



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Reblozyl

International non-proprietary name: luspatercept

Procedure No. EMEA/H/C/004444/II/0011

Note

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



Status of this report and steps taken for the assessment				
Current step ¹	Description	Planned date	Actual Date	Need for discussion ²
<input type="checkbox"/>	Start of procedure	18 Jul 2022	18 Jul 2022	<input type="checkbox"/>
<input type="checkbox"/>	CHMP Rapporteur Assessment Report	22 Aug 2022	23 Aug 2022	<input type="checkbox"/>
<input type="checkbox"/>	CHMP members comments	05 Sep 2022	05 Sep 2022	<input type="checkbox"/>
<input type="checkbox"/>	Updated CHMP Rapporteur Assessment Report	08 Sep 2022	08 Sep 2022	<input type="checkbox"/>
<input type="checkbox"/>	Request for supplementary Information	15 Sep 2022	15 Sep 2022	<input type="checkbox"/>
<input type="checkbox"/>	Responses	25 Nov 2022	25 Nov 2022	<input type="checkbox"/>
<input type="checkbox"/>	Start of procedure	28 Nov 2022	28 Nov 2022	<input type="checkbox"/>
<input type="checkbox"/>	CHMP Rapporteur Assessment Report	03 Jan 2023	03 Jan 2023	<input type="checkbox"/>
<input type="checkbox"/>	CHMP members comments	16 Jan 2023	16 Jan 2023	<input type="checkbox"/>
<input type="checkbox"/>	Updated CHMP Rapporteur Assessment Report	19 Jan 2023	19 Jan 2023	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Opinion	26 Jan 2023	26 Jan 2023	<input type="checkbox"/>

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 24 June 2022 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.4, and 4.8 of the SmPC in order to include new safety information about Extramedullary Hematopoietic Masses in transfusion-dependent β -thalassemia patients based on the open-label phase of the ACE-536-B-THAL-001 Phase III study, the long-term follow-up study and post marketing data. The Package Leaflet is updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

After the occurrence of EMH masses in the clinical development program for luspatercept (Reblozyl) in the currently not approved indication of non-transfusion dependent (NTD) β -thalassemia, EMH was added as an Important Identified risk in the proposed RMP (submitted for the ongoing type II variation for extension of indication to non-transfusion dependent β -thalassemia, EMEA/H/C/004444/II/0009) and was included as a safety concern in the Reblozyl PSUR. A safety review evaluating the risk for EMH masses in all patients treated with Reblozyl was conducted. Overall exposure with luspatercept was estimated by considering cumulative subject exposure in clinical trials, cumulative patient exposure from real-world post-marketing experience and literature review.

This safety review identified several cases of EMH masses also in the approved indication transfusion-dependent (TD) β -thalassemia after extended treatment duration.

Based on these findings, the MAH initially proposed to update sections 4.2, 4.4 and 4.8 of the SmPC to inform healthcare providers and patients about this risk and mitigation/management measures.

Overall, the proposed changes seem to adequately reflect the new safety findings regarding the occurrence of EMH masses in TD β -thalassemia. Further amendments in sections 4.2, 4.3, 4.4 and 4.8 of the SmPC were included as requested.

The benefit-risk balance of Reblozyl remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.4, and 4.8 of the SmPC in order to include new safety information about

Extramedullary Hematopoietic Masses in transfusion-dependent β -thalassemia patients based on the open-label phase of the ACE-536-B-THAL-001 Phase III study, the long-term follow-up study and post marketing data. The Package Leaflet is updated accordingly.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

New contraindication in patients requiring treatment to control the growth of EMH masses and new warning in section 4.4 of SmPC providing information based on the pivotal study and the long term follow-up study, on frequencies of occurrence of extramedullary haemopoiesis (EMH) masses and spinal cord compression symptoms due to EMH masses in transfusion-dependent β -thalassaemia patients. EMH has also been recorded as ADR as common for the β -thalassaemia indication in section 4.8 of the SmPC.

Please refer to Scientific Discussion 'Reblozyl-H-C-4444-II-11'.

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur's assessment comments on the type II variation

5. Introduction

Reblozyl (luspatercept) is currently approved by the European Commission for the treatment of adult patients with anaemia associated with transfusion-dependent (TD) β -thalassemia (as well as with Myelodysplastic syndrome (MDS)). In parallel to this procedure, an ongoing type II variation (EMA/H/C/004444/II/0009) is aimed at extending the approved β -thalassaemia indication to include adult patients with non-transfusion dependent (NTD) β -thalassemia (decision pending).

Disease or condition

β -thalassemia comprises a group of inherited disorders characterized by a reduction in the production of β -globin chains of haemoglobin (Hb) and a subsequent imbalance in globin chains (α :non- α ratio). All of the pathophysiologic features of β -thalassemia can be linked to this primary imbalance and accumulation of unpaired α -globin chains within the developing erythrocytes, resulting in ineffective erythropoiesis and peripheral haemolysis that lead to clinical complications including chronic anaemia. Profound anaemia triggers a number of compensatory mechanisms responsible for the clinical sequelae associated with β -thalassemia such as erythroid marrow expansion, splenomegaly, increased intestinal iron absorption (leading to iron overload), leg ulcers, peripheral haemolysis, hypercoagulable state, and pulmonary hypertension.

Previously, individuals with β thalassemia were classified as having β thalassemia major, intermedia, and minor (decreasing severity). Subsequent classification has changed to the terms Transfusion dependent (TD) β -thalassemia or Non-Transfusion Dependent (NTD) β -thalassemia.

Patients with TD β -thalassemia (which includes conventional β -thalassemia major and severe forms of HgbE/ β -thalassemia) commonly present to clinical attention in early childhood (before 2 years of age) with severe anaemia (< 7 g/dL). These patients require life-long, regular blood transfusion therapy. In contrast, NTD β -thalassaemia do not depend on regular transfusion therapy for survival. They sporadically need transfusion therapy, e.g. with significant infection, during surgery or pregnancy or for limited periods of time with growth retardation in children or when the chronic anaemia cause clinical morbidity such as splenomegaly, extramedullary hematopoietic (EMH) masses, pseudotumours, or leg ulcers.

Clinical development program

The luspatercept global clinical development program for β -thalassemia comprised the pivotal Phase 3 studies ACE-536-B-THAL-001 (TD β -thalassemia) and ACE-536-B-THAL-002 (NTD β -thalassemia), and 2 supportive Phase 2 studies (Studies A536-04 and A536-06), which included TD as well as NTD patients. TD and NTD patients from both pivotal studies were eligible to receive luspatercept treatment in the ongoing, open label, single-arm, rollover study to evaluate the long-term safety of luspatercept (ACE-536-LTFU-001).

Proposed changes

Based on a numerical imbalance favouring placebo in the NTD ACE-536-B-THAL-002 study, EMH was added as an Important Identified risk in the proposed Risk Management Plan (RMP v1.2, submitted within the ongoing procedure EMA/H/C/004444/II/0009) and was included as a safety concern in the Reblozyl PSUR.

The Applicant proposes to amend the Reblozyl SmPC based on a safety topic review evaluating the risk of EMH masses and their complications in patients treated with Reblozyl for TD β -thalassemia. In this evaluation, in addition to the EMH safety finding from the NTD ACE-536-B-THAL-002, EMH cases and complications were also identified in the TD population from the pivotal ACE-536-B-THAL-001, from the long-term ACE-536-LTFU-001 follow-up study as well as from spontaneous reports in this population.

Consistent with the original method for defining adverse drug reactions in the product label, TD safety data presented in the Company Core Data Sheet (CCDS) is based on the pivotal Phase 3 TD ACE-536-B-THAL-001 β -thalassemia study and from ACE-536-B-THAL-001 subjects who transitioned into the long-term ACE-536-LTFU-001 study.

Incidence of adverse events from the supportive studies (i.e., A536-04/06) are not described or presented in the CCDS. According to the Applicant, this methodology is consistent with the Council for International Organizations of Medical Sciences' Guidelines for Preparing Core Clinical-Safety Information on Drugs, 2nd Edition (Council for International Organizations of Medical Sciences [CIOMS] III and V, 1999) and the Management of Safety Information from Clinical Trials (CIOMS VI, 2005).

Based on these new findings the Marketing Authorization Holder (MAH) proposes to update the language of the Posology (Discontinuation), Warnings and Precautions and the Adverse reactions sections of the Luspatercept CCDS to inform healthcare providers and patients about this risk and mitigation/management measures.

Accordingly, sections 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC have been updated.

The following amendments are suggested:

- 4.2 Posology/Discontinuation recommendations section for β -thalassemia patients:
 - Discontinuation of luspatercept in case of EMH masses causing serious complications
- 4.4 Warning and Precautions section
 - Cases of EMH masses and spinal cord compression observed in TD and NTD β -thalassemia
 - Information on known risk factors for β -thalassemia patients with EMH masses
 - Monitoring of β -thalassemia patients at initiation and during treatment and discontinuation in case of serious complications due to EMH masses
 - Not recommending luspatercept for patients requiring treatment to control the growth of EMH masses
- 4.8 Adverse reactions / undesirable effect from clinical experience
 - Inclusion of EMH masses and spinal cord compression as adverse reactions seen in TD β -thalassemia patients in TD β -thalassemia clinical trial

6. Clinical Safety aspects

6.1. Methods – analysis of data submitted

Estimated Drug Exposure

Overall exposure with luspatercept was estimated by considering (a) cumulative subject exposure in clinical trials, (b) cumulative patient exposure from real-world post-marketing experience and (c) literature review.

- (a) **Cumulative exposure** represents the number of unique subjects exposed to Luspatercept at least once. Subjects were exposed to Luspatercept in **clinical trials** in blinded and unblinded

fashion. Exposure was based on populations defined by protocol or as estimated from randomization scheme for the study, if appropriate.

A comprehensive, cumulative search of the clinical databases for all Luspatercept studies and a search of the corporate safety database was performed to identify all reports in which Luspatercept was considered a suspect drug and at least one of the reported adverse event terms including serious adverse events (SAEs) was mapped to extramedullary hematopoiesis masses (PTs: Cutaneous extramedullary haemopoiesis and Extramedullary hematopoiesis) using MedDRA Version 24.1.

- (b) Patient Exposure is based on an algorithm that uses sales data and **Real-World Data** (claims) to produce the estimates of unique patients exposed to a drug (active substance). The sales data allows the MAH to estimate the total number of patients exposed to a drug every month, based on the expected dose per patient per month per the label. The claims data inform the MAH on the average pattern of exposure to the drug for patients in a real life setting. Combining these, the MAH estimates how many of the patients exposed to the drug in a given period are taking it for the first time, and how many have taken it before, which allows the MAH to estimate the number of unique patients for periods of multiple months.

In addition, when a drug is first available on the market the MAH does not have any claims data to estimate treatment duration in the real world setting and therefore the MAH uses the expected time on drug from the clinical trials and applies the assumption of exponential decay of the probability of taking additional doses over time. Once data from claims become available the MAH is able to use this to determine treatment duration in the real-world setting. The sales data are then used as the basis for the total amount of drug available and then the duration of treatment in the real-world setting is used to estimate how much drug each patient takes.

The median duration used in the calculation for Luspatercept was 1 year modelled on clinical trials due to limited post marketing treatment duration experience in the real-world setting.

