIEVE study, HRQoL was measured using 2 instruments, the TranQoL and SF-36.

TranQoL – Physical Health

In the luspatercept treatment group, the mean (SD) change from baseline at week 24 (Table 22) in the TranQoL physical health score was −1.5 (14.26) and, in the placebo treatment group, it was −0.7 (14.24). In the luspatercept treatment group, the mean (SD) change from baseline at week 48 in the TranQoL physical health score was −1.9 (17.26) and, in the placebo treatment group, it was 0.6 (14.51) (Table 23).

TranQoL Total Score

In the luspatercept treatment group, the mean (SD) change from baseline at week 24 in the TranQoL total score was 0.8 (11.56) and, in the placebo treatment group, it was −0.4 (11.62) (Table 24). In the luspatercept treatment group, the mean (SD) change from baseline at week 48 in the TranQoL total score was 0.5 (13.51) and, in the placebo treatment group, it was 0.3 (12.01) (Table 25).

SF-36 – Physical Functioning

In the luspatercept treatment group, the mean (SD) change from baseline at week 24 in the SF-36 physical functioning score was −0.3 (6.93) and, in the placebo treatment group, it was −0.2 (7.86) (Table 26). In the luspatercept treatment group, the mean (SD) change from baseline at week 48 in the SF-36 physical functioning score was −0.3 (7.33) and, in the placebo treatment group, it was −0.4 (7.64) (Table 27).

Table 21: Time From First Dosing Date to First Erythroid Response (ITT Population)

Characteristics	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
Time from first dosing date to first erythroid response (≥ 33% reduction in RBC transfusion burden)		
Number of responders, n (%)	158 (70.5)	33 (29.4)
Mean (SD) days	56.1 (82.21)	119.2 (112.21)
Median (minimum, maximum) days	12.0 (2, 360)	107.0 (2, 386)
Difference, luspatercept minus placebo (95% CI),[a] days	−63.1 (−96.3 to −29.9)	
P value	0.0002	
Time from first dosing date to first erythroid response (≥ 50% reduction in RBC transfusion burden)		
Number of responders, n (%)	90 (40.17)	7 (6.25)
Mean (SD) days	80.5 (103.81)	90.3 (89.27)
Median (minimum, maximum) days	24.5 (2, 416)	43.0 (2, 213)
Difference, luspatercept minus placebo (95% CI),[a] days	−9.8 (−90.0 to 70.4)	
P value	0.8091	

BSC = best supportive care; CI = confidence interval; ITT = intention to treat; RBC = red blood cell; SD = standard deviation.

Note: Only patients who had a response are included in the table.

[a]Estimates were based on the t-test.

Source: Clinical Study Report for BELIEVE.[5]

SF-36: General Health

In the luspatercept treatment group, the mean (SD) change from baseline at week 24 in the SF-36 general health score was 0.4 (7.18) and, in the placebo treatment group, it was 0.3 (7.03) (Table 28). In the luspatercept treatment group, the mean (SD) change from baseline at week 48 in the SF-36 general health score was 0.1 (7.73) and, in the placebo treatment group, it was −0.5 (7.32) (Table 29).

SF-36: Physical Component Summary

In the luspatercept treatment group, the mean (SD) change from baseline at week 24 in the SF-36 physical component summary score was −0.4 (7.01) and, in the placebo treatment group, it was −0.3 (7.97) (Table 30). In the luspatercept treatment group, the mean (SD) change from baseline at week 48 in the SF-36 physical component summary score was −0.9 (7.45) and, in the placebo treatment group, it was 0.1 (6.07) (Table 31).

Iron Accumulation

A total of 97.3% of patients received at least 1 prior iron chelation therapy. The most frequently used iron chelation therapy was deferasirox, with 62.3% of patients in the luspatercept group and 57.8% of patients in the placebo group receiving this therapy. The other most frequently used prior medications in the overall population included vitamin D and

Table 22: Summary of TranQoL Change From Baseline in Physical Health by Visit at 24 Weeks (HRQoL Evaluable Population)

Characteristics[a]	BELIEVE	
	Luspatercept + BSC (N = 211)	Placebo + BSC (N = 103)
Baseline		
n (%)	211 (100)	103 (100)
Mean (SD)	67.4 (14.71)	69.5 (16.34)
Median (minimum, maximum)	67.5 (37.5, 100.0)	72.5 (22.5, 97.5)
Week 24		
n (%)	200 (94.7)	94 (91.2)
Mean (SD)	66.4 (16.58)	69.8 (15.19)
Median (minimum, maximum)	70.0 (10.0, 100.0)	68.8 (35.0, 100.0)
Change from baseline at week 24		
n (%)	200 (94.7)	94 (91.2)
Mean (SD)	−1.5 (14.26)	−0.7 (14.24)
Median (minimum, maximum)	0.0 (−70.0, 37.5)	0.0 (−52.5, 40.0)
P value[b]	0.666	

BSC = best supportive care; HRQoL = health-related quality of life; SD = standard deviation; TranQoL = Transfusion-Dependent Quality of Life questionnaire.

[a]TranQoL is considered evaluable if at least 27 of the 36 items in the questionnaire are answered.

[b]The P value was calculated based on a 2-sample, 2-sided t-test.

Source: Clinical Study Report for BELIEVE.[5]

analogues (49.4%), folic acid and derivatives (45.2%), calcium (25%), and platelet aggregation inhibitors, excluding heparin (15.7%).

Liver Iron Concentration

Among the patients with baseline and follow-up measurements, the mean (SD) change in liver iron concentration from baseline to week 48 (Table 32) was 0.10 mg/g (5.760 mg/g) dry weight in the luspatercept treatment group and 0.08 mg/g (5.229 mg/g) dry weight in the placebo treatment group. The least squares mean difference at week 48 for the luspatercept treatment group versus the placebo treatment group was 0.11 mg/g dry weight (95% CI, −1.16 to 1.38; P = 0.8685).

Myocardial Iron Concentration

Among the patients with baseline and follow-up measurements, the mean change in myocardial T2* from baseline to week 48 (Table 33) was −1.83 ms in the luspatercept treatment group and 0.02 ms in the placebo treatment group. The least squares mean difference for the luspatercept treatment group versus the placebo treatment group was −2.39 ms (95% CI, −4.67 to −0.12; P = 0.0391).

A total of 60.7% of the patients in both treatment groups were on iron chelation monotherapy at both baseline and post-baseline. In the luspatercept treatment group, 23.2% of the patients

Table 23: Summary of TranQoL Change From Baseline in Physical Health by Visit at 48 Weeks (HRQoL Evaluable Population)

Characteristics[a]	BELIEVE	
	Luspatercept + BSC (N = 211)	Placebo + BSC (N = 103)
Baseline		
n (%)	211 (100)	103 (100)
Mean (SD)	67.4 (14.71)	69.5 (16.34)
Median (minimum, maximum)	67.5 (37.5, 100.0)	72.5 (22.5, 97.5)
Week 48		
n (%)	179 (84.8)	88 (85.4)
Mean (SD)	66.1 (18.30)	70.4 (16.25)
Median (minimum, maximum)	70.0 (10.0, 100.0)	70.0 (32.5, 100.0)
Change from baseline at week 48		
n (%)	179 (84.8)	88 (85.4)
Mean (SD)	−1.9 (17.26)	0.6 (14.51)
Median (minimum, maximum)	−2.5 (−77.5, 45.0)	0 (−37.5, 57.5)
P value[b]	0.238	

BSC = best supportive care; HRQoL = health-related quality of life; SD = standard deviation; TranQoL = Transfusion-Dependent Quality of Life questionnaire.

[a]TranQoL is considered evaluable if at least 27 of the 36 items in the questionnaire are answered.

[b]The P value was calculated based on a 2-sample, 2-sided t-test.

Source: Clinical Study Report for BELIEVE.[5]

were using an iron chelation combination therapy at baseline and the post-baseline periods compared with 19.6% of the patients in the placebo group. The changes in the mean daily doses of iron chelation therapies are presented in Table 34.

Health Care Resource Utilization

In the luspatercept treatment arm, 70.5% of the patients compared with 58.0% of the patients in the placebo treatment arm visited a doctor during the study. In the luspatercept treatment arm, 21.4% of the patients compared with 19.6% of the patients in the placebo treatment arm had to visit the emergency department. The proportions of patients requiring hospitalization were 18.8% and 3.6% in the luspatercept and placebo treatment groups, respectively. Patients in the luspatercept treatment arm spent a mean (SD) of 3.6 (5.36) days in a higher-care unit, while patients in the placebo treatment arm spent a mean (SD) of 0.6 (0.55) days in a higher-care unit (Table 35).

Serum Ferritin

The post-baseline mean serum ferritin level was calculated during the last 12 weeks of the 48-week double-blind treatment period, or the last 12 weeks of study treatment for patients who discontinued study participation early. Among those with both a baseline and a follow-up measurement, the mean change in serum ferritin level from baseline (Table 36) was −248.02 mcg/L in the luspatercept treatment group and 106.62 mcg/L in the placebo treatment group.

Table 24: Summary of TranQoL Change From Baseline in Total Score by Visit at 24 Weeks (HRQoL Evaluable Population)

Characteristics[a]	BELIEVE	
	Luspatercept + BSC (N = 211)	Placebo + BSC (N = 103)
Baseline		
n (%)	211 (100)	103 (100)
Mean (SD)	66.9 (15.20)	70.4 (14.01)
Median (minimum, maximum)	68.1 (26.4, 99.2)	72.2 (35.7, 96.0)
Week 24		
n (%)	200 (94.7)	94 (91.2)
Mean (SD)	68.3 (16.49)	71.2 (14.49)
Median (minimum, maximum)	70.3 (25.0, 99.3)	73.4 (35.6, 96.2)
Change from baseline at week 24		
n (%)	200 (94.7)	94 (91.2)
Mean (SD)	0.8 (11.56)	−0.4 (11.62)
Median (minimum, maximum)	0.1 (−29.2, 39.3)	−1.3 (−36.6, 36.8)
P value[b]	0.384	

BSC = best supportive care; HRQoL = health-related quality of life; SD = standard deviation; TranQoL = Transfusion-Dependent Quality of Life questionnaire.

[a]The TranQoL is considered evaluable if at least 27 of the 36 items in the questionnaire are answered.

[b]The P value was calculated based on a 2-sample, 2-sided t-test.

Source: Clinical Study Report for BELIEVE.[5]

The least squares mean difference for the luspatercept treatment group versus placebo treatment group was −347.80 mcg/L (95% CI, −516.95 to −178.65; P < 0.0001).

Subgroup Analyses

The subgroup analyses identified in the CADTH review protocol were splenectomy status (yes versus no) and baseline hematological status. For the primary end point, the effects of luspatercept were consistent in those with and without a spleen. Among splenectomized patients, there was a treatment effect in 24% of these patients in the luspatercept treatment group versus 3.1% in the placebo group (OR = 9.72; 95% CI, 2.22 to 42.53; P = 0.0003). In the non-splenectomized patients, a treatment effect was observed in 17.9% in the luspatercept group and 6.4% in the placebo group (OR = 2.94; 95% CI, 0.81 to 10.69; P = 0.0918).

Harms

Only those harms identified in the review protocol are reported subsequently. See Table 37 for detailed harms data.

Adverse Events

In BELIEVE, 96.0% and 92.7% of the patients in the luspatercept and placebo groups, respectively, reported at least 1 adverse event. The most commonly occurring adverse events were back pain (27.4% and 29.4% of the patients in the luspatercept and placebo

Table 25: Summary of TranQoL Change From Baseline in Total Score by Visit at 48 Weeks (HRQoL Evaluable Population)

Characteristics[a]	BELIEVE	
	Luspatercept + BSC (N = 211)	Placebo + BSC (N = 103)
Baseline		
n (%)	211 (100)	103 (100)
Mean (SD)	66.9 (15.20)	70.4 (14.01)
Median (minimum, maximum)	68.1 (26.4, 99.2)	72.2 (35.7, 96.0)
Week 48		
n (%)	179 (84.8)	88 (85.4)
Mean (SD)	67.9 (17.79)	71.3 (15.46)
Median (minimum, maximum)	70.0 (13.2, 98.6)	71.9 (32.1, 99.2)
Change from baseline at week 48		
n (%)	179 (84.8)	88 (85.4)
Mean (SD)	0.5 (13.51)	0.3 (12.01)
Median (minimum, maximum)	0.1 (−33.7, 54.9)	−0.7 (−25.8, 40.8)
P value[b]	0.873	

BSC = best supportive care; HRQoL = health-related quality of life; SD = standard deviation; TranQoL = Transfusion-Dependent Quality of Life questionnaire.

[a]The TranQoL is considered evaluable if at least 27 of the 36 items in the questionnaire answered.

[b]The P value was calculated based on a 2-sample, 2-sided t-test.

Source: Clinical Study Report for BELIEVE.[5]

groups, respectively), upper respiratory tract infection (26.5% and 33.0% of the patients in the luspatercept and placebo arms, respectively), headache (26.0% and 23.9% of the patients in the luspatercept and placebo groups, respectively), and bone pain (19.7% and 8.3% of the patients in the luspatercept and placebo groups, respectively).

Serious Adverse Events

In BELIEVE, SAEs were reported by 15.2% of the patients in the luspatercept treatment arm and 5.5% of the patients in the placebo group. The most commonly reported SAE was infections and infestations, which was reported by 5.8% of the patients in the luspatercept group and 2.8% of the patients in the placebo group. In the luspatercept treatment group, 1 patient reported a portal vein thrombosis and 2 patients reported a deep vein thrombosis.

Withdrawals Due to Adverse Events

The proportion of patients who stopped treatment due to an adverse event was 5.4% and 0.9% in the luspatercept and placebo treatment groups, respectively. The most common reasons for stopping treatment were arthralgia (2 patients in the luspatercept treatment group), back pain (2 patients in the luspatercept treatment group), and deep vein thrombosis (2 patients in the luspatercept treatment group).

Table 26: Summary of SF-36 Change From Baseline in Physical Functioning by Visit at 24 Weeks (HRQoL Evaluable Population)

Characteristics[a]	BELIEVE	
	Luspatercept + BSC (N = 210)	Placebo + BSC (N = 103)
Baseline		
n (%)	210 (100)	103 (100)
Mean (SD)	49.2 (7.05)	49.5 (7.29)
Median (minimum, maximum)	51.8 (23.1, 57.5)	51.8 (30.8, 57.5)
Week 24		
n (%)	197 (93.8)	91 (88.3)
Mean (SD)	49.1 (8.27)	50.0 (7.78)
Median (minimum, maximum)	51.8 (19.3, 57.5)	51.8 (21.2, 57.5)
Change from baseline at week 24		
n (%)	197 (93.8)	91 (88.3)
Mean (SD)	−0.3 (6.93)	−0.2 (7.86)
Median (minimum, maximum)	0.0 (−38.3, 19.1)	0.0 (−34.5, 26.8)
P value[b]	0.918	

BSC = best supportive care; HRQoL = health-related quality of life; SD = standard deviation; SF-36 = Short Form (36) Health Survey.

[a]The SF-36 is considered evaluable if at least 18 of the 36 items are answered.

[b]The P value was calculated based on a 2-sample, 2-sided t-test.

Source: Clinical Study Report for BELIEVE.[5]

Mortality

One patient in each treatment group died during the study. In the luspatercept treatment group, the patient died due to urosepsis and, in the placebo group, the patient died due to acute cholecystitis.

Notable Harms

The notable harms identified in the protocol for this review included the following: hypertension, thromboembolic events, hepatic and renal events, hypersensitivity reactions, and bone health. Hypertension was reported as an adverse event in 8.1% of the patients in the luspatercept treatment group and 2.8% of the patients in the placebo group. Under the hepatobiliary disorders SOC, 6.7% of patients in the luspatercept treatment group and 3.7% of patients in the placebo group reported at least 1 associated adverse event. Under the renal and urinary disorders SOC, 9.0% of patients in the luspatercept treatment group and 8.3% of patients in the placebo group reported at least 1 associated adverse event. Bone pain was reported by 19.7% of the patients in the luspatercept treatment arm and 8.3% of the patients in the placebo arm. In the luspatercept treatment arm, osteopenia and osteoporosis were reported by 2.2% and 4.0% of patients, respectively. In the placebo arm, osteopenia and osteoporosis were reported by 4.6% and 5.5% patients, respectively. Information regarding hypersensitivity reactions was not included in the study.

Table 27: Summary of SF-36 Change From Baseline in Physical Functioning by Visit at 48 Weeks (HRQoL Evaluable Population)

Characteristics[a]	BELIEVE	
	Luspatercept + BSC (N = 210)	Placebo + BSC (N = 103)
Baseline		
n (%)	210 (100)	103 (100)
Mean (SD)	49.2 (7.05)	49.5 (7.29)
Median (minimum, maximum)	51.8 (23.1, 57.5)	51.8 (30.8, 57.5)
Week 48		
n (%)	176 (83.8)	88 (84.4)
Mean (SD)	49.4 (8.34)	49.1 (8.25)
Median (minimum, maximum)	51.8 (21.2, 57.5)	51.8(19.3, 57.5)
Change from baseline at week 48		
n (%)	176 (83.8)	88 (84.4)
Mean (SD)	−0.3 (7.33)	−0.4 (7.64)
Median (minimum, maximum)	0.0 (−24.9, 19.1)	0.0 (−38.3, 24.9)
P value[b]	0.929	

BSC = best supportive care; HRQoL = health-related quality of life; SD = standard deviation; SF-36 = Short Form (36) Health Survey.

[a]The SF-36 is considered evaluable if at least 18 of the 36 items are answered.

[b]The P value was calculated based on a 2-sample, 2-sided t-test.

Source: Clinical Study Report for BELIEVE.[5]

Critical Appraisal

Internal Validity

The BELIEVE study was a randomized placebo-controlled, double-blind study. Overall, randomization and treatment allocation were appropriately conducted, and the baseline characteristics were generally well balanced.

The study used appropriate double-blinding techniques; however, lack of efficacy within the placebo group and the occurrence of more adverse events in the luspatercept group could have unblinded patients. Although it is unlikely to affect the primary or key secondary end points of the study, which were objective measures, it could result in bias with respect to the self-reporting of adverse events and subjective end points, including changes in HRQoL. Moreover, the study design allowed for unblinding at the discretion of the study investigator, although it was unclear how many patients were unblinded and, for patients who discontinued the study drug but remained in the study, it is unclear if blinding was maintained or how many patients elected to be unblinded.

For patients missing data, imputation that assumed the patients were nonresponders was used appropriately for the primary and key secondary end points. However, for other end points in the study, analyses were completed only in those patients with both baseline and follow-up measurements (complete-case analysis). As the amount of missing data was

Table 28: Summary of SF-36 Change From Baseline in General Health by Visit at 24 Weeks (HRQoL Evaluable Population)

Characteristics[a]	BELIEVE	
	Luspatercept + BSC (N = 210)	Placebo + BSC (N = 103)
Baseline		
n (%)	210 (100)	103 (100)
Mean (SD)	46.1 (9.71)	47.7 (10.63)
Median (minimum, maximum)	46.1 (23.7 to 66.5)	48.4 (21.3 to 66.5)
Week 24		
n (%)	197 (93.8)	91 (88.3)
Mean (SD)	46.7 (9.62)	48.5 (10.40)
Median (minimum, maximum)	48.4 (19.0 to 66.5)	46.1 (23.7 to 66.5)
Change from baseline at week 24		
n (%)	197 (93.8)	91 (88.3)
Mean (SD)	0.4 (7.18)	0.3 (7.03)
Median (minimum, maximum)	0.0 (−24.7 to 24.7)	0.0 (−16.6 to 29.5)
P value[b]	0.857	

BSC = best supportive care; HRQoL = health-related quality of life; SD = standard deviation; SF-36 = Short Form (36) Health Survey.

[a]The SF-36 is considered evaluable if at least 18 of the 36 items are answered.

[b]The P value was calculated based on a 2-sample, 2-sided t-test.

Source: Clinical Study Report for BELIEVE.[5]

greater than 10% for many of these end points, these assessments are likely to be biased due to the missing data.

The primary and 3 key secondary end points were appropriately controlled for multiplicity and a hierarchical statistical plan was followed. However, all other end points (HRQoL, iron accumulation, health care resource utilization, and serum ferritin) were not part of the statistical testing plan and were not controlled for multiplicity; thus, all significant P values are at risk of type I error and should be interpreted as supportive evidence for the overall efficacy of luspatercept.

An MID for patients with transfusion-dependent anemia associated with beta-thalassemia could not be identified from the literature for either of the instruments used to assess HRQoL, namely, the TranQoL and SF-36. Moreover, only a complete-case analysis was completed for this data, with different subsets of patients at each time point. As that is not a true ITT population, the HRQoL would be subjected to an increased risk of bias due to the complete-case analysis approach and should be considered as supportive evidence for the overall efficacy of luspatercept.

Although numerous subgroup analyses were presented for the primary and key secondary efficacy end points, the only subgroup of interest for this review according to the protocol was splenectomy. Importantly, this subgroup analysis was 1 of numerous subgroups tested.

Table 29: Summary of SF-36 Change From Baseline in General Health by Visit at 48 Weeks (HRQoL Evaluable Population)

Characteristics[a]	BELIEVE	
	Luspatercept + BSC (N = 210)	Placebo + BSC (N = 103)
Baseline		
n (%)	210 (100)	103 (100)
Mean (SD)	46.1 (9.71)	47.7 (10.63)
Median (minimum, maximum)	46.1 (23.7, 66.5)	48.4 (21.3, 66.5)
Week 48		
n (%)	176 (83.8)	88 (84.4)
Mean (SD)	46.5 (11.20)	47.7 (9.68)
Median (minimum, maximum)	46.1 (19.0, 66.5)	48.0 (21.3, 66.5)
Change from baseline at week 48		
n (%)	176 (83.41)	88 (84.4)
Mean (SD)	0.1 (7.73)	−0.5 (7.32)
Median (minimum, maximum)	0.0 (−35.7, 17.6)	0.0 (−21.4, 22.8)
P value[b]	0.564	

BSC = best supportive care; HRQoL = health-related quality of life; SD = standard deviation; SF-36 = Short Form (36) Health Survey.

[a]The SF-36 is considered evaluable if at least 18 of the 36 items are answered.

[b]The P value was calculated based on a 2-sample, 2-sided t-test.

Source: Clinical Study Report for BELIEVE.[5]

It is at risk of type I error and was not included in the randomization scheme; therefore, imbalances in characteristics between luspatercept and placebo would be expected, which could affect the results observed within the subgroup. Overall, the results of the subgroups were largely consistent with the overall findings; these data should be considered as supportive evidence of the overall effect of luspatercept.

The clinical experts consulted by CADTH believed that the other efficacy outcomes would have been more meaningful if the outcomes were also presented in the subgroup of responders, as variability by response cannot be interpreted currently. The analyses from the rolling 12-week and 24-week periods were not included in the statistical testing hierarchy; hence, there is a risk of type I error. Therefore, the results of these analyses should be considered as supportive evidence of the overall effect of luspatercept.

A large number of the end points in the study are considered to be outcomes with unclear importance to clinicians or patients. For example, the clinical experts were of the opinion that serum ferritin levels are not a reliable indicator of iron overload, as there are frequent fluctuations in its measurements. The clinical experts also suggested that liver iron concentration and myocardial iron concentration were more reliable indicators of iron overload. The sponsor states that in the BELIEVE study, liver iron concentration is the more reliable indicator of body iron overload. To address this issue, CADTH conducted a search of the published literature on the reliability and validity of serum ferritin in patients with

Table 30: Summary of SF-36 Change From Baseline in Physical Component Summary by Visit at 24 Weeks (HRQoL Evaluable Population)

Characteristics[a]	BELIEVE	
	Luspatercept + BSC (N = 210)	Placebo + BSC (N = 103)
Baseline		
n (%)	210 (100)	103 (100)
Mean (SD)	49.0 (7.59)	49.2 (8.23)
Median (minimum, maximum)	49.2 (18.8, 66.1)	50.1 (26.2, 64.4)
Week 24		
n (%)	197 (93.8)	91 (88.3)
Mean (SD)	48.7 (8.25)	49.5 (8.05)
Median (minimum, maximum)	50.3 (15.1, 61.2)	51.3 (27.0, 62.7)
Change from baseline at week 24		
n (%)	197 (93.8)	91 (88.3)
Mean (SD)	−0.4 (7.01)	−0.3 (7.97)
Median (minimum, maximum)	−0.4 (−28.2, 18.8)	−0.8 (−26.8, 31.9)
P value[b]	0.839	

BSC = best supportive care; HRQoL = health-related quality of life; SD = standard deviation; SF-36 = Short Form (36) Health Survey.

[a]The SF-36 is considered evaluable if at least 18 of the 36 items are answered.

[b]The P value was calculated based on a 2-sample, 2-sided t-test.

Source: Clinical Study Report for BELIEVE.[5]

thalassemia. Results were limited to the past 5 years. Generally, the majority of evidence reviewed supports the association between serum ferritin and complications such as iron overload of the pituitary,[21] spleen,[22] heart,[23-27] and liver,[24,26-28] and irregularities with QT parameters.[29] In some studies, the correlation between serum ferritin and iron overload was weak.[30,31] Correlation was not supported in all studies, specifically, those where serum ferritin was compared with cardiac T2*,[28] adrenal T2*,[32] and carotid artery structure or vascular health.[33] Additionally, evidence from 1 study that investigated the relationships between changes in liver iron concentrations and changes in serum ferritin determined that serum ferritin nonresponse was associated with a decrease in liver iron concentrations in more than half of patients and concluded that the use of liver MRI may be particularly useful, as serum ferritin trends can be misleading.[34] Overall, given the low quality of evidence and absence of studies assessing reliability and responsiveness, strong conclusions on the use of serum ferritin levels cannot be made.

External Validity

The clinical experts noted that based on baseline demographic and disease characteristics, the study population was representative of Canadian patients with transfusion-dependent anemia associated with beta-thalassemia. In Canada, the age of starting transfusion is in the first year of life; the trial had a median starting age of 2.0 years. The clinical experts consulted by CADTH felt the splenectomy population was overrepresented in the trial compared with

Table 31: Summary of SF-36 Change From Baseline in Physical Component Summary by Visit at 48 Weeks (HRQoL Evaluable Population)

Characteristics[a]	BELIEVE	
	Luspatercept + BSC (N = 210)	Placebo + BSC (N = 103)
Baseline		
n (%)	210 (100)	103 (100)
Mean (SD)	49.0 (7.59)	49.2 (8.23)
Median (minimum, maximum)	49.2 (18.8, 66.1)	50.1 (26.2, 64.4)
Week 48		
n (%)	176 (83.8)	88 (84.4)
Mean (SD)	48.4 (8.80)	49.5 (7.45)
Median (minimum, maximum)	49.2 (21.5, 62.2)	51.1 (30.2, 65.3)
Change from baseline at week 48		
n (%)	176 (83.8)	88 (84.4)
Mean (SD)	−0.9 (7.45)	0.1 (6.07)
Median (minimum, maximum)	0.0 (−33.5, 19.2)	0.3 (−18.9, 17.5)
P value[b]	0.303	

BSC = best supportive care; HRQoL = health-related quality of life; SD = standard deviation; SF-36 = Short Form (36) Health Survey.

[a]The SF-36 is considered evaluable if at least 18 of the 36 items are answered.

[b]The P value was calculated based on a 2-sample, 2-sided t-test.

Source: Clinical Study Report for BELIEVE.[5]

the Canadian population, and more patients with organ damage would be expected in clinical practice.

The luspatercept dosing regimen used in the BELIEVE trial followed the general dosing recommendation included in the product monograph and is consistent with its anticipated use in clinical practice. Use of concomitant iron chelation therapy was permitted throughout the study. Of the 4 iron-chelating medications used in the trial, 3 drugs (deferasirox, deferiprone, and deferoxamine mesylate) are used in the Canadian population; however, as noted by the clinical experts consulted by CADTH for this review, deferasirox is used in a higher proportion of patients in Canadian clinical practice. The clinical experts also noted that since there were no alternative treatments available to patients, the use of placebo is appropriate as a comparator.

The primary end point, a 33% or greater reduction from baseline in transfusion burden (RBC units/time) with a reduction of at least 2 units from week 13 to week 24, was relevant to clinical practice, as indicated by the clinical experts. The clinical experts also noted that if patients met the 50% or greater reduction from baseline in transfusion burden, it would be more clinically meaningful; however, only 8% of the patients achieved this end point. The other end points that the clinical experts noted were of importance were the HRQoL and the

Table 32: Mean Change in Derived LIC at Week 48 (ITT Population)

Characteristics	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
Baseline		
n (%)	211 (94.1)	110 (98.2)
Mean (SD), mg/g dw	9.62 (9.963)	9.36 (10.241)
Median (minimum, maximum), mg/g dw	5.47 (0.8, 42.0)	4.89 (0.2, 43.0)
Week 48		
n	202 (90.17)	103 (91.96)
Mean (SD), mg/g dw	9.93 (10.194)	9.27 (10.357)
Median (minimum, maximum), mg/g dw	5.81 (0.8, 41.6)	4.74 (0.8, 43.0)
Change from baseline at week 48		
n (%)	202 (90.1)	103 (91.96)
Mean (SD), mg/g dw	0.10 (5.760)	0.08 (5.229)
Median (minimum, maximum), mg/g dw	0.03 (−24.9, 19.9)	−0.02 (−19.5, 16.9)
LS mean (SE)[a]	0.34 (0.384)	0.23 (0.531)
LS mean difference (95% CI)[a]	0.11 (−1.16 to 1.38)	
P value	0.8685	

ANCOVA = analysis of covariance; BSC = best supportive care; CI = confidence interval; dw = dry weight; ITT = intention to treat; LIC = liver iron concentration; LS = least squares; SD = standard deviation; SE = standard error.