The methodology for estimating commercial patient exposure utilizes up to 3 data sources:

- 1) Celgene's Sales/Shipment Data – this data consists of all shipments of Celgene product to all applicable countries and includes commercial and free-of-charge units. The data are used to determine the units (e.g., milligrams) of a product that was sold to a geographical region to estimate the number of patients who would have been exposed to that product, based on expected dosing in the region. Shipment data are used to estimate the active patients for a period of time by dividing the total units sold by the average units per patient (note that average units per patient is derived from epidemiologic or market research).
- 2) Claims Data – this data consists of 2 distinct sources of electronic health care claims data in the USA: Optum Clinformatics Datamart and Symphony Claims for Hematology/Oncology. Claims data consisting of distinct patient IDs and prescription fill rates for each product are used to understand usage patterns. For newly approved products, until sufficient claims data are available, patterns are based on discontinuation rates derived from clinical trial experience.
- 3) Controlled Distribution Database – this data source is not applicable for Luspatercept, since Luspatercept does not have a controlled distribution program.

A comprehensive, cumulative search of the corporate safety database was performed to identify all spontaneous and literature cases in which Luspatercept was considered a suspect or concomitant interacting drug and at least one of the reported adverse event terms including

SAEs, was mapped to extramedullary hematopoiesis masses (PTs: Cutaneous extramedullary haemopoiesis and Extramedullary hematopoiesis masses) using MedDRA Version 24.1.

- (c) A **literature review** was performed to identify if any published scientific articles since year 2000 in luspatercept therapy have been associated the occurrence of EMH masses. For each set of references retrieved, titles were screened for possible relevance to the subject.

6.2. Results

(a) Clinical Data

As of 24 December 2021, it is estimated that a cumulative total of 1,100 subjects received treatment with luspatercept in Celgene-sponsored and Acceleron-sponsored clinical trials (note by the Assessor: in different indications: (N)TD- β -thalassemia and MDS).

A total of 26 subjects with adverse events associated with EMH events were identified across the luspatercept clinical development program. All 26 cases were reported in subjects from the β -thalassemia clinical program. Of the 26 subjects with EMH events, 10 subjects were reported in TD β -thalassemia subjects [from the pivotal ACE-536-B-THAL-001 or from long-term ACE-536-LTFU-001 (in patients who had participated in the pivotal ACE-B-THAL-001 parent study)].

The following data have been provided upon request (see section 9.2 for further details):

The 26 subjects with AEs associated with EMH are distributed as follows:

- 12 subjects with transfusion-dependent β -thalassemia (TDT)
 - 10 from the pivotal trial ACE-536-B-THAL-001 (including 5/10 from the parent study ACE-536-B-THAL-001 and 5/10 subjects that transitioned into the long-term follow up study ACE-536-LTFU-001)
 - 2 subjects from the Phase 2 studies A536-04/06 (including 1 subject from the parent study A536-06 and 1 subject who transitioned from A536-04 into the long-term follow-up study ACE-536-LTFU-001)
- 14 subjects with non-transfusion-dependent β -thalassemia (NTDT)
 - 9 subjects from the pivotal trial ACE-536-B-THAL-002 (1 subject, ID 2031011 excluded as the subject was diagnosed on first day of treatment)
 - 6 subjects from the Phase 2 studies A536-04/06 (5 subjects in the parent study and 1 subject who transitioned from A536-06 into ACE-536-LTFU-001)

Eight subjects reported EMH mass-related complications, including 2 NTD subjects, 1 from ACE-536-B-THAL-002 and 1 from the supportive phase 2 study A536-06. The remaining 6 subjects with complications (all TD β -thalassemia) are summarized below in Table 1.

There have been no cases of EMH events reported in the MDS and MF BMS-sponsored clinical programs with luspatercept.

During the double-blind placebo-controlled period of the ACE-536-B-THAL-001 study, no EMH masses were reported as adverse events (AEs) after 259.82 patient-years of treatment. During the open-label phase and after subjects transitioned into the ACE-536-LTFU-001 study, a total of 10/315 (3.2%) subjects treated with luspatercept reported EMH masses (5/10 subjects within the open-label phase of the ACE-536-B-THAL-001 study and 5/10 subjects within the ACE-536-LTFU-001 study). Four of the 10

subjects had a medical history of EMH events, and 5/10 were splenectomized. In 6/10 subjects, the EMH events were non-serious, 5 of which were Grade 1/2 in severity. In 4/10 subjects, luspatercept treatment was continued after onset of event. Six of 315 (1.9%) subjects were noted to have EMH masses with associated symptoms or complications (Table 1). All 6 subjects had onset of EMH at least 1 year after initiating luspatercept treatment (range 1 to 4 years). The complications included spinal cord compression (diagnosed by MRI imaging) in 4/6 subjects (Table 1), 2/4 of which required laminectomy, 1/4 was treated with hyper-transfusions and steroids, and the remaining one showed radiological improvement after discontinuing treatment.

Table 1: Summary of Extramedullary Hematopoietic Cases with Complications in the Transfusion Dependent Population Thalassemia Pivotal Clinical Trials											
Subject ID Age(Y)/ Gender	Preferred Term / Verbatim Term	Splenectomy/ Pre- existing EMH/Spleen size increase wk48	Hx Hydroxyurea	Baseline Hb/Hb /Hb at or close to event (g/L)	Study Days since start of luspatercept/ No. of Doses	Toxicity Grade/ Serious (Yes/No)/ Sponsor Causality	Action Taken with luspatercept	Outcome	Treatment for EMH	Location	Other/Responde r or non- responder to primary endpoint
Phase 3 ACE-536-B-THAL-001 (TD)											
	Extramedullary haemopoiesis	Yes/No/NA	N/A	92/78	890 (Dose950) /44	4/Yes /Not Suspected	Discontinued	Resolved	Hydroxyurea & Spinal laminectomy	C7/T1 and T3- T11 (myelon compressi on)	Back Pain on Study Day 890 Grade 2 then Grade 3 on Study Day 947. [Responder]
	Extramedullary haemopoiesis/ Extramedullary hematopoiesis Spinal Cord Compression	No/No/No	No	68 /71	386/19	3/Yes /EMH suspected/ Spinal cord compression Not-suspected	Discontinued	Resolved with sequelae	Dexamethasone 13U of RBC	multiple posterior epidural nodules along thoracic level bodies; spinal canal and cord compressi on at level of T2,3,6,7,8 ,9 and 11; multiple paravertebr al and presacral soft tissue masses, masses adjacent to ribs and expansibl e ribs; masses involving bilateral	History of Splenomegaly. Progressive back pain, spinal cord compression, mild paraparesis of both lower extremities, numbness of both lower extremities up to both knees (patient was unable to work), decreased pin prick sensation up to T11 level, and motor power grade IV at right lower extremity reported at the time of the EMH [Non-Responder]

										neural foramina and sacral spinal canal	
	Extramedullary haemopoiesis	No/No/NA	No	95/91	1068/51	3/No /Suspected	Dose reduced	Resolved to Grade 1	Local radiotherapy Hydroxyurea (initiated 5 months after event)	T3-T9	History of splenomegaly. Grade 2 bilateral foot numbness (related to EMH) reported at the same day as EMH. EMH and foot numbness resolved to Grade 1 after 80 days. [Responder]
ACE-536- LTFU-001 (Parent Study Phase 3 ACE-536-B-THAL-001)											
	Extramedullary haemopoiesis Sciatica/ lumbosacralgia	Yes/No/NA	No	96/102	718/36	1/No / Not Suspected 2/No / Not Suspected	None	Recovere d	None	Epidural space L5	Sciatica recovered, no documented association of sciatica to EMH [Non-responder]
	Extramedullary haemopoiesis	Yes/No/NA	No	114/113	1503/73	3/Yes/Suspect ed	Discontinued	Ongoing	None	Lower spine and pelvis L2- S1, Retro- vertebral D12, L4, L5, S1	Low back pain for several months. Radiological improvement post discontinuation [Non-responder]
	Extramedullary haemopoiesis	No/Yes/No	No	81/94	1720/60	3/Yes/Not Suspected	Discontinued	Ongoing	Decompression laminectomy T3-6	T8 prior paraspinal and T9	The subject had been experiencing
	Spinal cord compression					3/Yes/ Not Suspected			Paracetamol	paraspinal regions. Other smaller paraspinal masses at the thoracic level and no masses at the epidural space	back pain for 1 week and on the day of diagnosis, complained of presented weakness, unsteady gait, fecal incontinence and dysuria. [Non- responder]

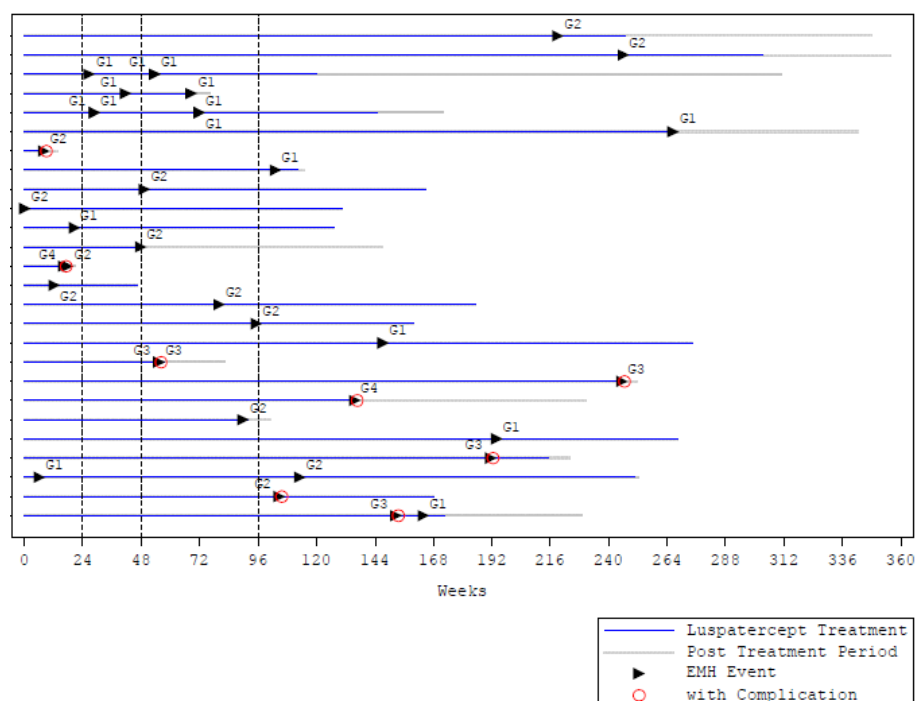
The following data have been provided upon request (see section 9.2 for further details):

A longitudinal assessment of all EMH events as of the data cutoff of 24-Dec-2021 (used for the Clinical Overview), including recurrent cases, is shown graphically as a swimmer plot in Figure 1 (cases occurring during clinical development).

There was a wide range of times to onset of the first EMH event during the luspatercept clinical program. Among the 26 subjects with EMH events during the luspatercept clinical development program:

- 11 subjects experienced the first event during the first 48 weeks of treatment
- 4 subjects experienced the first event between Weeks 48-96
- 11 subjects experienced the first event after Week 96 (including 6 subjects whose first EMH event occurred after transitioning from the ACE-536-B-THAL-001 study to the ACE-536-LTFU-001 study).

Figure 1: Subjects with Extramedullary Hematopoiesis Events in the Luspatercept Program by Study



(b) Post-marketing Data

As of 24 Dec 2021, overall, cumulative commercial exposure to Luspatercept is estimated to be approximately 16,171 patients. This is an estimate and should be interpreted with caution, taking into account all of the above-mentioned limitations.

The search revealed a total of 6 EMH cases, 5 serious and 1 non-serious met the search criteria. Four of the 6 cases described the patient as receiving luspatercept for the treatment of β -thalassemia, 1 for MDS and for the remaining one case, the indication was not reported. There were no events of EMH reported with off-label use. Two of the 4 β -thalassemia cases reported pain secondary to the EMH mass, but the locations of the masses were not provided. In 1 of the remaining 2 β -thalassemia cases, lumbar/sacral involvement with pain and severe neurologic symptoms were reported and in the other case, parasternal pre-existing EMH mass growth with pain and dyspnea due to compression was reported.