Note: Only those with baseline and follow-up measurements were included.

[a]Estimates were based on an ANCOVA model with geographical regions defined at randomization and baseline LIC as covariates.

reduction in transfusion frequency outcomes. However, although these 2 outcomes were analyzed in the study, they were not part of the statistical testing plan and were not controlled for multiplicity, and they were interpreted as supportive evidence for the overall efficacy of

Table 33: Mean Change in Myocardial T2* MRI at Week 48 (ITT Population)

Characteristics	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
Baseline		
n (%)	224 (100)	112 (100)
Mean (SD), ms	33.52 (16.170)	34.76 (10.665)
Median (minimum, maximum), ms	34.65 (3.0, 205.9)	36.30 (6.4, 57.5)
Week 48		
n	201 (89.7)	100 (89.2)
Mean (SD), ms	31.99 (11.304)	34.78 (10.680)
Median (minimum, maximum), ms	33.50 (2.7, 79.8)	36.07 (5.9, 53.9)
Change from baseline		
n	201 (89.7)	100 (89.2)
Mean (SD), ms	−1.83 (15.084)	0.02 (6.843)
Median (minimum, maximum), ms	−0.80 (−174.5, 45.4)	−0.82 (−18.0, 24.2)
LS mean (SE)[a]	−2.20 (0.684)	0.20 (0.961)
LS mean difference (95% CI)[a]	−2.39 (−4.67 to −0.12)	
P value	0.0391	

ANCOVA = analysis of covariance; BSC = best supportive care; CI = confidence interval; ITT = intention to treat; LS = least squares; SD = standard deviation; SE = standard error.

Note: Only those with baseline and follow-up measurements were included.

[a]Estimates were based on an ANCOVA model with geographical regions defined at randomization and baseline myocardial T2* MRI as covariates.

Table 34: Patient's ICT Category (ITT Population)

ICT categories	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
Patients with monotherapy[a] at baseline and post-baseline, n (%)	136 (60.7)	68 (60.7)
Patients with monotherapy at baseline and combination therapy[b] post-baseline	10 (4.5)	8 (7.1)
Patients with combination therapy at baseline and monotherapy post-baseline	10 (4.5)	4 (3.6)
Patients with combination therapy at baseline and post-baseline	52 (23.2)	22 (19.6)

BSC = best supportive care; ICT = iron chelation therapy; ITT = intention to treat.

Note: Only patients with no missing ICT category at both visits were included.

[a]Monotherapy was defined as 1 ICT drug taken by a patient during the specified baseline or post-baseline period.

[b]Combination therapy was defined as more than 1 ICT drug taken by a patient during the specified baseline or post-baseline periods.

luspatercept. The duration of the trial was a limitation, as it cannot be conclusively said how long the treatment effects would be maintained. The clinical experts also noted that the other hematologic outcomes measured in the trial would also be clinically meaningful, particularly the reduction in RBC units and transfusion independence. The occurrence of thromboembolic events was a concern for the clinical experts.

Discussion

Summary of Available Evidence

One ongoing phase III study, BELIEVE (N = 336), was included in the systematic review. BELIEVE included adult patients 18 years and older with transfusion-dependent anemia associated with beta-thalassemia.

BELIEVE is a multi-centre, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of luspatercept in adult patients with transfusion-dependent anemia associated with beta-thalassemia. One site in Canada enrolled 13 patients in the trial.

Table 35: Health Care Resource Utilization (ITT Population)

Characteristics	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
Patients who had a doctor office visit, n (%)	158 (70.5)	65 (58.0)
Patients who had an emergency department visit, n (%)	48 (21.4)	22 (19.6)
Patients who were admitted to the hospital, n (%)	42 (18.8)	4 (3.6)
Reasons for hospitalization, n (%)		
Adverse events	35 (15.6)	4 (3.6)
Transfusion	11 (4.9)	1 (0.9)
Non–protocol-driven assessments or procedures	9 (4.0)	0
Elective procedure for a pre-existing condition	9 (4.0)	2 (1.8)
Social, technical, or practical reason in the absence of an AE	3 (1.3)	0
Number of days in a higher-care unit, n	31	5
Mean (SD)	3.6 (5.36)	0.6 (0.55)
Median (minimum, maximum)	1.0 (0, 21)	1.0 (0, 1)
Type of unit		
Intensive care unit	1 (0.4)	0
Cardiac care unit	2 (0.9)	0
Other	40 (17.9)	7 (6.3)

AE = adverse event; BSC = best supportive care; ITT = intention to treat; SD = standard deviation.

Eligible patients were randomized in a 2:1 double-blind manner to receive either luspatercept or placebo along with best supportive care for 48 weeks. Patients received a starting dose of 1 mg/kg of the study drug administered by subcutaneous injection every 3 weeks for 48 weeks. During this period, the dose levels were titrated (increased) stepwise up to a maximum of 1.25 mg/kg.

- The measure upon which the primary end point of the BELIEVE trial was based was an erythroid response measured as a 33% or greater reduction from baseline in transfusion burden (RBC units/time), with a reduction of at least 2 units from week 13 to week 24. The key secondary end points were proportion of patients who achieved a 33% or greater reduction in transfusion burden from baseline to week 37 to 48 with a reduction of at least 2 RBC units
- proportion of patients who achieved a 50% or greater reduction in transfusion from baseline burden t week 13 to 24 with a reduction of at least 2 RBC units
- proportion of patients who achieved a 50% or greater reduction from baseline in transfusion burden from week 37 to 48 with a reduction of at least 2 RBC units
- mean change in transfusion burden from baseline to week 13 to 24.

Table 36: Mean Change in Mean Serum Ferritin Level (ITT Population)

Characteristics	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
Baseline		
n (%)	220 (98.21)	111 (99.1)
Mean (SD), mcg/L	2,096.91 (1,756.649)	1,845.05 (1,669.133)
Median (minimum, maximum), mcg/L	1,441.25 (88.0, 6,400.0)	1,301.50 (136.0, 6,400.0)
Post-baseline		
n (%)	214 (95.5)	104 (92.8)
Mean (SD), mcg/L	1,831.97 (1,844.266)	1,988.91 (1,783.991)
Median (minimum, maximum), mcg/L	1,000.25 (63.3, 6,400.0)	1,224.67 (144.8, 6,400.0)
Change from baseline		
n (%)	212 (94.6)	104 (92.8)
Mean (SD), mcg/L	−248.02 (800.021)	106.62 (526.174)
Median (minimum, maximum), mcg/L	−192.88 (−2,971.1, 3,066.5)	106.00 (−1,334.3, 2,055.0)
LS mean (SE)	−233.51 (50.471)	114.28 (71.049)
LS mean difference (95% CI)[a]	−347.80 (−516.95 to −178.65)	
P value	< 0.0001	

ANCOVA = analysis of covariance; BSC = best supportive care; CI = confidence interval; ITT = intention to treat; LS = least squares; SD = standard deviation; SE = standard error.

Note: Missing data were excluded from this analysis.

[a]Estimates were based on an ANCOVA model with geographical regions defined at randomization and baseline serum ferritin as covariates among those patients with baseline and follow-up measurements.

Table 37: Summary of Harms (Safety Population)

Harms	BELIEVE	
	Luspatercept + BSC (N = 223)	Placebo + BSC (N = 109)
Patients with ≥ 1 AE, n (%)		
n (%)	214 (96.0)	101 (92.7)
TEAE	117 (52.5)	29 (26.6)
NCI CTCAE grade ≥ 3 TEAE	65 (29.1)	17 (15.6)
Patients with at least 1 thromboembolic event	9 (4.0)	1 (0.9)
Patients with ≥ 1 SAE, n (%)		
n (%)	34 (15.2)	6 (5.5)
Infections and infestations	13 (5.8)	3 (2.8)
Blood and lymphatic system disorders	4 (1.8)	0
Anemia	3 (1.3)	0
Portal vein thrombosis	1 (0.4)	0
Renal and urinary disorders	2 (0.9)	0
Deep vein thrombosis	2 (0.9)	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (0.4)	0
Pulmonary embolism	1 (0.4)	0
Patient with at least 1 TEAE leading to discontinuation of study drug, n (%)		
n (%)	12 (5.4)	1 (0.9)
Arthralgia	2 (0.9)	0
Back pain	2 (0.9)	0
Deep vein thrombosis	2 (0.9)	0
Deaths, n (%)		
n (%)	1 (0.4)	1 (0.91)
Urosepsis	1 (0.4)	0
Cholecystitis acute	0	1 (0.91)
Notable harms, n (%)		
Bone pain	44 (19.7)	9 (8.3)
Renal and urinary disorders	20 (9.0)	9 (8.3)
Hypertension	18 (8.1)	3 (2.8)
Hepatobiliary disorders	15 (6.7)	4 (3.7)
Osteoporosis	9 (4.0)	6 (5.5)
Osteopenia	5 (2.2)	5 (4.6)

Harms	BELIEVE	
	Luspatercept + BSC (N = 223)	Placebo + BSC (N = 109)
Hypersensitivity reactions	NR	NR

AE = adverse event; BSC = best supportive care; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NR = not reported; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Source: Clinical Study Report for BELIEVE.[5]

Other efficacy outcomes identified as per the review protocol were HRQoL, iron accumulation, health care resource utilization, and serum ferritin levels. The clinical experts also expressed their opinion on the treatment discontinuation after a 15-week dose delay from the prior dose administration and stated that the time frame may not be sufficient to estimate an appropriate response.

The BELIEVE trial was a well conducted trial overall. The trial used appropriate randomization and blinding, and the primary and key secondary end points accounted for multiplicity of testing using gate-keeping approaches. The main limitations were the lack of multiplicity controls for all other end points; the potential for unblinding due to lack of efficacy or adverse events, which could have affected the self-reported measures (e.g., HRQoL, adverse events); missing data for some end points (i.e., HRQoL); and the duration of the trial was not long enough to estimate whether treatment effect was maintained.

Interpretation of Results

Efficacy

In BELIEVE, the primary end point of a hematological response demonstrated a reduction in transfusion burden and was statistically significant in favour of the luspatercept treatment group. The primary efficacy end point demonstrated that a significantly greater number of patients responded to the luspatercept treatment compared with placebo and achieved a 33% or greater reduction from baseline in the fixed week 13 to week 24 period. The clinical experts consulted by CADTH accepted the 33% and 50% reduction in transfusion as a clinically meaningful outcome. However, the clinical experts were cautious about the time frame of the trial and response duration and would prefer to make conclusive decisions based on the results from a longer-duration trial.

The first of the 3 key secondary outcomes of the BELIEVE study demonstrated that a significantly higher proportion of patients responded to the luspatercept treatment compared with placebo and achieved a 33% or greater reduction from baseline in transfusion burden (RBC units/time), with a reduction of at least 2 units in the fixed week 37 to week 48 period.

The second of the 3 key secondary outcomes of the BELIEVE study demonstrated that a significantly higher proportion of patients responded to the luspatercept treatment compared with placebo and achieved a 50% or greater reduction from baseline in transfusion burden (RBC units/time), with a reduction of at least 2 units in the fixed week 13 to week 24 period.

The third key secondary outcome of the BELIEVE study demonstrated that a significantly higher proportion of patients responded to the luspatercept treatment compared with placebo and achieved a 50% or greater reduction from baseline in transfusion burden (RBC units/time), with a reduction of at least 2 units in the fixed week 37 to week 48 period.

The fourth key secondary outcome of the BELIEVE study was outside of the statistical hierarchy testing and was at risk of type I error; hence, it was viewed as supportive evidence for the overall effect of luspatercept. Overall, the responses from the fourth key secondary efficacy end point were clinically meaningful, according to the clinical experts consulted by CADTH.

Other efficacy end points were also reported descriptively and should be interpreted as supportive evidence. The sponsor reported a number of tertiary end points that were assessed within the trial, including a rolling period with results that were generally consistent and in favour of luspatercept. The clinical experts consulted by CADTH acknowledged that HRQoL is considered to be important to patients. The BELIEVE trial analyzed HRQoL using 2 instruments, namely, the TranQoL and SF-36. No major differences in HRQoL were noted between the groups; however, interpretation is limited due to substantial missing data due to the complete-case design for the end points and the lack of an MID for the measures.

The outcomes related to iron accumulation, as presented through liver iron concentration and myocardial T2* MRI, did not show any changes. The opinion of the clinical experts consulted by CADTH was that the duration of the treatment assessment may need to be longer to see a clinically meaningful change, if any. These clinical experts suggested that serum ferritin levels are not a reliable indicator of iron overload and that there are frequently large fluctuations with this measurement. The clinical experts suggested that liver iron concentration and myocardial iron concentration were more reliable indicators of iron overload.

Harms

In BELIEVE, 96% of the patients in the luspatercept safety population had at least 1 adverse event and 4% of the patients had at least 1 thromboembolic event. The most commonly occurring treatment-emergent adverse events were back pain (27.4% and 29.4% of the patients in the luspatercept and placebo groups, respectively), upper respiratory tract infection (26.5% and 33.0% of the patients in the luspatercept and placebo groups, respectively), headache (26.0% and 23.9% of the patients in the luspatercept and placebo groups, respectively), and bone pain (19.7% and 8.3% of the patients in the luspatercept and placebo groups, respectively). Of consideration was the 3.1% of patients in the luspatercept group who reported an adverse event of neoplasms (benign, malignant, or unspecified).

Patients with at least 1 SAE comprised 15.2% in the luspatercept group. The most-reported SAE was infections and infestations, with 5.8% of the patients in the luspatercept group and 2.8% of the patients in the placebo group reporting it. In the luspatercept treatment group, 1 patient reported a portal vein thrombosis and 2 patients reported a deep vein thrombosis.