Consistent with what has been reported in medical literature regarding EMH, majority of the reports of EMH involved patients with β -thalassemia (4 of 5 cases). Of the 4 β -thalassemia cases, 2 EMH complications described compression with neurologic and/or painful symptoms; the remaining 2 cases had no complications. One EMH case was reported in an MDS patient, and the other case had no indication reported. Six post-marketing cases with EMH events represent an estimated reporting rate of 0.04% (6/16,171).

Limited information is available for these cases. Vignette summaries are presented below:

One case was regarding a female patient of unspecified age who received Reblozyl for β -Thalassemia. Medical history, past medications, concurrent medical conditions, and concomitant medications were not provided. The patient received 3 doses of Reblozyl injection. Treatment dates and dosage information was not provided.

On an unspecified date, the patient experienced increase of the extramedullary mass, poor heart function, could not be administered the amount of transfusion needed. The reporter did not mention any hospitalization or any other seriousness criteria for the events; however, the company considered the event of "heart function not good" and increase of extramedullary mass as a serious important medical event, and transfusions as a non-serious event. Lab data and corrective treatment, if any, was not provided. Reblozyl was permanently discontinued in response to the events. At the time of reporting, the outcome of the events was not provided.

One case was regarding a female patient of unspecified age who received Reblozyl for the treatment of thalassemia diagnosed on an unspecified date. Medical history and past medication were not reported. Concomitant medications included Deferoxamine, Hydrea, and Jakavi; all for unknown indications. The patient received subcutaneous Reblozyl injection (1 mg/kg every 3 weeks) from 26Aug2021 to 28Oct2021.

On 24Oct2021, the patient experienced excruciating back pain (pain score 10) and dyspnea secondary to an increase in extramedullary erythropoiesis. She was hospitalized on an unknown date. A CT scan of the abdomen showed a remarkably increased right parasternal extramedullary erythropoiesis mass (9.4*9.1 cm vs 4.0*5.2 cm). Corrective treatment, if any, was not provided. Reblozyl was permanently discontinued in response to the event. At the time of reporting, the event of increase in extramedullary erythropoiesis was resolving.

One case was regarding a patient who received Reblozyl for the treatment of β thalassemia diagnosed on an unspecified date. Medical history, past medications, concurrent medical conditions, and concomitant medications if any, were not provided.

This patient experienced severe pains due to extramedullary foci: At the time of reporting, outcome of the event severe pains due to extramedullary foci was not provided.

One case was regarding a male patient of an unspecified age who received Reblozyl for an unknown indication. Medical history, past medication, concurrent medical conditions, and concomitant medication were not provided. The patient received subcutaneous Reblozyl injection.

It was reported that the patient was responding to Reblozyl; however, dose continuation was of concern as the patient had developed extramedullary hematopoiesis, muscle aches, headaches, and severe facial pain after the 3rd dose. The patient was admitted to the hospital and orders were placed for an MRI of the brain and a neurology consult. Corrective treatment was not provided. Action taken with Reblozyl in response to the events was unknown; however, discussion related to lowering the dose and/or discontinuation was pending. At the time of reporting, the events had resolved.

One case was regarding a patient of an unspecified gender and age who received Reblozyl for myelodysplastic syndrome. Medical history, past medication, concurrent medical conditions, and concomitant medication, if any, were not provided. The patient received Reblozyl injection (dosage and frequency unknown) from 11Ma021 to an unknown date.

On 19Ma021, the patient experienced extramedullary hematopoiesis. The reporter did not provide any seriousness criteria for the event; however, the company assessed the event as an important medical event. Lab data, if any, was not provided. The patient received radiation therapy for the event. Reblozyl was interrupted in response to the event and on rechallenge, the event recurred. At the time of reporting, the outcome of the event had not been provided.

The reporter did not provide the causal relationship between Reblozyl therapy, and the event of extra medullary haematopoiesis.

One case was regarding a 36-year-old, female patient who received Reblozyl for transfusion-dependent anaemia associated with β -thalassaemia, developed paresthesias in the perineal area, gluteal region and

both thighs and inability to urinate secondary to extra-medullary erythropoiesis masses as well as thalassemia major and Horse tail syndrome and was hospitalized.

The patient was initially diagnosed in 1988 and has been receiving transfusions of 2 red blood cell units every 3 weeks. Her past medical history and past medications were not reported. Concurrent medical conditions include catheterization, extramedullary erythropoiesis, pain, fecal incontinence, Horse tail syndrome, and radiotherapy. The patient has no prior history of extramedullary erythropoiesis mass nor associated symptoms. Concomitant medication includes Deferasirox for iron overload.

The patient received subcutaneous Reblozyl injection (1 mg/kg once every 3 weeks) from 15Jul2021 to 22Sep2021 (patient was on 4th cycle of luspatercept treatment). On 22Sep2021, the patient presented to the emergency room with paresthesias in the perineal area, gluteal region and both thighs and inability to urinate, thalassemia major, horse tail syndrome and extra-medullary erythropoiesis masses. Incontinence and atony of the anal and bladder sphincter was observed by electromyogram and patient was diagnosed with extramedullary erythropoiesis and compression in the sacral and lumbar area. An MRI was done but results were not provided. Patient underwent urgent surgical intervention on 23Sep2021. Excisional biopsy of spinal epidural tissue showed connective tissue and abundant hematopoietic precursors (predominantly erythroid) compatible with extramedullary hematopoiesis. Due to no improvement in symptoms, corrective treatment including Hydroxyurea was on 01Oct2021 and is currently ongoing. Additional corrective treatment including radiotherapy and RBC transfusions (2 red blood cell units each 3 weeks) were also initiated. The patient continues to be hospitalized and undergoing radiotherapy treatment without evident improvement of the symptoms, persisting complications like urinary and fecal incontinence and diarrhoea. The anatomical location of the paravertebral masses is at the level of T7 and T8. Intraspinal involvement was also observed at the lumbar level above the L5-S1 level and lumbosacral space that contacts the horsetail roots.

On 22Sep2021, Reblozyl was permanently discontinued in response to the events of compression in the sacral and lumbar area and extramedullary erythropoiesis. At the time of reporting, the events had not resolved. The physician assessed the causal relationship between Reblozyl therapy and the event of extramedullary erythropoiesis as possible but then also assessed the causal relationship between Reblozyl therapy and the events of extramedullary erythropoiesis and compression in the sacral and lumbar area as unknown.

(c) Literature Review

The search revealed 15 articles of interest; however, on further review of the articles it was observed that none of the articles contained individual patient reports of the occurrence of EMH masses while undergoing treatment with luspatercept.

6.3. Discussion

Currently, luspatercept is approved for the treatment of adult patients with anaemia associated with transfusion-dependent (TD) β -thalassemia as well as with Myelodysplastic syndrome (MDS). In addition, an ongoing type II variation procedure is aimed at extending the approved β -thalassaemia indication to include adult patients with non-transfusion dependent (NTD) β -thalassemia (decision pending).

After the occurrence of EMH masses in the NTD ACE-536-B-THAL-002 clinical study (NTD β -thalassemia indication currently not approved for Reblozyl), EMH was added as an Important Identified risk in the proposed Risk Management Plan (submitted for the ongoing type II variation for extension of indication to non-transfusion dependent β -thalassemia, EMEA/H/C/004444/II/0009) and was included as a safety concern in the Reblozyl (luspatercept) PSUR. A safety topic review evaluating the risk of EMH masses and their complications in patients treated with luspatercept was conducted and overall exposure with

luspatercept was estimated by considering cumulative subject exposure in clinical trials, cumulative patient exposure from real-world post-marketing experience and literature review. The analysis revealed EMH cases and respective complications in the in clinical studies (pivotal study ACE-536-B-THAL-001 and long-term ACE-536-LTFU-001 follow-up study in TD β -thalassemia) as well as in post-marketing reports in TD β -thalassemia and MDS.

In the current type II variation the MAH initially proposed to amend sections 4.2, 4.4 and 4.8 of the Reblozyl (luspatercept) SmPC to include the risk of EMH masses and their complications in patients treated with luspatercept for TD β -thalassemia. Upon request, section 4.3 of the SmPC was also updated.

Data from clinical trials

As of the cut-off date 24-Dec-2021 a total of 26 subjects reported adverse events associated with EMH across the luspatercept clinical development program, which overall comprised approximately 1,100 subjects (including subjects from the β -thalassemia and MDS clinical programs). All 26 cases of EMH were reported in patients with β -thalassemia, whereas none were reported in patients with MDS. Of those, 10 cases of EMH were reported in TD β -thalassemia subjects (i.e. 10/315, 3.2%) and spinal cord compression symptoms due to EMH masses occurred in 6/315 (1.9%) of patients during the open-label phase from pivotal study ACE-536-B-THAL-001 or from long-term study ACE-536-LTFU-001. This information was included in sections 4.4 and 4.8 of the SmPC, which is considered appropriate. The remaining 16 cases with EMH occurred in patients with NTD β -thalassemia subjects and are discussed in detail in an ongoing type II variation aiming at extending the indication (EMA/H/C/004444/II/0009).

The summary presented by the MAH regarding NTD β -thalassemia patients and TD β -thalassemia patients in phase 2 supportive studies A536-04/06 was completed upon request. Narratives are also provided for NTD β -thalassemia patients from study ACE-536-B-THAL-002, for whom luspatercept is currently not approved, but an extension of indication to NTD β -thalassemia is subject to an ongoing type II variation (EMA/H/C/004444/II/0009). Upon request, the MAH provided information about dosing and treatment duration for each identified case in a tabular summary.

Among the 10 TD β -thalassemia patients with reported EMH related events in pivotal ACE-536-B-THAL-001 or from long-term study ACE-536-LTFU-001, 4/10 (40%) subjects had a medical history of EMH and 5/10 (50%) were splenectomised. Overall, EMH mass-related complications were reported in 6/10 (60%) subjects. Of those with EMH mass-related complications 1/6 (16.7%) subject had a medical history of EMH and 3/6 (50%) were splenectomised. Although splenectomy was reported in 50% of the reported EMH cases in both categories, a relation seems unlikely since it was reported at a similar frequency at baseline in study ACE-536-B-THAL-001 (57.2%) and at the same frequency in patients with newly occurring EMH events irrespective of EMH associated complications (50%). Of note, the minority of patients reporting EMH events or complications had a medical history of EMH. This might indicate a risk of new development of EMH masses in these patients. In particular, the majority of patients with EMH mass-related complications (5/6; 83.3%) had no medical history of pre-existing EMH.

Among the TD β -thalassemia patients with EMH mass-related complications 2/6 (33.3%) had neither pre-existing EMH masses nor splenectomy, and there was no indication of splenomegaly (or hepatomegaly) in any of those 6 patients at week 48. Moreover, comorbidities are common among TD β -thalassaemia patients, especially low baseline Hb, and identification of any risk factors in this limited number of cases will likely not be reliable. As the presented data suggests that EMH masses may also occur without any known risk factors, and since it cannot be excluded that patients without known complications to date may develop complications due to EMH masses in the future, the highlighting of known risk factors prior to the occurrence of EMH masses was omitted in the SmPC upon request.

Further, section 4.4 of the SmPC was amended to include recommendations regarding the monitoring of EMH masses, regardless of indication, as requested. Instead of including a recommendation not to treat patients requiring treatment to control the growth of EMH masses in section 4.4, the MAH agreed that the occurrence of EMH masses constitutes a situation where the medicinal product must not be given for safety reasons, which was therefore included as contraindication in section 4.3 of the SmPC.

Upon request, section 4.2. was also amended to reflect that treatment *must* be discontinued in case of EMH masses causing serious complications.

The addition of the section *Spinal cord compression* in section 4.8 of the SmPC is therefore endorsed. The MAH is reminded to align all changes also with the parallel type II variation EMEA/H/C/004444/II/0009.

Post-marketing data

Shipment and sales data were used as the basis for the total amount of drug available. Claims data inform on the average pattern of exposure in a real life setting. Patient exposure is based on an algorithm combining these data sources. This algorithm was not further described. It is critically noted that a median treatment duration of 1 year modelled on clinical trials likely underestimates the true treatment duration with luspatercept, since luspatercept is intended for life-long treatment. In any case, results need to be interpreted with caution due to inevitable incompleteness of the data. No further information is requested.

Cumulative patient exposure from real-world post-marketing experience revealed 6 post-marketing cases with EMH events, representing an estimated reporting rate of 0.04% (6/16,171). Again, since post-marketing data likely underestimate the true frequency due to underreporting, and the level of detail provided is usually low, results need to be interpreted with caution. Four of 6 reported EMH events were observed in patients with β -thalassemia, and one event in MDS (one remaining event in an unknown indication).

In the single patient with MDS, an EMH event was reported only one week after the first dose of luspatercept, and hence previously undetected pre-existent EMH masses cannot be excluded, but neither can a causal relationship or a worsening of pre-existent EMH masses. However, one of the latter seem more likely, since the event reoccurred on re-challenge after luspatercept was interrupted in response to the first event. Since these events occurred in a single patient so far, no final conclusion concerning treatment of MDS can be made. As requested, regarding the discontinuation criteria for luspatercept, the MAH removed the restriction to the β -thalassaemia indication in sections 4.2 and 4.4 in the SmPC. Luspatercept treatment must be discontinued in all patients experiencing EMH causing serious complications, regardless of indication. In addition, the possible occurrence of EMH in MDS was included in section 4.8.

The majority of reported EMH cases (4/6) was observed in β -thalassemia patients. For most of them, it was not reported whether a patient had TD or NTD β -thalassemia, but it is assumed that all had TD β -thalassemia, since Reblozyl is currently approved for TD, but not for NTD β -thalassemia. In the TD clinical development program, all EMH cases occurred during the open-label phase after subjects transitioned into the long-term follow-up study, i.e. patients were treated for at least 48 weeks before EMH occurred. In contrast, in the post-marketing setting EMH was reported comparatively early during luspatercept treatment, with the caveat of very scarce information provided. When definite information was available (in 2/4 cases), EMH occurred around the 3rd-4th treatment cycle, i.e. 2 months after treatment initiation. According to the available information, another patient with β -thalassemia reported the event most likely after the third dose as well, as did the one patient treated for an unknown indication. No information is available for the remaining patient with β -thalassemia. Medical history was not available in most cases. In

the only case with known medical history, no prior history of EMH or associated symptoms was reported, further supporting that EMH masses may occur without pre-existing risk factors.

Upon request, the MAH provided a comprehensive summary of the timing of first occurrence of EMH after treatment initiation in all patients during the clinical development, including the NTD β -thalassemia population. The majority of patients reporting EMH masses within the first 48 weeks of treatment were NTD β -thalassemia patients (9/11), whereas the majority of patients reporting EMH masses for the first time after Week 96 were TD β -thalassemia patients (8/11). While the discrepancy between indications may be a chance finding, and may partially be attributed to different screening strategies, upon request the MAH included information in section 4.8 of the SmPC that EMH masses may also occur after extended treatment with luspatercept, i.e. after Week 96, for the first time.

Literature review

Upon literature review, 15 articles of interest were identified. Upon request, details on the methodology for the literature search were provided. However the MAH also clarified that the performed literature search was not related to the occurrence of EMH masses while on luspatercept therapy, but rather to generate an overview of published incidence and prevalence of EMH in the overall population and in the patient population with β -thalassemia. Further there were only 14 articles as one has been counted twice by mistake.

Initially, the MAH claimed that none contained individual patient reports of the occurrence of EMH masses while undergoing treatment with luspatercept. Based on the information provided upon request, no such claim can be made or rather, since the identified articles are not related to Luspatercept treatment, no such finding can be made per definition.

Although the MAH did not provide the requested information, this issue is not further pursued, since the occurrence of EMH masses is adequately reflected in the SmPC with the requested amendments.

Additional comments

According to the MAH, an updated RMP v1.2, which includes EMH as an Important Identified risk, has not been submitted with this variation but has been submitted within the ongoing procedure EMEA/H/C/004444/II/0009. A respective update to the RMP is considered necessary but it is acceptable that the respective assessment of the updated RMP will be performed during the other variation procedure.

Conclusion

In conclusion, the inclusion of the risk of EMH in TD β -thalassemia to the Reblozyl SmPC is appropriate and supported.

7. Changes to the Product Information

As a result of this variation, sections 4.2, 4.3, 4.4 and 4.8 of the SmPC are being updated to include new safety information about Extramedullary Hematopoietic Masses in transfusion-dependent β -thalassemia patients based on the open-label phase of the ACE-536-B-THAL-001 Phase III study, the long-term follow-up study and post marketing data.

The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information, as well as further requests as detailed in the RSI section below.

8. Request for supplementary information

8.1. Major objections

Clinical Safety aspects

None

8.2. Other concerns

Clinical Safety aspects

- 1) The data presentation provided by the MAH concerning EMH cases occurring in the luspatercept clinical development program is incomplete. The MAH is asked to provide a listing of all EMH cases across all studies included in the luspatercept clinical development program. The listing should also contain total numbers of patients treated, respective indication, dosing and treatment duration.
- 2) A discrepancy in the timing of first occurrence of EMH events after treatment initiation was observed between patients enrolled in the TD β -thalassemia clinical program and post-marketing data. The MAH should provide a comprehensive summary of the timing of the first occurrence of EMH events after treatment initiation in all patients during the clinical development, including the NTD β -thalassemia population. Furthermore, possible reasons for a potential discrepancy between patient groups as well as the observed differences between patients enrolled in clinical trials vs post-marketing reporting, should be discussed.
- 3) Insufficient detail has been provided regarding the methodology for literature search to identify published reports on the occurrence of EMH masses. The MAH should state which search terms were used, how they were weighted, which databases were screened, and how articles of interest were identified.
- 4) According to the Applicant, 15 published articles were of interest regarding luspatercept therapy and the occurrence of EMH masses, but no further details were provided. The MAH is asked to discuss the information provided in these articles irrespective of individual patient reports.
- 5) The amended text in section 4.4 of the SmPC currently reads " *β -thalassaemia patients with EMH masses had known risk factors such as medical history of EMH masses at baseline or comorbidity of splenectomy, splenomegaly, hepatomegaly, low baseline Hb (<8.5 g/dL).*" This statement is not sufficiently justified and EMH events also occurred in patients without any of these "risk factors". Thus, the MAH is requested to omit the highlighting of known risk factors prior to the occurrence of EMH masses in this section of the SmPC. This also applies for the respective statement in section 4.8. (see also respective comments in the attached document).
- 6) The MAH is asked to align the wording in section 4.2. regarding discontinuation of treatment in case of serious complications due to EMH masses (...treatment *should* be discontinued, see also SmPC comment) according to the warning in section 4.4 (...treatment with luspatercept *must* be discontinued...).
- 7) Currently, in sections 4.2 and 4.4 of the SmPC, discontinuation and monitoring of EMH masses are only recommended in patients with β -thalassaemia. The MAH is requested to remove this

restriction to the β -thalassaemia indication. Luspatercept treatment must be discontinued in all patients experiencing EMH causing serious complications, regardless of indication. In addition, section 4.8 requires respective amendments (see SmPC comment).

- 8) Currently, SmPC Section 4.4. (Special warnings and precautions for use) includes a recommendation not to use luspatercept in patients requiring treatment to control the growth of EMH masses. The MAH is asked to discuss why those patients should only be mentioned in Section 4.4. and not included as contraindication in Section 4.3.

9. Assessment of the responses to the request for supplementary information

9.1. Major objections

None

9.2. Other concerns

Clinical aspects

Question 1:

The data presentation provided by the MAH concerning EMH cases occurring in the luspatercept clinical development program is incomplete. The MAH is asked to provide a listing of all EMH cases across all studies included in the luspatercept clinical development program. The listing should also contain total numbers of patients treated, respective indication, dosing and treatment duration.

Summary of the MAH's response:

As of the 24-Dec-2021 submission cutoff date, it is estimated that a cumulative total of 1100 subjects received treatment with luspatercept across the luspatercept clinical development program. Of these, 26 subjects had AEs associated with EMH, all of which were reported in the β -thalassemia clinical program. These cases were summarized in subject narratives and vignettes provided in Appendix 1.1 and 1.2 of the Clinical Overview submitted within this application (EMA/H/C/004444/II/0011). As requested, a tabular listing of these subjects is provided below in Table 1.

The 26 subjects with AEs associated with EMH are distributed as follows:

- 12 subjects with transfusion-dependent β -thalassemia (TDT)
 - 10 from the pivotal trial ACE-536-B-THAL-001 (including 5/10 from the parent study ACE-536-B-THAL-001 and 5/10 subjects that transitioned into the long-term follow up study ACE-536-LTFU-001)
 - 2 subjects from the Phase 2 studies A536-04/06 (including 1 subject from the parent study A536-06 and 1 subject who transitioned from A536-04 into the long-term follow-up study ACE-536-LTFU-001)
- 14 subjects with non-transfusion-dependent β -thalassemia (NTDT)

- 9 subjects from the pivotal trial ACE-536-B-THAL-002 (1 subject, ID 2031011 excluded as the subject was diagnosed on first day of treatment)
- 6 subjects from the Phase 2 studies A536-04/06 (5 subjects in the parent study and 1 subject who transitioned from A536-06 into ACE-536-LTFU-001)

For the majority (20/26) of subjects, EMH events were Grade 1 (n = 8) or Grade 2 (n = 12) in severity, nonserious, and generally did not lead to any change in luspatercept dosing (n = 14), with dose reductions (n = 4) and discontinuations (n = 2) being less common outcomes. The remaining 6 subjects all experienced SAEs related to EMH (4 Grade 3, 2 Grade 4), and luspatercept was discontinued.

There have been no cases of EMH reported in the MDS or MF clinical development programs.

It should be noted that EMH masses are an important identified risk in the list of safety concerns in the in the EU RMP.