The proportion of patients who stopped treatment due to an adverse event was 5.4% in the luspatercept treatment group. The most common reason in the luspatercept treatment group for stopping treatment was arthralgia (2 patients), back pain (2 patients), and deep vein thrombosis (2 patients). One patient in each treatment group died. In the luspatercept treatment group, the patient died due to urosepsis; in the placebo group, the patient died due to acute cholecystitis. Under the renal and urinary disorders SOC, 9.0% of patients in the luspatercept treatment group and 8.3% of patients in the placebo group reported at least 1 associated adverse event. Under the hepatobiliary disorders SOC, 6.7% of patients in the luspatercept treatment group and 3.7% of patients in the placebo group reported at least 1 associated adverse event. Hypertension was reported as an adverse event in 8.1% of the patients in the luspatercept treatment group and 2.8% of the patients in the placebo group.

Conclusions

One phase III randomized controlled trial (BELIEVE, N = 336) was included in the CADTH systematic review of luspatercept. The study demonstrated that treatment with luspatercept was superior to placebo in terms of reducing transfusion burden by at least 33% during the fixed week 13 to week 24 period, which was the primary end point. The study also demonstrated that, in the 3 key secondary end points, luspatercept was superior to placebo in reducing transfusion burden by at least 33% during the fixed week 37 to week 48 interval, and by at least 50% during the fixed week 13 to week 24 interval and week 37 to week 48 interval, in adult patients with transfusion-dependent anemia associated with beta-thalassemia. The primary and secondary end points of the study were found by the clinical experts consulted by CADTH to be clinically meaningful. The other end points of the study that were evaluated were transfusion burden reduction, transfusion independence, time to first erythroid response, HRQoL, iron accumulation, health care resource utilization, and serum ferritin. However, due to limitations associated with the statistical methodology, the effect of luspatercept on these outcomes is currently unknown. HRQoL was an outcome noted as important to patients, but the effect of luspatercept on HRQoL outcomes was uncertain due to a lack of control for multiplicity and major limitations around the data. Clinical experts have suggested that serum ferritin levels are not a reliable indicator of iron overload and that there are frequently large fluctuations with this measurement.

Key safety issues with luspatercept include thromboembolic events, which were higher in the luspatercept treatment group compared with the placebo group. A higher number of patients in the luspatercept treatment group experienced arthralgia, back pain, bone pain, and myalgia.

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Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946-present)
- Embase (1974–present)
- **Note:** Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: November 22, 2020

Alerts: Weekly search updates until project completion

Study types: No filters were applied to limit the retrieval by study type.

Limits:

- Publication date limit: No date limits used
- Humans
- Language limit: No language limits used
- Conference abstracts: excluded

Table 38: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary

Syntax	Description
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase);
.dq	Candidate term word (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.nm	Name of substance word (MEDLINE)
.yr	Publication year
.jw	Journal title word (MEDLINE)
.jx	Journal title word (Embase)
freq=#	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multi-Database Strategy

Search Strategy

1. (luspatercept* or reblozyl* or ACE-536 or ACE536 or AQK7UBA1LS).ti,ab,rn,ot,kf, nm,hw.
2. 1 use medall
3. *luspatercept/
4. (luspatercept* or reblozyl* or ACE-536 or ACE536).ti,ab,kw,dq.
5. 3 or 4
6. use oemezd
7. 2 or 6
8. conference abstract.pt.
9. conference review.pt.
10. 8 or 9
11. 7 not 10
12. remove duplicates from 11

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search — Studies with results for: luspatercept and beta-thalassemia]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms — luspatercept and beta-thalassemia]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms — luspatercept and beta-thalassemia]

Grey Literature

Search dates: December 18, 2020

Keywords: [luspatercept and beta-thalassemia]

Limits:

- Publication years: No date limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health technology assessment agencies
- Health economics
- Clinical practice guidelines
- Drug and device regulatory approvals
- Advisories and warnings
- Drug class reviews
- Clinical trials registries
- Databases (free)
- Health Statistics
- Internet search

Appendix 2: Excluded Studies

Note that this appendix has not been copy-edited.

Table 39: Excluded Studies

Reference	Reason for Exclusion
Piga A, Perrotta S, Gamberini MR, et al. Luspatercept improves hemoglobin levels and blood transfusion requirements in a study of patients with beta-thalassemia. *Blood.* 2019;133(12):1279-1289.[35]	Study design, not RCT

RCT = randomized controlled trial.

Appendix 3: Detailed Outcome Data

Note that this appendix has not been copy-edited.

Table 40: RBC Transfusion Burden Reduction (≥ 33% Reduction and ≥ 50% Reduction From Baseline) During Any Rolling 12-Week Interval (ITT Population)

Characteristics	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
≥ 33% reduction in RBC transfusion burden		
Number of respondents, n (%)	158 (70.5)	33 (29.5)
Difference in proportions, % (95% CI)[a]	41.1 (30.7 to 51.4)	
Odds ratio (95% CI)[b]	5.69 (3.46 to 9.35)	
P value	< 0.0001	
≥ 50% reduction in RBC transfusion burden		
Number of respondents, n (%)	90 (40.2)	7 (6.3)
Difference in proportions, % (95% CI)[a]	33.9 (26.1 to 41.8)	
Odds ratio (95% CI)[b]	9.95 (4.44 to 22.33)	
P value	< 0.0001	

BSC = best supportive care; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intention to treat; RBC = red blood cell.

[a]Difference in proportions (luspatercept minus placebo) and 95% CIs were estimated from the unconditional test.

[b]The odds ratio (luspatercept over placebo), 95% CIs, and P values were estimated from the CMH test stratified by the geographical regions defined at randomization.

Source: Clinical Study Report for BELIEVE.[5]

Table 41: RBC Transfusion Burden Reduction (≥ 33% Reduction and ≥ 50% Reduction From Baseline) During Any Rolling 24-Week Interval (ITT Population)

Characteristics	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
≥ 33% reduction in RBC transfusion burden		
Number of respondents, n (%)	92 (41.1)	3 (2.7)
Difference in proportions, % (95% CI)[a]	38.4 (31.3 to 45.5)	
Odds ratio (95% CI)[b]	25.02 (7.76 to 80.71)	
P value	< 0.0001	
≥ 50% reduction in RBC transfusion burden		
Number of respondents, n (%)	37 (16.5)	1 (0.9)
Difference in proportions, % (95% CI)[a]	15.6 (10.5 to 20.8)	
Odds ratio (95% CI)[b]	20.37 (2.86 to 144.94)	

Characteristics	BELIEVE	
	Luspatercept + BSC (N = 224)	Placebo + BSC (N = 112)
P value	< 0.0001	

BSC = best supportive care; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intention to treat; RBC = red blood cell.

[a]Difference in proportions (luspatercept minus placebo) and 95% CIs were estimated from the unconditional test.

[b]The odds ratio (luspatercept over placebo), 95% CIs, and P value were estimated from the CMH test stratified by the geographical regions defined at randomization

Source: Clinical Study Report for BELIEVE.[5]

Appendix 4: Description and Appraisal of Outcome Measures

Note that this appendix has not been copy-edited.

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

- TranQoL
- SF-36v2

Findings

Table 42: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
TranQoL	TranQoL is a disease-specific questionnaire for adults and children with thalassemia major that focuses on quality of life issues related to transfusion burden based on the following domains: emotional health, family functioning, school and career functioning, and physical health. The total score and domain scores range from 0 (worst) to 100 (best).	**Validity** TranQoL scores showed substantial agreement (P < 0.001) with the Health Utilities Index Mark 3 (r = 0.65), the SF-36 physical summary score (adults, r = 0.69) and mental summary score (r = 0.76).[16] **Reliability** Test-retest reliability showed almost excellent agreement (intra-class correlation coefficient, 0.94).[16] Internal consistency was good (Cronbach alpha = 0.96).[16] **Responsiveness** In patients who rated their QoL as better, there was a 4.0-point (SD 9.0) improvement in TranQoL scores, from baseline of 67.1 to 71.1 1 week later (P = 0.008).[16]	An MID for patients with transfusion-dependent thalassemia was not identified in the literature.
SF-36v2	The SF-36 is a generic self-reported questionnaire consisting of 8 domains: physical functioning, role — physical, bodily pain, general health, vitality, social functioning, role — emotional, and mental health.	The SF-36 has been validated in the general population and in several disease-specific populations.[17-20] Validity, reliability, and responsiveness for patients with transfusion-dependent thalassemia were not identified in the literature for the English version of the scale. However, when compared with US norms, patients with thalassemia had statistically significantly (P < 0.05) worse HRQoL on 5 of the 8 subscales (physical functioning, role — physical, general health, social functioning, and role — emotional) and on both summary scales (physical component summary and mental component summary).[36]	An MID for patients with transfusion-dependent thalassemia was not identified in the literature.

Outcome measure	Type	Conclusions about measurement properties	MID
	The SF-36 also yields 2 summary measures of physical health (the PCS) and mental health (the MCS) derived from scale aggregates. The scores range from 0 to 100, with higher scores indicating better health.	**Validity** The Persian language SF-36 was assessed in patients with thalassemia major showed convergent validity (Spearman correlation) for each item that ranged from 0.57 to 0.69 for physical functioning scales, 0.61 to 0.70 for role – physical scale, 0.85 to 0.90 for bodily pain scales, 0.64 to 0.74 for general health scales, 0.62 to 0.75 for vitality scales, 0.77 to 0.88 for social functioning scales, 0.56 to 0.73 for role – emotional scales and 0.69 to 0.77 for mental health scales.[37] **Reliability** The reliability of the Persian language SF-36 was obtained by Cronbach alpha (0.915).[37] No test-retest or responsiveness data were available.	In the general population, a change of 2 points on the PCS and 3 points on the MCS of the SF-36v2 indicates a clinically meaningful improvement as determined by the patient.[17]

HRQoL = health-related quality of life; LIC = liver iron concentration; MCS = Mental Component Score; MID = minimal important difference; PCS = Physical Component Score; QoL = quality of life; SF-36v2 = Short Form (36) Health Survey version 2; SD = standard deviation; TranQoL = Transfusion-Dependent Quality of Life questionnaire.

Transfusion-Dependent Quality of Life Questionnaire

The Transfusion-Dependent Quality of Life questionnaire (TranQoL) is a disease-specific questionnaire for adults and children with thalassemia major that focuses on quality of life issues related to transfusion burden.[16] The TranQoL has 4 versions: a child self-report, an adult self-report, a parent self-report (measuring the impact of the disease on the parent), and a parent proxy report (measuring the child's quality of life). The length of the questionnaire ranges from 29 to 39 items for the different versions. The TranQoL assesses the following 4 domains: physical health, emotional health, family functioning, school and career functioning, and physical health. The total score and domain scores range from 0 (worst) to 100 (best).

In a study by Klaasen et al., the validity, reliability, and responsiveness of the TranQoL were evaluated over a period of 2 to 5 weeks in 106 English speaking participants (51 adults and 55 children) with thalassemia major.[16] Participants were recruited from 6 North American thalassemia treatment centres and the majority had multiple comorbidities.

The TranQoL scores showed substantial agreement with generic quality of life measures including the Health Utilities Index Mark 3 (all patients, $r = 0.65$; $P < 0.001$), the Short Form (36) physical summary score (adults, $r = 0.69$; $P < 0.001$) and mental summary score (adults, $r = 0.76$; $P < 0.001$).[16] The physical health domain of the TranQoL showed substantial agreement with the 3 relevant SF-36 scales in adult patients: physical functioning, role – physical, bodily pain (all $P < 0.001$). The SF-36 mental component summary showed moderate to substantial correlation with the TranQoL domains (all $P < 0.001$). Patients with comorbidities had significantly lower TranQoL summary scores than patients who did not (63 versus 75, $P = 0.001$).[16]

Internal consistency of the TranQoL was assessed using Cronbach alpha which was "good" (0.96 for the adult version).[16] Test-retest reliability was assessed during the participants initial blood transfusion and subsequent transfusion 2 to 5 weeks later and showed excellent agreement (intra-class correlation coefficient = 0.94; $P < 0.001$).[16] Reliability of individual TranQoL domains had acceptable reliability (intra-class correlation coefficient = 0.74 to 0.88; $P < 0.001$). The ability for the TranQoL to detect a meaningful change in quality of life was determined, as patients who rated their quality of life as better had a 4.0-point (SD 9.0) improvement in TranQoL scores, from baseline of 67.1 to 71.1 points 1 week later ($P = 0.008$).[16]

An MID for the TranQoL in patients with transfusion-dependent thalassemia was not identified in the literature.

Short Form (36) Health Survey Version 2

The SF-36 is a 36-item, generic, self-reported questionnaire that has been used extensively in clinical trials in many disease areas.[17-20] The SF-36 consists of 8 domains: physical functioning, role — physical, bodily pain, general health, vitality, social functioning, role — emotional, and mental health. For each of the 8 domains, a subscale score can be calculated. The SF-36 also yields 2 summary

measures of physical health (the PSC) and mental health (the MSC) derived from scale aggregates. Higher global scores are associated with better quality of life. The scores can also be standardized to the general US population, where an average score is 50 and has an SD of 10.

Validity, reliability, and responsiveness for patients with transfusion-dependent thalassemia was not identified in the literature for the English version of the scale.

In a study by Sobota et al., HRQoL using the SF-36 was assessed in 264 adult and adolescent patients with thalassemia via the Thalassemia Clinical Research Network's Thalassemia Longitudinal Cohort study and compared with US norms.[36] Patients with thalassemia had statistically significant ($P < 0.05$) worse HRQoL on 5 of the 8 subscales (physical functioning, role – physical, general health, social functioning and role-emotional) and on both summary scales (physical component summary and mental component summary).[36]

The Persian language version of the SF-36 (version 2) was evaluated in 200 patients with thalassemia major. Translation was performed using a standard "forward-backward" procedure and relevant cultural adaptation was also carried out (e.g., substituting golf and billiards as examples of "mild" sports and changing mile to kilometre). The reliability of the questionnaire was assessed by Cronbach alpha (0.915).[37] The convergent validity (via Spearman correlation) for each item that ranged from 0.57 to 0.69 for physical functioning scales, 0.61 to 0.70 for role – physical scale, 0.85 to 0.90 for bodily pain scales, 0.64 to 0.74 for general health scales, 0.62 to 0.75 for vitality scales, 0.77 to 0.88 for social functioning scales, 0.56 to 0.73 for role – emotional scales and 0.69 to 0.77 for mental health scales. The Persian language version of the SF-36 was not used in the pivotal trial for luspatercept but is included here under the assumption that the patients assessed with the Persian language version would have comparable psychometrics as patients assessed in the trial with the English version. No test-retest or responsiveness data were available.

MID for patients with transfusion-dependent thalassemia was not identified in the literature.