Table 1: Summary of EMH Cases in Luspatercept-treated Subjects by Study (All Indications)

(Indication; Parent study)	Preferred Term/Verbatim Term	Pre-existing EMH	Study Days Since Start of Luspatercept/No. of Doses/Last dose level	Toxicity Grade/ Seriousness (Yes/No)	Action Taken With Luspatercept	Outcome
Study A536-04 (β-thalassemia)						
(NTD)	Bone Pain/ Extramedullary masses in thoracic MRI pressuring thoracic spine resulting in bone back and nerve pain	Yes	56/3 0.8 mg/kg	2/No	Discontinued	Ongoing
Study A536-06 (β-thalassemia)						
(NTD)	Extramedullary haemopoiesis/ Extramedullary masses increase	Yes	1533/65 1.25 mg/kg	2/No	Dose reduction	Ongoing
(NTD)	Extramedullary haemopoiesis/ Extramedullary masses increase	No	1722/87 1.25 mg/kg	2/No	Dose reduction	Ongoing
(NTD)	Extramedullary haemopoiesis/ Extramedullary mass paravertebral, cranial, dorsal right	No	186/14 1.25 mg/kg	1/No	None	Ongoing
	Extramedullary haemopoiesis/ New paravertebral thoracic left EMH mass		375/22 1.25 mg/kg	1/No	None	Ongoing
	Extramedullary haemopoiesis/ New extramedullary mass inferior vena cava		375/22 1.25 mg/kg	1/No	None	Ongoing
(TD)	Extramedullary haemopoiesis/ New extramedullary hematopoietic mass, left at last dorsal vertebrae	Yes	291/13 1.25 mg/kg	1/No	None	Ongoing
	Extramedullary haemopoiesis/ New extramedullary hematopoietic mass, right at last dorsal vertebrae		480/21 1.25 mg/kg	1/No	None	Ongoing

(Indication; Parent study)	Preferred Term/Verbatim Term	Pre-existing EMH	Study Days Since Start of Luspatercept/No. of Doses/Last dose level	Toxicity Grade/ Seriousness (Yes/No)	Action Taken With Luspatercept	Outcome
(NTD)	Extramedullary haemopoiesis/ Left Paravertebral Dorsal EMH Mass (3.9*3*2.6)	No	201/15 1.25 mg/kg	1/No	None	Ongoing
	Extramedullary haemopoiesis / Right Paravertebral Dorsal EMH Mass (2.6*3.2*1.4)		201/15 1.25 mg/kg	1/No	None	Ongoing
	Extramedullary haemopoiesis/ Left Paravertebral Dorsal EMH Mass (2.7X1.5)		502/29 0.8 mg/kg	1/No	None	Ongoing
	Extramedullary haemopoiesis / Right Paravertbral Dorsal EMH Mass (2.9X1.4)		502/29 0.8 mg/kg	1/No	None	Ongoing
ACE-536-B-THAL-001 (TD β-thalassemia)						
	Spinal Cord Compression/ Spinal cord compression	No	386/19 1.25 mg/kg	3/Yes	None	Resolved with sequelae
	Extramedullary haemopoiesis/ Extramedullary hematopoiesis		386/19 1.25 mg/kg	3/Yes	Discontinued	Resolved with sequelae
	Extramedullary haemopoiesis/ Extramedullary hematopoiesis on TH C7/TH1 and TH3- TH11 vertebrae	No	950/44 1.25 mg/kg	4/Yes	Discontinued	Resolved with sequelae
	Extramedullary haemopoiesis/ Deterioration of extramedullary haematopoiesis	Yes	629/29 1.25 mg/kg	2/No	Discontinued	Ongoing
	Mass/ Extramedullary mass	Yes	43/2 1 mg/kg	1/No	None	Not resolved
	Extramedullary haemopoiesis/ Worsening extramedullary masses		792/39 1 mg/kg	2/No	Dose reduced	Ongoing
	Extramedullary haemopoiesis/ Extramedullary haematopoiesis	No	1068/51 1.25 mg/kg	3/No	Dose reduced	Resolved
	Extramedullary haemopoiesis/ Extramedullary haematopoiesis		1147/54 1.25 mg/kg	1/No	Dose reduced	Ongoing

(Indication; Parent study)	Preferred Term/Verbatim Term	Pre-existing EMH	Study Days Since Start of Luspatercept/No. of Doses/Last dose level	Toxicity Grade/ Seriousness (Yes/No)	Action Taken With Luspatercept	Outcome
ACE-536-B-THAL-002 (NTD β-thalassemia)						
	Extramedullary haemopoiesis/ Increase in size of extramedullary haematopoiesis	Yes	722/31 1.25 mg/kg	1/No	None	Ongoing
	Extramedullary haemopoiesis/ Extramedullary haematopoiesis masses: paravertebral, dorsal, and sacral	No	345/17 1.25 mg/kg	2/No	None	Ongoing
	Extramedullary haemopoiesis/ Extramedullary haematopoiesis masses	Yes	1/1 1 mg/kg	2/No	None	Ongoing
	Extramedullary haemopoiesis/ Extramedullary haematopoiesis masses: paravertebral and sacral	No	144/8 1 mg/kg	1/No	None	Ongoing
	Chest wall mass/ Worsening of chest wall extramedullary mass	Yes	334/17 1.25 mg/kg	2/No	None	Ongoing
	Spinal cord compression/ Extramedullary hemopoiesis masses expansion into spinal canal causing compression	Yes	113/6 1.25 mg/kg	4/Yes	Discontinued	Recovered with Sequelae
	Extramedullary haemopoiesis/ Extramedullary hematopoiesis masses expansion into spinal canal		124/6 1.25 mg/kg	2/No	Discontinued	ongoing
	Extramedullary haemopoiesis/ EMH extramedullary haematopoiesis	No	85/5 1.25 mg/kg	2/No	None	Resolved
	Extramedullary haemopoiesis/ Extramedullary hematopoiesis sacral area	No	560/27 1 mg/kg	2/No	None	Ongoing
	Extramedullary haemopoiesis/ Extramedullary hemopoiesis at thoracic and lumbar level of spine	Yes	667/29 1.25 mg/kg	2/No	None	Ongoing

(Indication; Parent study)	Preferred Term/Verbatim Term	Pre-existing EMH	Study Days Since Start of Luspatercept/No. of Doses/Last dose level	Toxicity Grade/ Seriousness (Yes/No)	Action Taken With Luspatercept	Outcome
ACE-536-LTFU-001 (All Indications)						
	Extramedullary haemopoiesis/ Enlargement of extramedullary hematopoietic lesion	Yes	1358/64 1.25 mg/kg	1/No	None	Ongoing
	Extramedullary haemopoiesis/ Severe extramedullary haematopoiesis	No	1503/73 0.8 mg/kg	3/Yes	Discontinued	Ongoing
	Extramedullary haemopoiesis/ Masses of extramedullary hematopoiesis	No	718/36 1.25 mg/kg	2/No	None	Ongoing
	Extramedullary haemopoiesis/ Extramedullary foci	No	1865/12 1.25 mg/kg	1/No	Discontinued	Ongoing
	Extramedullary haemopoiesis/ Extramedullary hematopoiesis	Yes	1718/72 1.25 mg/kg	3/Yes	Discontinued	Ongoing
	Extramedullary haemopoiesis/ Benign bilateral thoracic spinal lesions	No	1030/41 1.25 mg/kg	1/No	None	Ongoing

Source: Celgene Clinical database

Assessment of the MAH's response:

As requested, the MAH provided a listing of EMH cases across all studies, including the respective indication, dosing and treatment duration, but the total numbers of patients treated per study were not included in the listing. Instead, the MAH reiterated the estimated cumulative number of patients treated (n=1100) across the luspatercept clinical development program. Hence, it can only be estimated how many patients are included in the ongoing clinical program across all indications.

Furthermore, although most relevant information can now be retrieved from the listings and narratives/vignettes provided, the following discrepancies were noted: In total, 26 subjects reported AEs associated with EMH, all of which are included in Appendix 1.1 and 1.2 of the Clinical Overview, and in the updated listing. Both listings include 1 subject. As this variation is mainly focussed on the currently granted indications MDS and TDT, the data regarding NTDT patients is discussed in more detail in the ongoing parallel variation procedure (EMA/H/C/004444/II/0009), which aims at extending the indication of luspatercept to NTDT patients.

Consequently this is not further pursued here and reference is made to the requested amendments in the parallel variation.

Conclusion:

Issue not further pursued.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 2:

A discrepancy in the timing of first occurrence of EMH events after treatment initiation was observed between patients enrolled in the TD β -thalassemia clinical program and post-marketing data. The MAH should provide a comprehensive summary of the timing of the first occurrence of EMH events after treatment initiation in all patients during the clinical development, including the NTDT β -thalassemia population. Furthermore, possible reasons for a potential discrepancy between patient groups as well as the observed differences between patients enrolled in clinical trials vs post-marketing reporting, should be discussed.

Summary of the MAH's response:

A longitudinal assessment of all EMH events as of the data cutoff of 24-Dec-2021 (used for the Clinical Overview), including recurrent cases, is shown graphically as a swimmer plot in Figure 1 (cases occurring during clinical development).

There was a wide range of times to onset of the first EMH event during the luspatercept clinical program. Among the 26 subjects with EMH events during the luspatercept clinical development program:

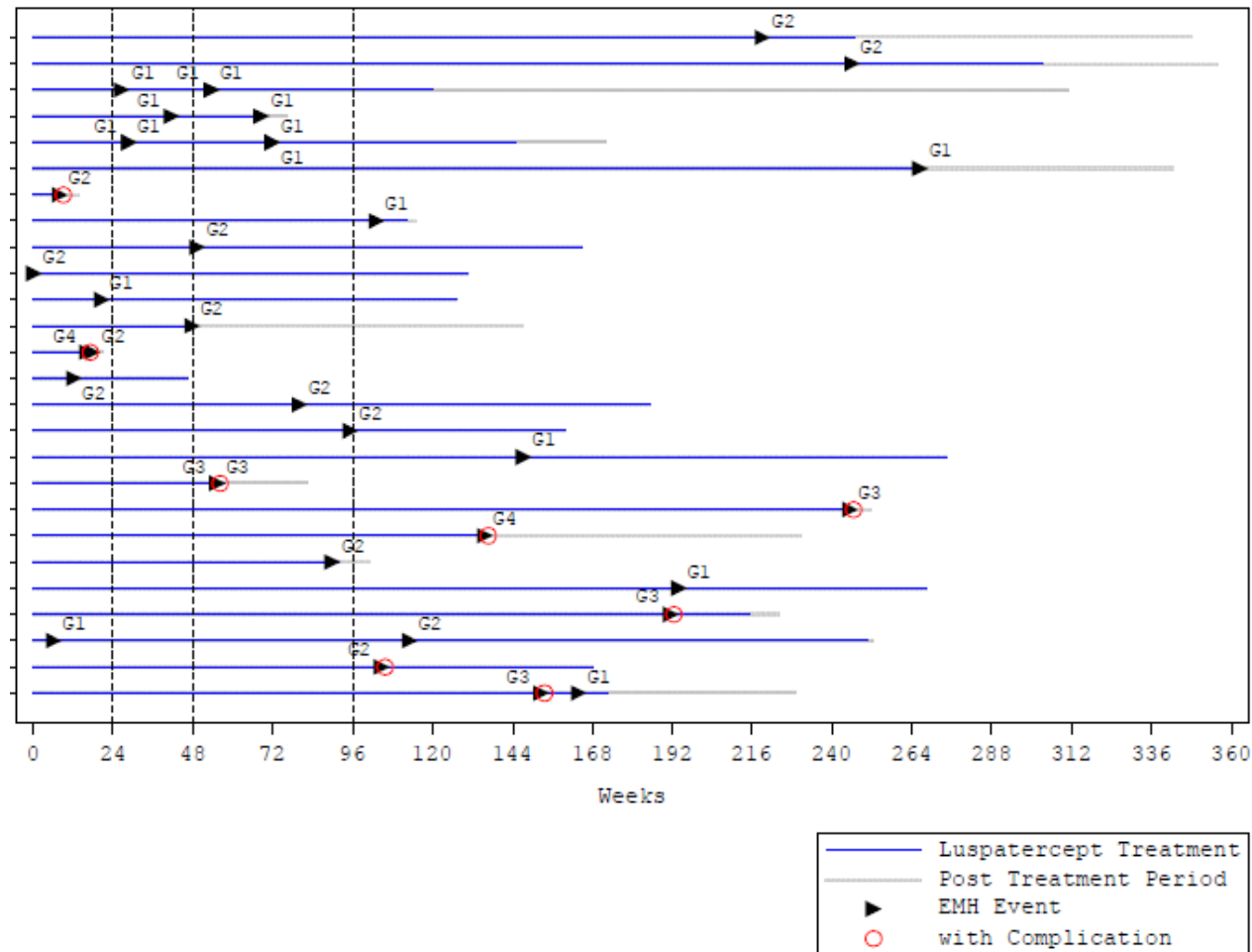
- 11 subjects experienced the first event during the first 48 weeks of treatment
- 4 subjects experienced the first event between Weeks 48-96
- 11 subjects experienced the first event after Week 96 (including 6 subjects whose first EMH event occurred after transitioning from the ACE-536-B-THAL-001 study to the ACE-536-LTFU-001 study).

With respect to postmarketing data, a limited number of reports have reported onset date, thus a similar longitudinal assessment is very limited. Six cases were reported as of the same data cut and the indication provided was β -thalassemia (4 of 6), MDS (1 of 6), and indication not provided (1 of 6). Only 3

of the 6 reports had information regarding the onset of the event. The time to onset (days after first day of therapy) was 79, 60, and 70 days, respectively. Notable discrepancies are due to the fact that clinical trials information is systematically collected and all details of a given patient can be investigated, whereas the postmarketing reports usually provide limited information given the spontaneous nature of these reports, and generally lack relevant details such as medical history, dates of therapy, date of adverse event, treatment given, and concomitant medication, among others. While the Applicant makes every effort to collect follow-up information, many times limited information is available.

Despite all its limitations, postmarketing reports allow for periodic aggregate safety and surveillance for known safety profile and for rare adverse drug reactions.

Figure 1: Subjects with Extramedullary Hematopoiesis Events in the Luspatercept Program by Study



Assessment of the MAH's response:

A comprehensive summary of the timing of the occurrence of EMH events after treatment initiation for all patients included in the clinical development was provided, as requested. While it is acknowledged that post-marketing reports may provide limited information, it is noted that within the clinical program, the majority of patients reporting EMH masses within the first 48 weeks of treatment were NTDT patients (9/11). In contrast, the majority of patients reporting EMH masses for the first time after Week 96 were TDT patients (8/11). While the discrepancy between indications may be a chance finding, and may partially be attributed to different screening strategies, it is considered important to inform prescribers/patients that EMH masses may occur for the first time after extended treatment with luspatercept, i.e. after Week 96. No conclusions regarding later occurrences in NTD patients can be drawn from post-marketing data, since luspatercept is currently only indicated for TDT patients.

Conclusion:

The MAH is asked to include information in section 4.8 of the SmPC that EMH masses may also occur after extended treatment with luspatercept, i.e. after Week 96, for the first time.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 3:

Insufficient detail has been provided regarding the methodology for literature search to identify published reports on the occurrence of EMH masses. The MAH should state which search terms were used, how they were weighted, which databases were screened, and how articles of interest were identified.

Summary of the MAH's response:

The literature search mentioned in the Clinical Overview was to assess the published rates of incidence and prevalence of EMH in the overall population and in the patient population with β -thalassemia. All searches were conducted in PubMed and included the search terms listed in Table 2. Articles of interest were identified as studies published after 2000 and involving a study population of ≥ 100 patients.

Table 2: Literature Search Terms and Publication Yield

Topic Search Terms	Number of Articles
Incidence and prevalence	
"Hematopoiesis, Extramedullary"[Majr] prevalence	21
"Thalassemia"[Majr] "Hematopoiesis, Extramedullary"[MeSH] prevalence	13
Association of EPO levels with EMH	
("Erythropoietin"[Mesh]) AND "Hematopoiesis, Extramedullary"[MeSH]	38
EMH in other populations	
"Primary Myelofibrosis/complications"[Majr] extramedullary hematopoiesis	122
"Primary Myelofibrosis/complications"[Majr] extramedullary hematopoiesis NOT "Case Reports" [Publication Type]	15
"Hematopoiesis, Extramedullary"[MeSH] AND "Myeloproliferative Disorders"[Majr] NOT "Case Reports" [Publication Type])	70
"Myelodysplastic Syndromes"[Majr] AND "Hematopoiesis, Extramedullary"[MeSH]	20 ^a
"Leukemia"[Majr] AND "Hematopoiesis, Extramedullary"[MeSH] prevalence	4
"Anemia, Hemolytic"[Majr] AND "Hematopoiesis, Extramedullary"[MeSH] prevalence	14 ^b

^a mostly case reports or subtypes of EMH by location

^b mostly overlapping with thalassemia

The MAH conducts a comprehensive search of scientific databases (including information available as electronic publications ahead of print) weekly to identify published literature that may affect or further inform the benefit-risk profile for luspatercept. Articles are also reviewed to identify individual case safety reports. The search strategy is derived by the cross-functional Safety Management Team and reviewed at least annually. The keywords and monitored events used during these searches are presented in the table below.

Table 3: Luspatercept Literature Search Strategy
Database: Embase® Medline
Product Keywords: ACE-536, ACE536, ACE 536, ace-536, ace536, ace 536, luspatercept, luspatercept – aamt, luspatercept aamt, Reblozyl.
Safety Specific Keywords: ((adverse OR undesirable OR untoward OR unwanted OR unintentional OR toxic OR noxious OR harm* OR serious OR side OR beneficial) NEAR/3 (event* OR reaction OR effect* OR risk* OR outcome* OR experience*) OR ‘embryo death’ OR ‘fetus death’ OR ‘suicide’ OR ‘lethality’ OR ‘perinatal death’ OR ‘newborn death’ OR ‘death’ OR ‘side effect’ OR ‘drug intoxication’ OR ‘pregnancy’ OR (exposure AND utero) OR (exposure NEAR/3 uter*) OR ‘teratogenic agent’/exp OR ‘teratogenesis’/exp OR ‘teratogenicity’ OR ‘genotoxicity’ OR ‘genotox*’ OR ‘mutagenic agent’ OR ‘mutagenesis’/exp OR ‘mutagenic activity’ OR ((congenital OR birth) NEAR/3 (defect* OR deformity)) OR ‘abortion’/exp OR ‘lactation’ OR ‘breast feeding’ OR ‘drug abuse’/exp OR off label drug use’ OR (off NEAR/3 label) OR ‘medical error’/exp OR ‘suicide attempt’ OR ‘drug overdose’ OR ‘paediatric*’ OR ‘pediatric8’ OR ‘adverse event’/exp OR ‘iatrogenic disease’ OR ‘case report’ OR (case AND report) OR ‘drug toxicity and intoxication’/exp OR ‘maternal exposure’ OR ‘paternal exposure’ OR ‘perinatal drug exposure’ OR ‘prenatal drug exposure’ OR ‘prenatal exposure’ OR ‘pregnancy complication’/exp OR ‘drug interaction’/exp OR ‘drug dependence’/exp OR ‘drug resistance’/exp OR ‘treatment failure’/exp OR ‘vaccine failure’ OR ‘drug contamination’ OR ‘occupational exposure’ OR ‘drug treatment failure’ OR ‘drug withdrawal’/exp OR ‘drug carcinogenicity’ OR ‘carcinogenicity’ OR ‘carcinogenic activity’ OR ‘child’/syn OR ‘clinical study’/syn
Luspatercept Monitored Events: All Malignancies (SPM (MDS) and de novo). All Malignancies (SPM (MDS) and de novo), Haematologic malignancies (including acute myeloid leukaemia [AML]), Kidney toxicity, Extramedullary hematopoietic masses, Thromboembolic events, Pregnancy or in-utero exposure and safety during lactation, Off-label use in pediatric patients and effects such as develop toxicity, Long-term safety.

Assessment of the MAH’s response:

The MAH provided the information regarding performed literature searches but none is suitable to identify if any published scientific articles since year 2000 in luspatercept therapy have been associated the occurrence of EMH masses, as initially stated by the Applicant.

While the presented details seem adequate for the intended overview of published incidence and prevalence of EMH in the overall population and in the patient population with β - thalassemia, the additional selection criteria of a study population of ≥ 100 patients seems rather high. However, to estimate background incidences, it might be acceptable.

Although the MAH did not provide the requested information but rather claimed a different purpose of the literature search than in the initially submitted overview (see Q4), this issue is not further pursued, since the occurrence of EMH masses is adequately reflected in the SmPC with the requested amendments.

Conclusion:

Issue not further pursued.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 4:

According to the Applicant, 15 published articles were of interest regarding luspatercept therapy and the occurrence of EMH masses, but no further details were provided. The MAH is asked to discuss the information provided in these articles irrespective of individual patient reports.

Summary of the MAH's response:

The Applicant wishes to clarify that the aforementioned publications of interest were not related to the occurrence of EMH masses while on luspatercept therapy, but rather were articles identified via the literature search described in Question 3, Table 2. It should also be noted that the total number of publications is 14, as 1 citation had been previously double-counted in error. The information provided in these articles is summarized in detail in the subsections below as relates to the epidemiology of EMH in thalassemias (Section 4.1.1), studies of risk factors for EMH in thalassemias (Section 4.1.2), and an evaluation of EMH in other populations outside of the thalassemias (Section 4.1.3). The publications are listed according to topic in Table 4.

In addition, the luspatercept-specific literature search (described in Question 3, Table 3) did not yield any publications related to EMH associated with luspatercept up to the 24-Dec-2021 data cut used for the Clinical Overview.

Table 4: EMH-related Publications by Topic

First Author, Year	Reference Title
<i>Incidence and Prevalence of EMH in Patients with Thalassemia (Section 4.1.1.1)</i>	
Orphanidou-Vlachou, 2014 ¹	Extramedullary hemopoiesis.
Rivella, 2009 ²	Ineffective erythropoiesis and thalassemias.
Rivella, 2012 ³	The role of ineffective erythropoiesis in non-transfusion-dependent thalassemia.
Haidar, 2010 ⁴	Paraspinal extramedullary hematopoiesis in patients with thalassemia intermedia.
Chuncharunee, 2019 ⁵	Review of disease-related complications and management in adult patients with thalassemia: A multi-center study in Thailand.
<i>Epidemiologic Studies in NTD Thalassemia (Section 4.1.1.2)</i>	
Taher, 2010 ⁶	Overview on practices in thalassemia intermedia management aiming for lowering complication rates across a region of endemicity: the OPTIMAL CARE study.
<i>Epidemiologic Studies in TD Thalassemia (Section 4.1.1.3)</i>	
Ricchi, 2015 ⁷	Extramedullary hematopoiesis is associated with lower cardiac iron loading in chronically transfused thalassemia patients.
Sousos, 2017 ⁸	Presence of the IVS-I-6-Mutated Allele in Beta-Thalassemia Major Patients Correlates with Extramedullary Hematopoiesis Incidence.
<i>Epidemiologic Studies in NTD and TD Thalassemia (Section 4.1.1.4)</i>	
Ricchi, 2019 ⁹	Prevalence of extramedullary hematopoiesis, renal cysts, splenic and hepatic lesions, and vertebral hemangiomas among thalassemic patients: a retrospective study from the Myocardial Iron Overload in Thalassemia (MIOT) network.

First Author, Year	Reference Title
Teawtrakul, 2018 ¹⁰	Epidemiologic study of major complications in adolescent and adult patients with thalassemia in Northeastern Thailand: the E-SAAN study phase I.
<i>Studies of Risk Factors in NTD Thalassemia (4.1.2.1)</i>	
Huang, 2019 ¹¹	Erythropoiesis and Iron Homeostasis in Non-Transfusion-Dependent Thalassemia Patients with Extramedullary Hematopoiesis.
Ricchi, 2012 ¹²	A useful relationship between the presence of extramedullary erythropoiesis and the level of the soluble form of the transferrin receptor in a large cohort of adult patients with thalassemia intermedia: a prospective study.
<i>Studies of Risk Factors in NTD Thalassemia (Section 4.1.2.2)</i>	
Ricchi, 2014 ¹³	Extramedullary haematopoiesis correlates with genotype and absence of cardiac iron overload in polytransfused adults with thalassaemia.
<i>EMH in Other Populations (Section 4.1.3)</i>	
Fan, 2018 ¹⁴	Extramedullary hematopoiesis in the absence of myeloproliferative neoplasm: Mayo Clinic case series of 309 patients.