In the general population, a change of 2 points on the PCS and 3 points on the MCS of the SF-36v2 indicates a clinically meaningful improvement as determined by the patient; however, it is uncertain if the MID applies to patients with transfusion-dependent thalassemia.[17]

CADTH

Pharmacoeconomic Review

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Abbreviations

BIA	budget impact analysis
ICER	incremental cost-effectiveness ratio
ICT	iron chelation therapy
ITT	intention to treat
QALY	quality-adjusted life-year
RBC	red blood cell
RDI	relative dose intensity
SF	serum ferritin

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Conclusions

The CADTH clinical review, which is based on BELIEVE (May 2018 data cut), found that luspatercept was superior to placebo in terms of reducing transfusion burden by at least 33% during the "fixed" period from week 13 to week 24, which was the primary end point. The other end points of the study that were evaluated were transfusion burden reduction, transfusion independence, time to first erythroid response, quality of life, iron accumulation, health care resource utilization, and serum ferritin (SF) level. However, due to limitations associated with statistical methodology, the effect of luspatercept on these outcomes is currently unknown.

In addition to the lack of long-term clinical data to inform the model, CADTH identified several key limitations of the sponsor's submission, including assumptions about the transfusion burden of luspatercept nonresponders, utility estimates, the dosing of luspatercept, and the different data cut-offs and populations from BELIEVE that were provided for the clinical submission compared with the pharmacoeconomic submission. The CADTH reanalyses included modification of the assumptions surrounding the efficacy of luspatercept and best supportive care (BSC); removing dose delays for luspatercept; using alternate utility values; and aligning the clinical data more closely with the clinical data package provided for the review (e.g., the full intention-to-treat [ITT] population, using a data cut-off of January 2019, use of a fixed assessment period). Based on the CADTH reanalyses, the incremental cost-effectiveness ratio (ICER) of luspatercept compared with BSC for patients with beta-thalassemia was $659,395 per quality-adjusted life-year (QALY), with a 0% chance of being cost-effective at a willingness-to-pay threshold of $50,000 per QALY. To achieve an ICER of $50,000 per QALY, the price of luspatercept would need to be reduced by 85%.

The model appears to be driven by clinical assumptions surrounding the treatment efficacy of luspatercept, expected trajectory of luspatercept nonresponders and patients on BSC, and the

Table 1: Submitted for Review

Item	Description
Drug product	Luspatercept (Reblozyl) lyophilized powder for solution for SC injection
Submitted price	• Luspatercept, 25 mg/vial, powder for solution for SC injection: $2,189.00 • Luspatercept, 75 mg/vial, powder for solution for SC injection: $6,567.00
Indication	For the treatment of adult patients with RBC transfusion-dependent anemia associated with beta-thalassemia
Health Canada approval status	NOC
Health Canada review pathway	Priority review
NOC date	September 25, 2020
Reimbursement request	As per indication
Sponsor	Celgene Inc., a Bristol Myers Squibb company
Submission history	Previously reviewed: No

NOC = Notice of Compliance; RBC = red blood cell; SC = subcutaneous.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	• Cost-utility analysis • Decision tree followed by semi-Markov model
Target population	Adults with RBC transfusion-dependent anemia associated with beta-thalassemia
Treatment	Luspatercept + BSC
Comparator	BSC alone, comprising regular RBC transfusions and ICT
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (70 years)
Key data sources	• The phase III BELIEVE trial of luspatercept plus BSC vs. placebo plus BSC was used to inform the categorization of patients into 4 discrete health states based on transfusion burden: transfusion-independent, LTB, MTB, and HTB. • Transitions from these health states to a module that included complications (cardiac, liver, and endocrine) were informed using risk ratios related to SF levels derived from the published literature.
Submitted results	ICER = $225,894 per QALY for luspatercept plus BSC vs. BSC alone (incremental QALYs: 1.371; incremental costs: $309,641).
Key limitations	• The sponsor based the clinical inputs from BELIEVE on a data cut from July 2019 (January 2019 data were also available in the model); however, this full dataset was not available to CADTH. The CADTH Clinical Report is based on the May 2018 data cut and, as such, the parameter inputs used by the sponsor from BELIEVE could not be fully validated. The sponsor also used the North American and European subpopulation data, which were not provided as part of the clinical data in the submission. Furthermore, response (defined as a ≥ 33% reduction in RBC transfusion from baseline) was assessed over a rolling 24-week period. This differed from the BELIEVE trial, which used a fixed 12-week assessment period. These aspects made validating the clinical data in the economic model challenging. • The sponsor's economic model was based on the reduction in RBC transfusion needs over the course of the BELIEVE trial (48 weeks), followed by assumptions around the benefit beyond the trial as well as the use of SF to predict longer-term outcomes associated with transfusion burden, and the need for iron chelation and complications associated with iron overload. Given the availability of clinical information, a number of key assumptions were made by the sponsor: ◦ The lack of long-term clinical information for luspatercept resulted in the need for assumptions by the sponsor that were optimistic regarding the durability of luspatercept response (maintaining the reduction in transfusion requirements). ◦ The predictive ability of SF (as detailed in the CADTH Clinical Report and confirmed by the clinical experts consulted for this review) is questionable and may not be reliable. ◦ Assumptions around dose delays for luspatercept, which may or may not occur in clinical practice, resulted in reductions in dose intensity and cost associated with luspatercept. • Based on the structure of the model, health states were defined by the level of transfusion needs. While the need for frequent transfusions is likely to affect patient quality of life, the values used by the sponsor are associated with uncertainty. The sponsor provided different estimates based on published sources. Based on feedback from the clinical experts consulted by CADTH, alternate values provided by the sponsor were felt to better represent patient preferences.

Component	Description
CADTH reanalysis results	• CADTH attempted to validate the clinical inputs as much as possible by selecting data closest to that reported in the CADTH Clinical Report (i.e., January 2019 data cut of BELIEVE, fixed response definition as observed over 24 weeks, data from the full ITT population). Further, to account for clinical uncertainty, CADTH considered more conservative assumptions: transfusion burden for luspatercept nonresponders and those receiving BSC were returned to baseline values; alternative utility values were used for the LTB, MTB, and HTB health states; and dose delays for luspatercept were not considered. • In the CADTH base case, the ICER for luspatercept is $659,395 per QALY compared with BSC. • Based on the CADTH reanalyses, the probability of luspatercept being cost-effective at a WTP threshold of $50,000 per QALY was 0%. A price reduction of 85% would be required for luspatercept to be cost-effective at this threshold. • Scenario analyses were performed to assess the other aspects of uncertainty, particularly pertaining to clinical aspects: predictive benefit of SF levels, mortality benefits, treatment starting age, the North American and European subpopulation, ICT, and treatment attenuation of luspatercept. Notably, the removal of the predictive nature of SF levels increased the ICER to $1,398,609 per QALY, and when the survival benefit of luspatercept was removed, the ICER increased to $1,198,773 per QALY when compared with BSC.

BSC = best supportive care; HTB = high transfusion burden; ICER = incremental cost-effectiveness ratio; ICT = iron chelation therapy; ITT = intention to treat; LTB = low transfusion burden; LY = life-year; MTB = medium transfusion burden; QALY = quality-adjusted life-year; RBC = red blood cell; SF = serum ferritin; WTP = willingness to pay.

choice of clinical data (e.g., assessment period, population modelled). Scenario analyses were performed to explore the predictive effects of SF levels, mortality benefits of luspatercept, choosing the North American and European subpopulation, and assuming a loss of the treatment efficacy of luspatercept. The ICERs from these analyses ranged from $500,932 to $1,398,609 per QALY.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups and provincial drug plans that participated in the CADTH review process.

The Thalassemia Foundation of Canada (TFC), which supports and funds thalassemia scientific research, treatment, and patient services, and the Canadian Organization for Rare Disorders (CORD) provided a joint response to CADTH's call for patient input. TFC and CORD conducted a focus group that was used to develop an online survey disseminated through email. Eight participants informed the focus group and 68 participants responded to the survey, of which 69% had a diagnosis of beta-thalassemia major. All patients reported living in Canada, with the majority (73%) residing in Ontario. All patients reported receiving red blood cell (RBC) transfusions, with half requiring a transfusion every 4 weeks and 40% requiring them more frequently. RBC transfusions were described as burdensome because they require a significant time commitment that interferes with familial and work responsibilities, and with travel and vacation. Patients were most concerned about serious complications due to thalassemia or its treatment, which includes iron overload not well managed by chelation. Seven percent of patients had received luspatercept through clinical trials and all spoke positively about the experience, with the most important benefit being the ability to decrease blood transfusion frequency.

Feedback from the drug plans identified challenges related to the assessment of therapeutic response and with administration and dispensing. Blood work monitoring hemoglobin and blood pressure monitoring before each dose is necessary, which may be particularly difficult in rural areas. The drug also needs to be reconstituted and administered by a health care professional, but it is unclear whether that is limited to hospitals and clinics as opposed to community pharmacies. It was noted that the subcutaneous nature of luspatercept would benefit patients by reducing inter-jurisdictional travel for treatment. A concern was raised by the drug plans about an assumption in the budget impact analysis (BIA) where the sponsor assumed care would be provided only in 10 specialized centres in certain provinces, with patients being required to travel from outside those provinces to receive care.

No registered clinician group input was received for this review.

Several of these concerns were addressed in the sponsor's model:

- Cardiac, endocrine, and liver complications were included as consequences of iron overload.
- Health states were defined by different levels of transfusion burden.
- Costs associated with RBC transfusions and monitoring of iron overload were included.

In addition, CADTH addressed some of these concerns as follows:

- Exploring the impact of uncertainty on transfusion burden in terms of definitions of response and burden over time, given the limitations with the clinical information.
- While there is limited information on patient residence and requirements for travel, CADTH attempted to explore the geographical distribution of residency in the BIA, assuming patients would not necessarily move to other provinces to obtain care.

CADTH was unable to address the following concerns raised in the stakeholder input:

- A broader perspective that would consider travel time and other societal costs related to beta-thalassemia in light of the scope of the sponsor's model.
- Accessibility issues for rural populations, given the requirement for reconstitution by a health care professional, as this was not an option within the sponsor's model.
- In the absence of information regarding luspatercept and the associated need for iron chelation therapy (ICT) and complication rates, CADTH could not examine this association in detail.

Economic Review

The current review is for luspatercept (Reblozyl) for the treatment of adults with transfusion-dependent anemia associated with beta-thalassemia.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis assessing luspatercept and BSC compared with BSC alone for the treatment of adult patients with transfusion-dependent anemia associated with beta-thalassemia. The modelled population aligned with the Health Canada indication and reimbursement request.[1]

Luspatercept is available as a powder that must be reconstituted and administered by a health care professional as a subcutaneous injection. The recommended starting dose of luspatercept is 1.0 mg/kg once every 3 weeks, but this may be increased to 1.25 mg/kg every 3 weeks if the patient does not achieve at least a 33% reduction in RBC transfusion burden after at least 2 consecutive doses (6 weeks).[1] Hemoglobin results should be assessed and reviewed before each administration of luspatercept and may influence the dose given. If the patient experiences an increase in hemoglobin of greater than 20 g/L within 3 weeks in the absence of a transfusion, then the dose every 3 weeks of luspatercept should be reduced by 0.20 mg/kg (e.g., from 1 mg/kg to 0.8 mg/kg, from 0.8 mg/kg to 0.6 mg/kg). If the patient is already receiving 0.6 mg/kg every 3 weeks and they experience a greater than 20 g/L increase in hemoglobin, they should discontinue luspatercept. Furthermore, if a patient does not experience a reduction in RBC transfusion burden after 3 consecutive doses (9 weeks) at 1.25 mg/kg, luspatercept should also be discontinued. The cost for luspatercept is $2,189.00 per 25 mg/vial and $6,567.00 per 75 mg/vial[2]; the annual cost of luspatercept ranges from $113,828 to $151,771 per patient, based on the mean weight of Canadian patients in the BELIEVE trial (64.8 kg).[3]

In the model, over a 24-week model cycle, the cost of luspatercept was calculated by the sponsor to be $53,368 based on the individual Canadian patient weights from BELIEVE and a calculated relative dose intensity (RDI) of 97.2%.[3] No vial sharing was assumed in the base case. Luspatercept was assumed to be given alongside BSC. The comparator for this economic analysis was BSC, consisting of regular RBC transfusions and ICT to prevent chronic iron overload due to regular RBC transfusions. The cost per RBC unit transfused was $422.00, and the cost per clinical visit to administer the treatment was $263.34. An administration cost of $54.25 was added, assuming the same cost as a standard chemotherapy delivery, and a cost of $89.83 was also considered for outpatient visits for crossmatching.[2] ICTs included deferoxamine mesylate, deferiprone, and deferasirox, with differential doses assumed based on SF levels. Over a 24-week model cycle, the costs for deferoxamine mesylate, deferiprone, and deferasirox were as follows: $0 to $6,247, $16,068 to $35,349, and $9,333 to $32,666 per patient, depending on the dose required for a given level of SF.[2]

The submitted model reported both QALYs and life-years over a lifetime time horizon of 70 years. The base-case analysis was conducted from the perspective of the Canadian public health care system, with discounting (1.5% per annum) applied to both costs and outcomes.

Model Structure

The submitted model was described as a semi-Markov model that included a decision tree up to 48 weeks followed by a Markov model (Figure 1). The decision tree was used to identify patients who would respond to luspatercept. Patients in the model began treatment with luspatercept plus BSC or BSC at week 0 and were assessed for response to treatment

at week 48. Response was defined as a reduction in RBC transfusion burden of 33% or greater at any 24-week interval during the first 48 weeks of treatment compared with the 24-week interval on or before the first day of dose administration (defined as a "rolling" response), as per the definitions used in the BELIEVE trial.[4] Those achieving a response continued on luspatercept during the Markov phase of the model and those who did not were switched to BSC.

Following the assessment of response, patients were assigned into 1 of 4 transfusion burden categories that were based on the average number of RBC units transfused in a 24-week period in BELIEVE: transfusion-independent, low transfusion burden, medium transfusion burden, and high transfusion burden.[3] From these states, patients could: stay in their current state; move into an alive with complications module, which tracked patients who develop complications of iron overload, the rate of which is determined by the level of SF observed in BELIEVE[3]; or they could move into a death state (from thalassemia, thalassemia-related complications, or iron overload–related complications). It was assumed that all patients initially entered the model without pre-existing iron-related complications, but could then experience cardiac, liver, endocrine, or a combination of complications (cardiac and liver, cardiac and endocrine, liver and endocrine) in this second module.

Model Inputs

The sponsor selected the North American and European subpopulation of BELIEVE for the clinical efficacy inputs, based on the justification that this randomized subgroup was most representative of the eligible Canadian population due to a similar model of beta-thalassemia care.[3] This care model includes such factors as earlier diagnosis, better access to transfusions, reduced lag time between transfusion and ICT initiation, and more frequent and accurate measurement of iron.