Note: Some publications support multiple topics. Publications are listed according to the topic under which they are first cited.

4.1.1 Epidemiology

4.1.1.1 Incidence and Prevalence of EMH in Patients with Thalassemia

EMH is a complication due to ineffective erythropoiesis or inadequate bone marrow function and is seen to occur in patients with β -thalassemia and other chronic hematologic disorders. In patients with such disorders, the ineffective erythropoiesis or inadequate bone marrow function can potentially precipitate extra marrow production of blood elements (ie, EMH). Expansion of the erythron in the bone marrow in non-transfusion-dependent (NTD) β -thalassemia during ineffective erythropoiesis is associated with homing and proliferation of erythroid precursors in the spleen and liver as a physiologic compensatory phenomenon, which leads to hepatosplenomegaly. Ineffective erythropoiesis in NTD β -thalassemia patients also forces expansion of the hematopoietic tissue in areas other than the liver and spleen, mostly in the form of masses termed EMH pseudotumors. These pseudotumors can occur anywhere in the body and can cause health risks especially when surrounding vital structure like the spinal cord, as they can lead to permanent damage and disability if not managed acutely.⁴ A paraspinal location for the hematopoietic tissue occurs in 11% to 15% of cases with EMH. Paraspinal EMH mainly presents as pseudotumors, which may cause a variety of neurological symptoms due to spinal compression. More than 80% of cases may remain asymptomatic and the lesions are discovered incidentally by imaging. The development of neurologic symptoms depends on the chronicity of the disease with neurologic symptoms most frequently being reported during the third and fourth decades of life.

There are few studies published on the frequency of EMH in thalassemia populations. Studies with a study population smaller than 100 were disregarded, as were publications older than 2000.

No prospective cohort studies with published results were found on the incidence of EMH in thalassemia. Only one study in Thailand (the E-SAAN study) had this objective but seemed to be ongoing and only the publication on baseline results was found (with prevalence rates and no incidence results). The remaining studies were retrospective cohorts or cross-sectional only detailing the prevalence of EMH in the study population. Studies have included either NTD thalassemia or transfusion-dependent (TD) thalassemia patients or both; often identified using the thalassemia intermedia (TI) or thalassemia major (TM)

terminology respectively. The majority of studies included primarily β -thalassemia genotypes although this was not always stated.

Details of the studies are provided in the following subsections. Overall, the prevalence of EMH was high ranging from 2.8-21.2% in NTD and 2.2-14% in TD thalassemia. Variations in prevalence rates may be attributed to the method of screening/diagnosis of EMH, definition of EMH, or variability in study sample characteristics (especially age). In general, the prevalence of EMH was higher in NTD than TD thalassemia. The prevalence was also higher in studies recruiting older patients. Even among NTD thalassemia, patients who did not receive transfusions had even higher rates (reaching 60%) of EMH than those who received occasional or regular transfusions. Most studies identified EMH cases only based on symptomatic presentation or incidentally through routine cardiac/hepatic MRI assessment for iron overload which can only assess the thoracic and abdominal areas. Thus, the true prevalence of EMH in thalassemia patients based on the current literature may even be underestimated.

4.1.1.2 Studies in NTD Thalassemia

In the OPTIMAL CARE study medical charts of all TI patients registered at 6 comprehensive care centers in Lebanon, Italy, Iran, Egypt, United Arab Emirates, and Oman were reviewed. For an EMH case to be ascertained, it required radiologic evidence of EMH foci with or without symptoms. A total of 584 TI patients were identified (mean age 25.44 ± 13.86 years, range, 2-76 years); 55.7% (325 patients) were splenectomized. In total, 124 (21.2%) patients had evidence of EMH. Patients were further categorized as regularly transfused (once every 1-3 months), occasionally transfused patients, and never transfused. The prevalence of EMH was 60.4% in 139 patients never transfused, 19.6% in 143 patients occasionally transfused, and 4% in 302 patients regularly transfused.

4.1.1.3 Studies in TD Thalassemia

Regularly transfused patients with TM consecutively enrolled in the Italian Myocardial Iron Overload in Thalassemia (MIOT) network (N = 1266) were retrospectively evaluated for EMH. Mean age was 31.3 ± 8.9 years (range: 4.2-66.6 years). MRI examinations for iron overload assessment were performed for all patients in a standardized manner. EMH was detected in 167 (13.2%) patients. Most EMH foci (98.8%) were thoracic-dorsal. The youngest EMH patient was 21.8 years old.

Similar results were found in Greece. All patients with chronically transfused TM followed in one institution for a 30-year period were identified to retrospectively measure the prevalence of EMH. There was no specific protocol for EMH investigation. In total, the study enrolled 104 patients with a median age of 32 years (range: 19-47 years). EMH was revealed in 15 patients (14%). In all cases, EMH was an incidental finding across the spinal cord without any clinical signs of compression.

4.1.1.4 Studies including Both NTD and TD Thalassemia

Ricchi et al. aimed at determining the prevalence of incidental extracardiac findings on MRI done for iron quantification in age- and sex-matched populations with TM and TI (N = 159 each) enrolled in the MIOT network. A comparator age- and sex-matched cohort of 159 patients without thalassemia referred to the core lab of the network for clinically indicated cardiovascular magnetic resonance was also included. Within the MIOT network, MRI exams are performed using homogeneous and standardized procedures. TI patients had a significantly higher frequency of EMH compared to patients with TM (15.1% vs 4.4%; $P = 0.002$). EMH was absent in the non- thalassemia population. Prevalence was higher in TI patients who received regular transfusions (termed transfusion-dependent in the study) than those who did not (20.6% vs 11%).

A multicentre cross-sectional study was conducted in four hospitals in Thailand in 2015-2017, among patients with thalassemia aged ≥ 18 years old.⁵ EMH was defined as the presence of clinical signs and symptoms or evidence of EMH by ultrasonography, CT scan or MRI. A total of 433 patients (306 NTD

thalassemia and 127 TD thalassemia) were enrolled. Mean age at study enrolment was 27.8 ± 11.4 and 29 ± 14.7 in TD and NTD thalassemia patients, respectively. All TD patients and 66.3% NTD thalassemia patients had a β -thalassemia. HbE/ β -thalassemia was the most common genotype in both groups (91.3% of the TD and 65% of the NTD thalassemia). EMH was observed as a previous complication in 12.5 % of TD and 4.9% of NTD thalassemia patients.

The E-SAAN study (Epidemiologic Study of Major Complications In Adult And Adolescent Patients With Thalassemia In Northeastern Thailand) is a multicentre prospective cohort study started in 2012. A total of 380 patients (240 females and 140 males) were enrolled. Out of 380 patients, 91 were TD and 289 were NTD thalassemia. All patients with TD had HbE/ β -thalassemia. The most common genotype in NTD patients was also HbE/ β -thalassemia (139 patients, 48.1%) and the remainder had α -thalassemia. The mean age of patients with TD and NTD thalassemia at the time of study enrolment was 19.5 and 28 years, respectively. CT scans and MRIs were only done when clinically indicated. The prevalence of EMH at enrolment was 2.2% in TD and 2.8% in NTD thalassemia.

Table 5: Characteristics of Studies on the Prevalence of Extramedullary Hematopoiesis in Thalassemia Populations

Country/Region Author/Year	N and Population Identifications	Age	Regular Transfusion	EMH Ascertainment	Prevalence	Risk Factors
Italy Ricchi 2019 ⁹	159 patients with TM 159 patients with TI 159 non-thalassemic controls Thalassemia population identified from the MIOT network and controls had been referred to the core lab of the MIOT network for clinically indicated cardiovascular MRI	Mean age \pm SD: TM 34.71 \pm 9.18 TI 34.71 \pm 9.20	All TM 57% of TI	Systematic use of MRI exams done for iron overload assessment performed in a standardized manner in routine practice	TM: 4.4% TI: 15.1% Non-thalassemic: 0% (P = 0.002) TI-NTD: 14/68 (20.6%) TI-TD: 10/91 (11.0%) (P = 0.094)	--
Italy Ricchi 2015 ⁷	1266 patients with TM Population identified from the MIOT network	Mean age \pm SD: 31.3 \pm 8.9 years (range: 4.2–66.6 years)	All TM	Systematic use of MRI exams done for iron overload assessment performed in a standardized manner in routine practice	EMH was detected in 167 TM (13.2%) patients	EMH+ patients: <ul style="list-style-type: none">•Older•Started transfusion later•Splenectomy more common•Lower serum ferritin
Greece Sousos, 2017 ⁸	104 patients with TM (β -thalassemia) Followed in one general hospital in Greece over a 30-year period. No exclusion criteria.	Median: 32 years (range: 19-47 years)	All TM	No specific protocol for EMH investigation. Routine MRI follow-up for iron overload assessment (heart/liver) as per international guidelines.	EMH was revealed in 15 TM (14%) patients	IVS-I-6 mutation associated with EMH. No other demographic or biological risk factors were detected. Note: EPO values only available in 19% of patients

Country/Region Author/Year	N and Population Identifications	Age	Regular Transfusion	EMH Ascertainment	Prevalence	Risk Factors
Lebanon, Italy, Iran, Egypt, United Arab Emirates, and Oman Taher, 2010 ⁶	584 TI patients Identified in 6 comprehensive care centers	Mean age \pm SD: 25.44 \pm 13.86 years (range: 2-76 years)	Transfusion history: ●never (139 patients) ●occasional (143 patients) ●regular (302 patients)	Confirmed through radiologic evidence with or without symptoms	Overall: 21.2% EMH in 60.4%, 19.6%, and 4% among those with never, occasional or regular transfusions	Splenectomy and transfusions were protective factors. EMH in 17.2% and 26.3% among those with and without splenectomy, respectively. Age, ferritin, and hydroxyurea not independently associated.
Thailand Chuncharunee, 2019 ⁵	127 TD thalassemia (all β - thalassemia) 306 NTD thalassemia (66.3% β - thalassemia) Aged \geq 18 years, followed in four hospitals.	Mean age \pm SD: TD: 27.8 \pm 11.4 years NTD: 29 \pm 14.7 years	All TD None NTD	Clinical signs and symptoms or evidence of EMH by ultrasonography, CT scan or MRI	TDT: 12.5% NTDT: 4.9%	Age > 25 years. But not: Post- splenectomy time >5 years, hemoglobin <8 g/dL, and serum ferritin >2500 ng/mL.
Thailand Teawtrakul, 2019 ¹⁰	91 TD thalassemia (all β - thalassemia) 289 NTD thalassemia (48.1% β - thalassemia) Aged \geq 10 years old	Mean age at study enrolment was 19.5 \pm 10 in TDT and 28 \pm 13.5 in NTDT	91 TDT patients (transfusions every 2–6 weeks) 289 NTDT patients (273 occas. and 16 never).	Clinical symptoms or evidence of EMH by ultrasonography, CT scan or MRI	2 patients (2.2%) among TD 8 patients (2.8%) among NTD	--

CT = computerized tomography; EMH = extramedullary hematopoiesis; EPO = erythropoietin; MIOT = myocardial iron overload in thalassemia; MRI = magnetic resonance imaging; NTD = non-transfusion dependent; SD = standard of deviation; TI = thalassemia intermedia; TD = transfusion dependent; TM = thalassemia major

Source: Epidemiology

4.1.2 Risk Factors of EMH

The few studies looking at the association between risk factors and EMH were small and had either cross-sectional or retrospective cohort designs, which means that data need to be interpreted with caution due to unclear temporality between cause and effect or missing data bias. Data are summarized in subsequent sections. In alignment with the aforementioned data on epidemiology, older age seems to consistently be associated with a higher prevalence of EMH while transfusion therapy was protective (looking at TD vs NTD or transfused NTD vs never-transfused NTD). This may also explain why lower serum ferritin levels and higher IVS-I-6 (mild β^{++}) mutation rates were found in patients with EMH than those without (since they are more commonly found in NTD patients). Splenectomy appeared to have a dual role, it was associated with higher rates of EMH in some studies as it may indicate a more severe disease and ineffective erythropoiesis, or lower rates of EMH as the intervention itself may optimize hemoglobin levels and improve ineffective erythropoiesis. Factors that indicate (ineffective) erythropoietic activity (sTfR, EPO, GDF15) were usually higher in patients with EMH than those without.