The transfusion burden categories were assigned based on the observed number of RBC units transfused in the 24 weeks preceding the time of assessment in BELIEVE (48 weeks after randomization).[3] The categories were defined as follows:

- transfusion-independent = 0 RBC units over 12 weeks
- low transfusion burden = more than 0 to no more than 5 RBC units over 12 weeks
- medium transfusion burden = more than 5 to no more than 7 RBC units over 12 weeks
- high transfusion burden = more than 7 RBC units over 12 weeks.

For the luspatercept responders who remained in the luspatercept plus BSC arm, it was assumed they would retain treatment efficacy after the 48-week assessment and remain in the same transfusion health state until they discontinue treatment (they could still develop complications of iron overload) or die. That is, patients in the luspatercept plus BSC arm did not cycle between transfusion burden states. To account for patients who lose response to luspatercept, an annual discontinuation rate was applied to responders equal to the rate of all-cause discontinuation in BELIEVE.[3] Conversely, patients in the BSC arm were able to cycle between transfusion burden categories, and it was assumed that transfusion burden tended to increase over a patient's lifetime.

In addition to their transfusion burden, the risk of complications due to iron overload in patients was modelled based on SF levels. Complication states (cardiac, liver, endocrine, multiple) were mutually exclusive and were based on the following categories for SF levels: less than 500 mcg/L, 500 mcg/L to less than 1,000 mcg/L, 1,000 mcg/L to less than

2,500 mcg/L, and 2,500 mcg/L or greater. In the model, patients responding to luspatercept were gradually moved toward an SF level of less than 1,000 mcg/L, while patients on BSC were assumed to have a steady increase in their SF level until about year 14, when all patients were assumed to have an SF level of 2,500 mcg/L or greater. These assumptions were derived from the observed trends in SF levels in BELIEVE, which were assumed to continue beyond week 96.[3] To estimate the probability of transitioning to a health state with complications, complication rates were derived from real-world data to determine a reference SF level.[5-7] Real-world data were also used to estimate the rate of developing complications for other SF levels from hazard ratios (HRs) comparing high, medium, and low SF levels.[5,8,9] These complications were assumed to increase a patient's risk of mortality and also incur additional health care costs due to complications.

The dosing of luspatercept was based on the dose received by patients in the BELIEVE trial.[4] This ranged from 0.6 mg/kg to 1.25 mg/kg every 21 days and is consistent with the product monograph. The probability of discontinuation of luspatercept beyond 48 weeks was assumed to be equal to the annual all-cause discontinuation rate reported in the BELIEVE Clinical Study Report.[3]

Utility estimates for the various transfusion burden health states were derived from 2 sources. A time trade-off study by Matza et al. was used to estimate the utility for transfusion-independent patients.[10] The utility estimates for the low, medium, and high transfusion burden states were estimated from a time trade-off study commissioned by the sponsor in the general UK population.[2] Alternate utility values derived from different sources are available, including a weighted average of the utility associated with requiring deferoxamine mesylate, deferiprone, or deferasirox treatment. The sponsor also considered utility decrements due to adverse events for luspatercept and BSC, specifically for back pain, bone pain, diarrhea, and vomiting. Utility decrements were also applied to adverse events associated with ICT, specifically for agranulocytosis, neutropenia, and hepatitis.

The costs included in the base case were the costs of luspatercept and ICT acquisition, luspatercept and deferoxamine mesylate administration, RBC transfusions, adverse event management, complication management, and ICT monitoring. Costs of luspatercept were based on the recommended dosage from the product monograph ranging from 0.6 mg/kg to 1.25 mg/kg every 3 weeks. Weight was derived from the individual patient data of the Canadian patients in BELIEVE by plotting a normal distribution around the mean and within the minimum and maximum observed weights.[3] An RDI of 97.2% was calculated based on the product of the weighted average dose received and the weighted average dose delay. Approximately 62% of patients in BELIEVE had 1 or more dose delays, assumed to be 3 weeks, and this weighted average was multiplied by the weighted average dose. The cost of luspatercept per 24-week model cycle was calculated to be $53,368, with an administration cost of $54.25 from the Ontario Schedule of Benefits for Physician Services.[11] Acquisition costs of ICTs were obtained from the Ontario and Saskatchewan provincial drug formularies, and an administration cost was applied to deferoxamine mesylate, as it is an IV therapy.[12,13] RBC costs included the unit and administrations costs obtained from Canadian Blood Services and Lagerquist et al.,[14] respectively, as well as a cost for outpatient visits for crossmatching. Costs of monitoring related to ICTs were obtained from the Ontario Schedule of Benefits for Laboratory Services.[15] Costs of complications were derived from a UK study[16] and the cost of monthly endocrinologist visits from Ontario data.[11] Costs of adverse events were obtained from the Canadian Institute for Health Information Patient Cost Estimator for the adverse events related to luspatercept plus BSC and for ICTs.[17]

Summary of Sponsor's Economic Evaluation Results

All analyses were run probabilistically (10,000 iterations for the base case and 5,000 for all scenarios). Deterministic and probabilistic results were similar. The probabilistic findings are presented subsequently. Note that the submitted analyses are based on the publicly available prices of the concomitant treatments (e.g., ICTs).

Base-Case Results

Luspatercept plus BSC was associated with incremental costs of $309,641 and QALYs of 1.371 in comparison with BSC, for an ICER of $225,894 per QALY (Table 3).

Sensitivity and Scenario Analysis Results

The sponsor conducted a number of sensitivity and scenario analyses. In these analyses, the ICERs for luspatercept plus BSC compared with BSC alone were most sensitive to the definition of being a luspatercept responder (a ≥ 50% reduction in RBC transfusion instead of ≥ 33%) and assumptions about the efficacy of luspatercept after 48 weeks.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations of the sponsor's analysis that have notable implications on the economic analysis:

- **Uncertainty pertaining to a lack of longer-term clinical information.** Clinical information for luspatercept is limited to 48 weeks, as reported in the CADTH Clinical Report (although data collection is ongoing), for a treatment that could be lifelong. As such, information on the durability of treatment effect, potential for dose escalation over time, impact on beta-thalassemia–related events and complications, and complications related to ICT are unknown. In the absence of longer-term clinical information, the sponsor made a number of assumptions in their model which were in favour of luspatercept (not conservative).

  First, the sponsor assumed patients responding to luspatercept (achieving a ≥ 33% reduction from baseline in RBC transfusions) would retain this response until treatment discontinuation or death (i.e., patients would remain in the same transfusion burden state for the remainder of the model). This was assumed based on the observed efficacy after a median treatment duration of 98.7 weeks in BELIEVE.[3] This is a major assumption in the absence of evidence to support no further decline in the patient's condition (e.g., transfusion needs) or the need for dose escalation to maintain the treatment effect. Loss of response to luspatercept was captured, in part, by assuming a fixed rate of treatment discontinuation (5.98% every 24 weeks) based on the overall discontinuations observed in BELIEVE (which included withdrawal due to adverse events, loss of efficacy, protocol violations, and patient choice). This estimate is a poor approximation, as adverse events

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. BSC ($/QALY)
BSC	1,849,494	Reference	6.395	Reference	Reference
Luspatercept + BSC	2,159,135	$309,641	7.766	1.371	$225,894

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
Source: Sponsor's pharmacoeconomic submission.[2]

are likely to manifest early on in the use of luspatercept and diminish over time, while lack of efficacy could increase over time.

Second, among luspatercept nonresponders and those receiving BSC, it was assumed that the observed transition of patients between transfusion burden categories at week 48 of BELIEVE was representative of the longer term and was thus applied beyond the 48-week assessment. This was based not on long-term clinical data on the trajectory of transfusion burden in patients with beta-thalassemia, but on expert opinion.

Third, the sponsor considered luspatercept responders to be assessed via a rolling response over a 24-week period (i.e., the reduction in RBC transfusion burden of 33% or greater could occur during any 24-week period, not during a fixed period comprising the 24 weeks before assessment). This differs from the primary end point in BELIEVE, in which luspatercept responders were defined as those achieving a reduction in transfusion burden of 33% or greater during the fixed 12-week period from week 13 to week 24.

All of these assumptions favour luspatercept and are not informed by clinical data. Given the uncertainty pertaining to a lack of long-term clinical information, CADTH made alternative assumptions about the efficacy of luspatercept, the trajectory of transfusion burden in patients receiving BSC, and the rolling response window. The assumptions were made possible within the sponsor's submitted model structure.

  - Longer-term efficacy of luspatercept as it pertains to transfusion burden was based on data from BELIEVE at 48 weeks (i.e., patients would not simply stay in the transfusion health state for the remainder of the time horizon, but response would be assessed every cycle based on the response observed at 48 weeks). While this may still represent an optimistic assumption in the absence of evidence to support the long-term effects of luspatercept, the model does not easily allow for alternative scenarios of attenuation of effect to be incorporated.
  - Nonresponders were assumed to revert back to baseline transfusion burden rather than staying in their 48-week transfusion state.
  - Luspatercept responders were defined based on a fixed assessment period of 24 weeks. The model structure did not allow for the consideration of a 12-week assessment window, as was reported in the CADTH Clinical Report.

- **Alternate estimates of utility in the low, medium, and high transfusion burden states.** The sponsor used a study from the general UK public to inform the utility estimates in the transfusion burden groups.[18] The clinical experts consulted by CADTH felt that the alternate set of utility estimates provided by the sponsor[19-21] were more reflective of preferences by the Canadian population; the values for these states were lower than expected. Specifically, it was felt that the utility of 0.370 in the high transfusion burden group was too low compared with the other transfusion burden groups, and that there was too much disparity between the health states overall.
  - CADTH used the alternate estimates of utility in the low, medium, and high transfusion burden states as part of the base case.
- **Uncertainty around dose delays for luspatercept.** The sponsor considered luspatercept dose delays from BELIEVE[3] as relevant to the analysis, resulting in an average dose intensity of 97.2%. This calculation considers 2 elements: dose delays for luspatercept decreasing the estimate to 92%, and dose modifications (i.e., dose reductions and dose escalations) for some patients resulting in a higher dose intensity of 106%. While less than full use and delays in clinical practice are possible, to understand the impact where the cost of full dosing of luspatercept is incurred by the payer, a more conservative assumption would be to assume 100% dose intensity.

- CADTH considered an average dose intensity of 100% as it pertained to dose delays as part of the base case.

- **Different data cuts and populations used in the clinical and pharmacoeconomic submissions.** The sponsor used a data cut-off of July 2019 for its pharmacoeconomic analysis, while its Clinical Study Report only provides data until May 2018. Therefore, CADTH was unable to validate the actual data used to inform the clinical input parameters.

  Further, the sponsor chose the North American and European subgroup of BELIEVE as the main population for analysis. The clinical submission to CADTH did not include separate North American and European data; as such, these data were not reported in the CADTH Clinical Report, nor could they be validated.

  To attempt to validate the data, CADTH looked at the most representative set of data used in the economic model to compare to the data reported in the CADTH Clinical Report (e.g., full ITT population, January 2019 data cut-off). While there were some numerical differences in response, the results appeared to be generally aligned.

  - CADTH considered the January 2019 data cut-off and full ITT population as part of the base case to more closely match the time frame and population for which clinical data were available and assessed by the CADTH review team. The North American and European subpopulation was used in a scenario analysis.

- **Uncertainty regarding the use of SF levels as an indicator of or precursor to iron overload–related complications.** In the second part of its model, the sponsor used several studies of real-world evidence to inform the probabilities that patients in certain SF categories would develop complications, which include cardiac, endocrine, and liver complications. While SF measurements are clinically useful due to their accessibility and ease of use, the clinical experts consulted by CADTH suggested that SF levels were not the most precise indicator of iron overload and that there may be fluctuations in this measurement. The clinical experts suggested that liver iron concentration and myocardial iron concentration were more reliable indicators of iron overload. Furthermore, the Clinical Study Report for the BELIEVE trial stated that liver iron concentration is the most reliable indicator of body iron overload.[3]

  To address this issue, CADTH conducted a search of the published literature on the reliability and validity of SF in patients with thalassemia. Results were limited to the past 5 years. Generally, the majority of the evidence reviewed supports the association between SF and complications such as iron overload of the pituitary,[22] spleen,[23] heart,[24-28] liver,[25,27-29] and irregularities with QT parameters.[30] In some studies, the correlation between SF and iron overload was weak.[31,32] Correlation was not supported in all studies, specifically, those where SF was compared with cardiac T2*,[29] adrenal T2*,[33] and carotid artery structure or vascular health.[34] Additionally, evidence from 1 study that investigated the relationships between changes in liver iron concentrations and changes in SF ICT determined that SF nonresponse was associated with a decrease in liver iron concentration in over half of patients and concluded that the use of liver MRI may be particularly useful, as SF trends can be misleading.[35] Overall, given the low quality of evidence and absence of studies assessing reliability and responsiveness, conclusions on the use of the SF are uncertain.

  - As part of an exploratory analysis, CADTH assumed that the risk of complications was not predicted by SF level.

- **Uncertain survival benefits with luspatercept.** The sponsor assumed that luspatercept improves RBC production, thereby reducing the need for RBC transfusions, which reduces the probability of iron overload and associated complications, which reduces the mortality risk associated with these complications, resulting in a gain of 0.39 years

with luspatercept. Given the indirect nature of this survival benefit and the uncertainty in long-term effects, there is significant uncertainty associated with the survival benefits directly related to luspatercept.

    - As part of an exploratory analysis, CADTH removed the survival benefit of luspatercept by equating the mortality risk due to cardiac, endocrine, and liver complications with luspatercept versus BSC.

Additional limitations were identified but were not considered to be key limitations:

- There was an increased number of thrombotic events in the luspatercept arm compared with placebo in BELIEVE.[3] While adverse events were included in the sponsor's base case, thrombotic events were omitted from consideration. The inclusion of these events would increase the ICER for luspatercept.
- The average age of patients in the sponsor's model is 30 years. However, the mean age of starting transfusions in BELIEVE[3] is approximately 6 years. As luspatercept is indicated in adults, it is expected that patients would begin treatment with luspatercept as soon as they reach 18 years of age. The starting age of patients was explored in scenario analyses.

The following key assumptions were made by the sponsor and have been appraised by CADTH (Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
Assessment of response to luspatercept was defined as a reduction in RBC transfusion burden of ≥ 33% during a 24-week period.	Uncertain. The clinical experts felt that a ≥ 33% reduction in RBC transfusion burden was clinically meaningful, but noted that the product monograph assessed response after 15 weeks instead of 24 weeks.[1] Furthermore, the BELIEVE trial considered a ≥ 33% reduction in RBC transfusion burden over a 12-week period as its primary end point. It is unclear how these differing assessment windows would affect the definition of a luspatercept responder and, thus, the proportion of patients who would continue to receive treatment.
Assessment of response to luspatercept was determined during any 24-week period (i.e., a rolling window).	Not appropriate. It differs from the primary end point in BELIEVE in which a fixed assessment window from week 13 to week 24 was used.
The proportion of patients who would be on deferasirox, deferiprone, and deferoxamine mesylate was assumed to be 66.23%, 31.79%, and 19.21%, respectively.[3]	Uncertain, but unlikely to affect results. CADTH used claims data from the IQVIA Pharmastat database[36] and found that the proportion of patients on the various ICTs was slightly different: for deferasirox, it was 81.4%; for deferiprone, it was 8.2%; and for deferoxamine mesylate, it was 10.4%.
Assumed that all patients initially entered the model without pre-existing iron-related complications.	Uncertain. May not be representative of a real-world setting in which patients already on RBC transfusions could also be experiencing complications.
Mortality related to multiple complications was assumed to be equivalent to the complication with the highest risk (cardiac).	Not appropriate. The sponsor explicitly stated that the multiple-complications health state could include any combination of complications, which includes an endocrine and liver combination for which the relative mortality risk is lower.
Patients discontinue luspatercept beyond week 48 at 5.98% every 24 weeks.	Uncertain. Based on this assumption, < 1% of patients would remain on luspatercept at a model time horizon of 21 years (or at a mean age of 51 years).

BSC = best supportive care; RBC = red blood cell.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

The CADTH base case was derived by making changes in model parameter values and assumptions, in consultation with clinical experts. The CADTH base-case changes were undertaken to address some of the limitations with the model and included the following: (1) changing the assumption around luspatercept efficacy, (2) returning nonresponders and patients on BSC to their baseline transfusion burdens, (3) using alternative utility estimates, (4) including the full ITT population, (5) using an average dose intensity of 100% for luspatercept, (6) using a fixed response definition, and (7) using a January 2019 data cut-off.

These changes are summarized in Table 5.

In the CADTH base case, luspatercept was associated with estimated total costs of $1,938,795 and total QALYs of 11.630, compared with total costs and QALYs of $1,723,321 and 11.303, respectively, for patients receiving BSC. The ICER for luspatercept compared with BSC was $659,395 per QALY, with a 0% chance of being below $50,000 per QALY. A detailed breakdown of the disaggregate results is available in Appendix 4 (Table 12).

Scenario Analysis Results

CADTH undertook price-reduction analyses based on the sponsor's and CADTH's base case. Based on the CADTH base case, a price reduction of 85% would be necessary to achieve cost-effectiveness at a threshold of $50,000 per QALY (Table 7).

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Changes to derive the CADTH base case		
1. Lack of long-term clinical information for luspatercept	Retained treatment efficacy of luspatercept	Luspatercept efficacy based on the observed effects at 48 weeks in BELIEVE[3]
2. Transfusion burden for nonresponders and those receiving BSC	Based on the observed transition in BELIEVE[3] at 48 weeks	Return to baseline distribution
3. Utility estimates		
Transfusion independent	0.915[10]	0.915[10]
Low transfusion burden	0.750[18]	0.810[19]
Medium transfusion burden	0.570[18]	0.763[20,21]
High transfusion burden	0.370[18]	0.500[19]
4. Population	North American and European subgroup only	Full ITT population
5. Dose of LUS	Average dose intensity: 97.2%	Average dose intensity: 100%
6. Type of response	Rolling response	Fixed response
7. Data cut-off	July 2019	January 2019
CADTH base case	—	Reanalysis 1 + 2 + 3 + 4 + 5 + 6 + 7

BSC = best supportive care; ITT = intention to treat.

CADTH undertook a series of exploratory analyses to determine the impact of alternative assumptions on the cost-effectiveness of luspatercept, which are outlined as follows:

1. Assumption that the risk of complications was not predicted by SF levels by setting the HRs of experiencing complications as a function of SF level to 1 and removing the link between ICT cost and SF levels.
2. Removing the mortality benefit of luspatercept by equating the mortality risk in the luspatercept responders and nonresponders and BSC groups in each of the complication health states.
3. Assumed an average starting age of 18 years in the model.
4. Considered the results from the North American and European subpopulations and the corresponding price-reduction analyses.
5. Used the relative market share distribution of ICTs calculated from IQVIA Pharmastat claims data.
6. Set the mortality risk in the multiple-complications group equal to that of liver complications (HR = 5.43) rather than cardiac complications (HR = 25.6).

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Sponsor's base case	BSC	1,849,494	6.395	Reference
	Luspatercept	2,159,135	7.766	225,894
CADTH reanalysis 1: Luspatercept efficacy	BSC	1,732,882	6.399	Reference
	Luspatercept	2,065,847	7.112	467,058
CADTH reanalysis 2: Transfusion burden in nonresponders and BSC	BSC	1,703,164	7.623	Reference
	Luspatercept	2,024,742	8.647	314,036
CADTH reanalysis 3: Alternative utility estimates	BSC	1,732,588	9.102	Reference
	Luspatercept	2,045,806	10.362	248,518
CADTH reanalysis 4: Full ITT population	BSC	1,746,335	7.470	Reference
	Luspatercept	2,044,049	8.524	282,329
CADTH reanalysis 5: 100% dose intensity	BSC	1,733,766	6.399	Reference
	Luspatercept	2,073,004	7.768	247,850
CADTH reanalysis 6: "Fixed" response	BSC	1,731,601	6.399	Reference
	Luspatercept	1,942,139	7.394	211,646
CADTH reanalysis 7: January 2019 data cut-off	BSC	1,727,463	6.391	Reference
	Luspatercept	2,045,625	7.776	229,820
CADTH base case (reanalysis 1 + 2 + 3 + 4 + 5 + 6 + 7)	BSC	1,723,321	11.303	Reference
	Luspatercept	1,938,795	11.630	659,395

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; ITT = intention to treat; QALY = quality-adjusted life-year.

7. Used a 50% or greater reduction in RBC transfusion burden as a response criterion rather than 33% or greater.
8. Assumed that luspatercept would lose treatment efficacy after 5 years.
9. Assumed that luspatercept would lose treatment efficacy after 10 years.
10. Luspatercept discontinuations beyond 48 weeks were reduced to 2.74% per 24 weeks (based on grade 3 and 4 adverse events).
11. Consideration of a rolling response criterion for the assessment of luspatercept responders.
12. Use of the sponsor's original utility values for the low, medium, and high transfusion burden health states from Grazzi.[18]

The results of these analyses are presented in Appendix 4 (Table 13). The scenarios that had the largest influence on the ICER were those that assumed a loss in treatment efficacy: when this was assumed to occur after 5 years, luspatercept was dominated by BSC (luspatercept is associated with greater costs and fewer QALYs); when it was assumed to occur after 10 years, the ICER for luspatercept compared with BSC was $1,352,159 per QALY. When a rolling response criterion was used, the resulting ICER was $479,609 per QALY. When the predictive nature of SF levels was removed, the resulting ICER was $1,398,609 per QALY. And, when the mortality benefit of luspatercept was removed, the resulting ICER was $1,198,773 per QALY. This highlights the impact of clinical uncertainty on the cost-effectiveness of luspatercept.

Issues for Consideration

The product monograph for luspatercept utilizes alternate criteria for assessment of response (6 weeks at 1 mg/kg and 9 weeks at 1.25 mg/kg),[1] which is shorter than the

Table 7: CADTH Price-Reduction Analyses (Probabilistic)

Price reduction	ICERs for luspatercept vs. BSC ($/QALY)	
	Sponsor base case	CADTH reanalysis (base case)
No price reduction	225,894	659,395
10%	201,421	587,885
20%	174,150	515,104
30%	146,962	444,056
40%	119,460	371,768
50%	92,276	299,157
60%	64,996	227,300
70%	37,659	155,289
80%	10,418	83,182
85%	Dominant	**47,156**
90%	Dominant	11,120
92%	Dominant	Dominant

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

24-week assessment period used in the BELIEVE trial. The sponsor did not consider these alternative assessment criteria for luspatercept in their model; as such, the impact of this on the cost-effectiveness of luspatercept is uncertain.

Overall Conclusions

The CADTH clinical review based on BELIEVE (May 2018 data cut) found that luspatercept was superior to placebo in terms of reducing transfusion burden by at least 33% during the fixed week 13 to week 24 period, which was the primary end point. The study also demonstrated in the 3 key secondary end points that luspatercept was superior to placebo in reducing transfusion burden by at least 33% during the week 37 to 48 period and by at least 50% during the fixed week 13 to week 24 period and week 37 to week 48 period in adult patients with transfusion-dependent anemia associated with beta-thalassemia. The other end points of the study that were evaluated were transfusion burden reduction, transfusion independence, time to first erythroid response, health-related quality of life, iron accumulation, health care resource utilization, and SF; however, due to limitations associated with the statistical methodology, the effect of luspatercept on these outcomes is currently unknown.

In addition to the lack of long-term clinical data to inform the model, CADTH identified several key limitations of the sponsor's submission, including assumptions about the transfusion burden of luspatercept nonresponders, utility estimates, the dosing of luspatercept, and the different data cut-offs and populations for BELIEVE that were provided for clinical information compared with the sponsor's pharmacoeconomic submission. The CADTH reanalyses included: modifying the assumptions surrounding the efficacy of luspatercept and BSC, using different utility values, removing dose delays for luspatercept, and aligning the clinical data more closely with the clinical data provided for the review (e.g., the full ITT population, using a data cut-off of January 2019, use of a fixed assessment period). Based on the CADTH reanalyses, the ICER for luspatercept versus BSC for patients with beta-thalassemia was $659,395 per QALY, with a 0% chance of being cost-effective at a willingness-to-pay threshold of $50,000 per QALY. To achieve cost-effectiveness of luspatercept at a $50,000 per-QALY threshold, a price reduction of 85% would be required.

The model appears to be driven by clinical assumptions surrounding the treatment efficacy of luspatercept, the expected trajectory of luspatercept nonresponders and patients on BSC, and the choice of clinical data (e.g., assessment period, population chosen). Scenario analyses were performed to explore the predictive effects of SF levels, mortality benefits of luspatercept, choosing the North American and European subpopulation, and assuming a loss of the treatment efficacy of luspatercept. The ICERs from these analyses ranged from $500,932 to $1,398,609 per QALY. Where benefits in terms of RBC transfusions are not maintained over the lifetime of the patient, the ICER will increase, with luspatercept being dominated by BSC in the scenario analysis, assuming a loss of treatment efficacy after 5 years.

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42. Cappellini M, Viprakasit V, Taher A. An overview of current treatment strategies for beta-thalassemia. *Expert Opinion on Orphan Drugs.* 2014;2:665-679.

Appendix 1: Cost Comparison Tables

Note that this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s). Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table for Adult Patients With Transfusion-Dependent Beta-Thalassemia

Treatment	Strength	Form	Price ($)	Recommended dosage	Daily cost ($)[a]	Average annual cost ($)
Luspatercept (Reblozyl)	25 mg 75 mg	Powder for SC injection	2,189.0000[b] 6,567.0000[b]	1.0 to 1.25 mg/kg every 3 weeks	312.71 to 416.95	113,828 to 151,771

SC = subcutaneous.

Note: Annual costs are based on 365 days per year and do not include mark-up or dispensing fees. Vial sharing was not assumed.

[a]Based on a mean weight of 64.8 kg in Canadian patients in the BELIEVE trial.[3]

[b]Sponsor-submitted price.[2]

Table 9: CADTH Cost Comparison Table for the Treatment of Chronic Iron Overload

Treatment	Strength	Form	Price ($)	Recommended dosage[a]	Daily cost ($)[b]	Average annual cost ($)
Deferasirox	125 mg 250 mg 500 mg	Tablet	9.2228 18.4453 36.8909	10 to 30 mg/kg daily	55.34 to 147.56	20,198 to 53,861
Deferiprone	1,000 mg 100 mg/mL	Tablet Oral solution	31.8800 3.1900	25 to 33 mg/kg 3 times daily	191.28 to 239.10[c]	69,817 to 87,272[c]
Deferoxamine mesylate	500 mg 2 g	Powder for SC or IV injection	7.2300[d] 28.3500[d]	20 to 60 mg/kg daily 4 to 7 times per week	12.39 to 56.70	4,524 to 20,696

SC = subcutaneous.

Note: All prices are from the Ontario Drug Benefit Formulary[12] or Ontario Exceptional Access Program Formulary[37] (accessed January 2021), unless otherwise indicated, and do not include mark-up or dispensing fees. Annual costs are based on 365 days per year.

[a]Recommended dosages are from the respective product's monograph.[38-40]

[b]Based on a mean weight of 64.8 kg in Canadian patients in the BELIEVE trial.[3]

[c]Tablets can be broken in half and this was considered in the cost calculation.[39]

[d]Saskatchewan drug benefit formulary (accessed January 2021).[13]

Appendix 2: Submission Quality

Note that this appendix has not been copy-edited.

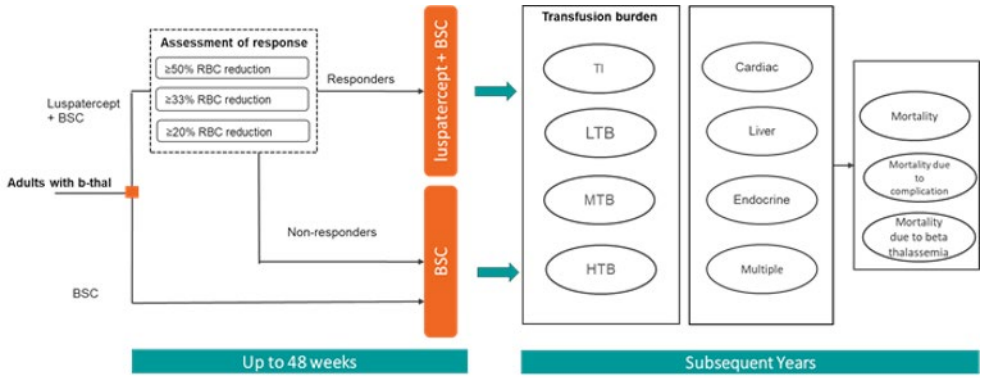
Table 10: Submission Quality

Description	Yes/ No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing.	No	Population based on the North American and European subpopulation of the BELIEVE trial.[4] CADTH felt it was more appropriate to include the full trial population. No other comparators are available for the treatment of beta-thalassemia and outcomes modelled were sufficient. Given the same datasets were not provided as part of the submission package, the CADTH clinical review was based on a different data cut of BELIEVE which made validating the clinical inputs challenging.
Model has been adequately programmed and has sufficient face validity.	Yes	No obvious errors in model programming.
Model structure is adequate for decision problem.	No	Model assesses response after a 48-week trial period, during which time treatment response is assessed throughout a 24-week rolling period. This differs from the BELIEVE trial[3] in which a 12-week period was used and the product monograph which implies a 15-week period will be used.[1] Further, the structure of the model does not allow for full examination of clinical uncertainty to be explored explicitly (e.g., attenuation of treatment effect over time).
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis).	Yes	As stated, the data informing the economic model was different from what was provided for the CADTH clinical review.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem.	Yes	No comment.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details).	Yes	Pharmacoeconomic Report clearly describes the assumptions underlying model structure/parameters.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Note that this appendix has not been copy-edited.

Figure 1: Model Structure



BSC = best supportive care; b-thal = beta-thalassemia; HTB = high transfusion burden; LTB = low transfusion burden; MTB = medium transfusion burden; RBC = red blood cell; TI = transfusion independent.

Source: Sponsor's pharmacoeconomic report.[2]

Table 11: Detailed Results of the Sponsor's Base Case

Category	Luspatercept + BSC	BSC	Incremental
Costs			
Luspatercept	**$375,460**	**$0**	**$375,460**
Drug cost	$373,933	$0	$373,933
Administration cost	$1,527	$0	$1,527
Chelation therapy	**$1,351,898**	**$1,388,779**	**−$36,881**
Drug cost	$1,343,626	$1,380,567	−$36,942
Monitoring	$8,273	$8,212	$61
RBC transfusion	**$342,818**	**$368,156**	**−$25,338**
Complications	**$85,265**	**$90,189**	**−$4,925**
Cardiac complication	$5,635	$5,617	$18
Endocrine complication	$17,652	$17,962	−$310
Liver complication	$2,072	$2,051	$21
Multiple complications	$59,905	$64,560	−$4,654
Adverse events	**$3,695**	**$2,370**	**$1,325**
Luspatercept	$1,301	$0	$1,301
ICT	$2,393	$2,370	$24
Total	**$2,159,135**	**$1,849,494**	**$309,641**

Category	Luspatercept + BSC	BSC	Incremental
LYs			
Total	**19.120**	**18.726**	**0.394**
QALYs (by health state)			
Complication-free	4.006	2.813	1.193
Transfusion visits	0.000	0.000	0.000
Single complication	2.790	2.562	0.224
Cardiac complication	0.243	0.204	0.039
Endocrine complication	2.445	2.275	0.170
Liver complication	0.098	0.083	0.015
Multiple complications	0.998	1.044	−0.046
Adverse event decrement	−0.024	−0.024	0.000
Total	**7.766**	**6.395**	**1.371**
ICER ($/QALY)			**$225,894**

ICER = incremental cost-effectiveness ratio; ICT = iron chelation therapy; LY = life-year; QALY = quality-adjusted life-year; RBC = red blood cell.

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Note that this appendix has not been copy-edited.

Detailed Results of CADTH Base Case

Table 12: Disaggregated Summary of CADTH's Economic Evaluation Results

Parameter	Luspatercept	BSC	Incremental
Discounted LYs			
Total	19.885	19.660	0.225
Discounted QALYs			
Total	**11.630**	**11.303**	**0.327**
Complication-free	4.581	4.171	0.410
Cardiac complications	0.410	0.405	0.004
Endocrine complications	4.749	4.765	−0.016
Liver complications	0.166	0.163	0.003
Multiple complications	1.745	1.818	−0.074
AE decrement	−0.020	−0.020	0.000
Discounted costs ($)			
Total	**1,938,795**	**1,723,321**	**215,474**
Acquisition	235,417	0	235,417
Administration	900	0	900
ICT acquisition cost	1,265,619	1,281,996	−16,377
ICT monitoring	8,615	8,556	59
RBC transfusion	338,891	341,599	−2,709
Cardiac complication	6,186	6,156	30
Endocrine complication	21,577	21,704	−127
Liver complication	2,357	2,327	30
Multiple complications	56,009	58,547	2,537
AEs due to drug	765	0	765
AEs due to ICT	2,460	2,436	24
ICER ($/QALY)	659,395		

AE = adverse event; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.
Source: Sponsor's pharmacoeconomic submission.[2]

Scenario Analyses

Table 13: Summary of Scenario Analyses Conducted on CADTH Base Case

Scenario	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
1. Removed predictive value of SF levels	BSC	2,722,098	14.003	Reference
	Luspatercept	2,945,325	14.163	1,398,609
2. Removed mortality benefit of luspatercept	BSC	1,723,545	11.308	Reference
	Luspatercept	1,918,349	11.471	1,198,773
3. Starting age 18 years old	BSC	2,120,256	13.808	Reference
	Luspatercept	2,335,915	14.134	660,717
4. North American and European subpopulation only	BSC	1,695,788	10.429	Reference
	Luspatercept	1,937,163	10.911	500,932[a]
5. ICT distribution according to IQVIA Pharmastat database	BSC	1,496,645	11.300	Reference
	Luspatercept	1,711,946	11.627	658,998
6. Mortality in the multiple-complications state is equal to that of liver complications	BSC	2,156,711	13.558	Reference
	Luspatercept	2,359,226	13.820	773,412
7. Used a response criteria of ≥ 50% reduction in transfusion burden	BSC	1,708,571	11.220	Reference
	Luspatercept	1,870,953	11.632	394,081
8. Luspatercept loses treatment efficacy after 5 years	BSC	1,720,895	11.302	Reference
	Luspatercept	1,841,282	11.167	Dominated
9. Luspatercept loses treatment efficacy after 10 years	BSC	1,722,727	11.309	Reference
	Luspatercept	1,895,392	11.437	1,352,159
10. Discontinuation rate beyond 48 weeks based on grade 3 to 4 AEs (2.74% per 24 weeks)	BSC	1,720,580	11.302	Reference
	Luspatercept	2,031,179	11.719	743,597
11. Use of a rolling response criterion	BSC	1,722,065	11.312	Reference
	Luspatercept	2,054,194	12.004	479,609
12. Use of the sponsor's original utility values from Grazzi (2020)[18]	BSC	1,723,991	8.354	Reference
	Luspatercept	1,939,278	8.711	602,499

AE = adverse event; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

[a]When considering the North American and European subpopulation, an 81% price reduction would be required to achieve an ICER of $50,000 per QALY.

Appendix 5: Submitted BIA and CADTH Appraisal

Note that this appendix has not been copy-edited.

Table 14: CADTH Summary Findings From the Sponsor's BIA

Key Takeaways of the BIA
• CADTH identified the following key limitations with the sponsor's analysis: ◦ The prevalence of beta-thalassemia in some jurisdictions was likely underestimated. ◦ The adherence estimate does not consider that costs will be incurred as soon as the prescription is filled, and thus underestimates the cost of iron chelation therapy (ICT). ◦ The relative dose intensity should be 100% as a most conservative estimate. • CADTH reanalysis increased the prevalence of beta-thalassemia in certain jurisdictions, increased adherence to ICTs, and increased the relative dose intensity of luspatercept. Based on the CADTH base case the budget impact is expected to be $8,293,059 in year 1, $12,332,090 in year 2, and $12,790,273 in year 3, with a 3-year budget impact of $33,415,422.

Summary of Sponsor's BIA

The submitted BIA assessed the introduction of luspatercept for the treatment of adult patients with RBC transfusion-dependent anemia associated with beta-thalassemia. The analysis was taken from the perspective of the Canadian public drug plans using an epidemiologic-based approach, with only drug acquisition costs considered. A 3-year time horizon was used, from 2022 to 2024, with 2021 as a base year. The population size was estimated using prevalence estimates from Canadian clinical experts, with an annual 1% incidence estimate applied after year 0. A summary of the sponsor's derivation of the eligible population size is presented in Figure 2.

In Canada, there are currently no medications specifically indicated for the treatment of anemia due to beta-thalassemia; thus, there are no comparators. The reference-case scenario consisted of BSC, which comprised RBC transfusions and ICTs. The new drug scenario included luspatercept given in conjunction with BSC, and BSC alone. As the costs for RBC units are not reimbursed via Canadian public drug plans the costs associated with BSC only included ICT costs in both arms. Key inputs to the BIA are documented in Table 16.

Figure 2: Sponsor's Estimation of the Size of the Eligible Population (Redacted)

Figure 2 has been redacted at the request of the sponsor.

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NIHB = Non-Insured Health Benefits; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PE = Prince Edward Island; RBCT = red blood cell transfusion; SK = Saskatchewan; TD = transfusion-dependent; Y1 = year 1; Y2 = year 2; Y3 = year 3.

Source: Sponsor's budget impact submission.[41]

Table 15: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3, if appropriate)
Target population	
Estimated prevalence of adult TD beta-thalassemia	
British Columbia	[redacted]
Alberta	[redacted]
Ontario	[redacted]
Nova Scotia	
Assumed prevalence of adult TD beta-thalassemia in all other jurisdictions	[redacted]
Number of patients eligible for drug under review	[redacted]
Market uptake (3 years)	
Uptake (reference scenario)	
Luspatercept + BSC	0% / 0% / 0%
BSC alone	100% / 100% / 100%
Uptake (new drug scenario)	
Luspatercept + BSC	[redacted]
BSC alone	[redacted]
Cost of treatment over 24 weeks (per patient)	
Luspatercept	$53,367.88
Deferoxamine mesylate	
LTB	$3,123.36
MTB	$4,164.48
HTB	$6,246.72
Deferiprone	
LTB	$32,135.04
MTB	$32,135.04
HTB	$48,202.56
Deferasirox	
LTB	$17,043.58
MTB	$24,790.68
HTB	$32,537.79

BSC = best supportive care; HTB = high transfusion burden; LTB = low transfusion burden; MTB = medium transfusion burden; TD = transfusion-dependent.

Summary of the Sponsor's BIA Results

The estimated budget impact of funding luspatercept for the treatment of adult patients with RBC transfusion-dependent anemia associated with beta-thalassemia was $7,224,520 in year 1, $10,795,274 in year 2, $11,245,729 in year 3 for a 3-year total of $29,265,523.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Lack of information on prevalence of beta-thalassemia in Canada:** In the absence of information on prevalence of beta-thalassemia and transfusion-dependent beta-thalassemia in Canada, the sponsor attempted to estimate the number of cases nationally and the distribution across jurisdictions. In doing so, the sponsor assumed that the prevalence of transfusion-dependent beta-thalassemia would be [redacted] in the jurisdictions [redacted], based on the assumption that care of beta-thalassemia is highly centralized. This was highlighted by the drug plan input as a questionable assumption. Furthermore, the clinical experts consulted by CADTH were skeptical that the prevalence was [redacted], though they agreed that care was centralized.
  - In the absence of information on prevalence of transfusion-dependent beta-thalassemia in Canada, CADTH approximated the population by applying the worldwide prevalence estimate from the literature (9 per million)[42] to the jurisdictions in which the estimate was [redacted] while maintaining the sponsor's estimates in the other provinces, as part of the base case.
- **Adherence of ICTs:** The sponsor assumed adherence rates of 64.0% to 89.0%, depending on the ICT administered. In some cases of nonadherence, however, the full cost of therapy is still incurred by the drug plans, as the product is dispensed and picked up by the patient. To reflect the full cost to drug plans, 100% adherence should be assumed.
  - CADTH used adherence rates of 100% for all ICTs, as part of the base case.
- **RDI of luspatercept:** The sponsor assumed an RDI of 97.2% for luspatercept. This calculation considers 2 elements: dose delays for luspatercept decreasing the estimate to 92%, and dose escalation for some patients resulting in a higher dose intensity of 106%. While less than full use and delays in clinical practice are possible, to understand the impact where the cost of full dosing of luspatercept is incurred by the payer, a more conservative assumption would be to assume 100% dose intensity.
  - CADTH used an RDI of 100%, as part of the base case.

CADTH Reanalyses of the BIA

Based on the limitations identified, CADTH's base case included adding patients to all jurisdictions based on the worldwide prevalence of beta-thalassemia, assuming 100% compliance of ICTs, and assuming an RDI of 100% for luspatercept.

Table 16: CADTH Revisions to the Submitted BIA

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None	—	—
Changes to derive the CADTH base case		
1. Increased prevalence of beta-thalassemia in certain jurisdictions	Patients in:	Patients in:
	[redacted]	MB = 11
	[redacted]	NB = 7
	[redacted]	NL = 5
	[redacted]	PEI = 1
	[redacted]	SK = 9
	[redacted]	NIHB = 8
2. Increased compliance rates of ICT		
Deferoxamine	64%	100%
Deferiprone	89%	100%
Deferasirox	74%	100%
3. Increased relative dose intensity	97.2%	100%
CADTH base case	—	Reanalysis 1 + 2 + 3

ICT = iron chelation therapy; MB = Manitoba; NB = New Brunswick; NIHB = Non-insured health benefits; NL = Newfoundland; PEI = Prince Edward Island; SK = Saskatchewan.

The results of the CADTH stepwise reanalysis are presented in summary format in Table 17 and a more detailed breakdown is presented in Table 18. Based on the CADTH base case, the budget impact of the reimbursement of luspatercept for the treatment of transfusion-dependent beta-thalassemia is expected to be $8,293,059 in year 1, $12,332,090 in year 2, and $12,790,273 in year 3, with a 3-year budget impact of $33,415,422. A scenario analysis using a price reduction of 85% from the pharmacoeconomic model appraisal resulted in a 3-year budget impact of $3,941,772 for luspatercept.

Table 17: Summary of the CADTH Reanalyses of the BIA

Stepped analysis	3-year total ($)
Submitted base case	29,265,523
CADTH reanalysis 1: Increased prevalence of beta-thalassemia	33,007,064
CADTH reanalysis 2: 100% adherence for iron chelation therapy	29,025,972
CADTH reanalysis 3: 100% relative dose intensity of luspatercept	29,867,142
CADTH base case	33,415,422

BIA = budget impact analysis.

Table 18: Detailed Breakdown of the CADTH Reanalyses of the BIA

Stepped analysis	Scenario	Year 1 ($)	Year 2 ($)	Year 3 ($)	3-year total ($)
Submitted base case	Reference	[redacted]	[redacted]	[redacted]	[redacted]
	New drug	[redacted]	[redacted]	[redacted]	[redacted]
	Budget impact	7,224,520	10,795,274	11,245,729	29,265,523
CADTH base case	Reference	27,900,952	28,179,962	28,461,761	112,167,380
	New drug	36,194,011	40,512,052	41,252,034	145,582,802
	Budget impact	8,293,059	12,332,090	12,790,273	33,415,422
CADTH scenario analysis: 85% price reduction	Reference	27,900,952	28,179,962	28,461,761	112,167,380
	New drug	29,069,735	29,660,738	29,753,974	116,109,151
	Budget impact	1,168,783	1,480,777	1,292,213	3,941,772

BIA = budget impact analysis.