4.1.2.1 Studies in NTD Thalassaemia

In the OPTIMAL CARE study, a multivariate analysis of the determinants of EMH in TI patients revealed that splenectomy was an independent protective factor (RR = 0.44 [95%CI: 0.26-0.73]; P = 0.001), as well as transfusion (transfused vs never transfused) (RR = 0.06 [95%CI: 0.03-0.09]; P <0.001). Age, ferritin, and hydroxyurea were not independently associated with EMH.

In a case-control study conducted by Huang et al, 52 patients with NTD thalassaemia (26 patients with EMH and 26 without) were enrolled in one Chinese University Hospital, between 2013 and 2016. The 52 patients were age, sex, and thalassaemia-type-matched. In addition, 26 age and sex matched healthy subjects without anemia or liver disease were enrolled as a control group. Hematological parameters were analyzed after patient inclusion in the study. In order to establish a correlation between erythropoiesis and iron metabolism, serum levels of hepcidin, EPO, growth differentiation factor 15 (GDF15), sTfR, and erythroferrone (ERFE) were measured. All indexes showed significant differences between NTD patients (EMH(+)) and EMH(-) patients and normal controls; however, only GDF15 and EPO levels in EMH(+) patients also showed significantly higher levels when compared to the EMH(-) group (P <0.001). EPO concentrations predictive values for EMH were: sensitivity 73.1% and specificity 81.5%, AUC: 0.701.

From January 2007 to December 2010, all TI patients attending one center in Italy were prospectively enrolled to undergo sTfR assay and MRI or CT scan evaluation for the presence of paraspinal EMH. None of the patients were regularly transfused. Out of 59 patients studied, EMH involved 23. The concentration of soluble form of transferrin receptor (sTfR) varied from 2.6 to 20.6 (mean \pm SD = 8.71 \pm 3.8) mg/L, but in patients with paraspinal EMH and those without it varied from 4.2 to 20.6 (mean \pm SD = 11.1 \pm 4.1) mg/L and from 2.6 to 13 (mean \pm SD=7.18 \pm 2.66) mg/L, respectively, with a statistically significant intergroup difference (P <0.01). EMH+ patients were more likely to be splenectomized than EMH- patients (83% vs 38.9%; P = 0.0012). Chelation therapy at baseline was also more frequent among EMH+ patients (87% vs 39%; P = 0.00035).

4.1.2.2 Studies in TD Thalassaemia

The largest study found that described risk factors for EMH in TM patients was conducted in the MIOT network. The following table shows the comparison between the EMH+ and EMH- patients. Despite comparable pretransfusion Hb levels, EMH+ patients were significantly older and had started transfusion and chelation therapies later. The adjustment for age did not change the systematic differences in the transfusion starting age (P = 0.012), regular transfusion starting age (P = 0.025), and duration of regular transfusions (P <0.0001). Conversely, after the adjustment, the difference in the chelation starting age lost its statistical significance (P = 0.084). The distribution of sex was similar in both groups. Splenectomy was significantly more common among EMH+ patients. The mean serum ferritin level was

significantly lower in the EMH+ group compared with the EMH- group. Serum ferritin levels were significantly associated with age. As a result, age was used as a covariate in the analysis of covariance, but the adjustment did not change the differences between the two groups ($P = 0.006$).

TABLE II. Comparison of Demographic and Clinical Data Between Patients Without and With EMH

	EMH- (N = 1,099)	EMH+ (N = 167)	P
Age (yrs)	30.08 ± 8.63	38.93 ± 6.10	<0.0001
Sex (M/F)	520/579	91/76	0.084
Age at first transfusion (yrs)	1.52 ± 1.69 (n = 929)	2.03 ± 2.05 (n = 145)	<0.0001
Regular transfusions starting age (yrs)	1.89 ± 2.52 (n = 751)	3.56 ± 6.24 (n = 126)	<0.0001
Duration of regular transfusions (yrs)	28.35 ± 8.79 (n = 751)	35.29 ± 7.36 (n = 126)	<0.0001
Chelation starting age (yrs)	4.64 ± 3.95 (n = 724)	7.71 ± 6.05 (n = 125)	<0.0001
Splenectomy, n (%)	565 (51.4)	122 (73.1)	<0.0001
Pretransfusion Hb (g/dl)	9.61 ± 0.72 (n = 1,006)	9.63 ± 0.91 (n = 160)	0.900
Serum ferritin (ng/ml)	1,562.06 ± 1,475.90 (n = 1,006)	993.90 ± 1,065.78 (n = 160)	<0.0001

In the Greek study, possible risk factors associated with the presence of EMH that were analyzed included: age, sex, pregnancy, blood group, thalassemia genotype, age at first transfusion, splenectomy status, hepatic and cardiac iron accumulation, chelation therapy, steady-state serum ferritin, and erythropoietin levels (note, however, that erythropoietin [EPO] levels were only available in 20 patients). In both univariate and bivariate analyses, the presence of the IVS-I-6 mutation either in homozygosity or compound heterozygosity was significantly related with the development of EMH ($p < 0.05$). No other demographic or biological factor studied was found to be associated with EMH.

Ricchi et al evaluated the influence of genotype and other factors on the presence of EMH in a small retrospective study of TM patients. All medical records of patients on regular and long-term transfusion therapy followed at one unit from 2006 to 2011 were reviewed. During the observation period EMH tissue was incidentally detected because most patients underwent CT or MRI scanning for different clinical evaluations. Almost all patients had twice yearly measurements of sTfR. Out of a total of 67 study participants, EMH was found in 18, all of whom had been splenectomized. Overall, the concentration of sTfR varied from 0.7 to 14 mg/L (4.7 ± 2.5 mg/L), but in patients with EMH it varied from 1.3 to 14 mg/L (6.6 ± 3.1 mg/L) while it varied from 0.7 to 8.9 mg/L (4.1 ± 1.9 mg/L) in patients without EMH, with a statistically significant intergroup difference ($P < 0.01$). A further analysis revealed that the different splenectomy rate among both groups did not influence sTfR level ($P < 0.05$).

4.1.2.3 Studies in Both NTD and TD Thalassemia

In the study reported by Chuncharunee,⁵ age above 25 years was a significant risk factor for EMH in both patients with TD thalassemia (adjusted OR = 8.1, 95%CI 1.7–37.9, $P = 0.008$) and patients with NTD thalassemia (adjusted OR = 5.3, 95%CI 1.1–24.6, $P = 0.03$). Post-splenectomy time >5 years, Hb <8 g/dL, and serum ferritin >2500 ng/mL were not significantly associated with the presence of EMH among TD or NTD patients.

4.1.3 EMH in Other Populations

4.1.3.1 EMH in the General Population

In the study published by Ricchi⁹ among 159 participants with no thalassemia in the comparator group, no EMH was identified.

A study conducted at the Mayo Clinic¹⁴ identified all patients during the period 1975–2018 who had a diagnosis of EMH. Out of 1933 cases of EMH, extensive review confirmed the absence of associated myeloproliferative neoplasm in 336 cases. Out of the 336, 27 cases involved pathology remarks during tissue biopsy for liver transplant and were excluded from further analysis. The most frequent associated conditions in the remaining 309 cases are included in Table 6. It is notable that the conditions for which luspatercept is indicated or being studied for have some of the highest prevalence of EMH as presented in Table 6.

Table 6: The Most Frequent Associated Conditions For Extramedullary Hematopoiesis

Associated Condition	Number	Percentage (%)
myelodysplastic syndromes (MDS)	41	13
acute myeloid leukemia (AML)	28	9
hemolytic anemia	24	8
thalassemia	22	7
non-Hodgkin's lymphoma (NHL), with excess cases with splenic marginal zone lymphoma	19	6
immune thrombocytopenic purpura (ITP)	17	6
metastatic cancer, with breast cancer being the most frequent	17	6
plasma cell neoplasms, including polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes	12	4
hereditary spherocytosis	8	3
cirrhosis	7	2
acute lymphoblastic leukemia	6	2
chronic lymphocytic leukemia	6	2
Associated Condition	Number	Percentage (%)
Hodgkin's lymphoma	5	2
"idiopathic" extramedullary hematopoiesis	12	4
Others: hematologic and non-hematologic conditions with less than 5 incident cases, including large granular lymphocyte and natural killer cell disorders, chronic myelomonocytic leukemia, hemophagocytic lymphohistiocytosis, anemia of chronic disease, bone marrow failure syndrome, and fungal or viral infection including human immunodeficiency virus and cytomegalovirus	93	30

Based on the 'idiopathic' cases and the total EMH cases (1906, if we disregard liver biopsies) there are 0.6% of the EMH where no underlying cause is found. So EMH appears to be very rare in the general population.

Assessment of the MAH's response:

The MAH presented details of the 15 identified publications. However, the MAH clarified that the publications of interest were not related to the occurrence of EMH masses while on luspatercept therapy, but rather were articles identified via the literature search described in Q3. Further, there were only 14 and one has been counted twice by mistake.

Although the MAH did not provide the requested information, this issue is not further pursued, since the occurrence of EMH masses is adequately reflected in the SmPC with the requested amendments.

Conclusion:

Issue not further pursued.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 5:

The amended text in section 4.4 of the SmPC currently reads "*β-thalassaemia patients with EMH masses had known risk factors such as medical history of EMH masses at baseline or comorbidity of splenectomy, splenomegaly, hepatomegaly, low baseline Hb (<8.5 g/dL).*" This statement is not sufficiently justified and EMH events also occurred in patients without any of these "risk factors". Thus, the MAH is requested to omit the highlighting of known risk factors prior to the occurrence of EMH masses in this section of the SmPC. This also applies for the respective statement in section 4.8. (see also respective comments in the attached document).

Summary of the MAH's response:

The MAH agrees to the requested change in sections 4.4 and 4.8 of the SmPC. The SmPC is updated accordingly.

Assessment of the MAH's response:

The requested changes have been implemented in the respective sections of the SmPC.

Conclusion:

Issue resolved.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 6:

The MAH is asked to align the wording in section 4.2. regarding discontinuation of treatment in case of serious complications due to EMH masses (...treatment *should* be discontinued, see also SmPC comment) according to the warning in section 4.4 (...treatment with luspatercept *must* be discontinued...).

Summary of the MAH's response:

The MAH agrees to align the wording in sections 4.2 and 4.4 of the SmPC, as requested.

The SmPC is updated accordingly.

Assessment of the MAH's response:

The requested change has been implemented in the respective section of the SmPC.

Conclusion:

Issue resolved.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 7:

Currently, in sections 4.2 and 4.4 of the SmPC, discontinuation and monitoring of EMH masses are only recommended in patients with β -thalassaemia. The MAH is requested to remove this restriction to the β -thalassaemia indication. Luspatercept treatment must be discontinued in all patients experiencing EMH causing serious complications, regardless of indication. In addition, section 4.8 requires respective amendments (see SmPC comment).

Summary of the MAH's response:

The Applicant agrees to remove the restriction to β -thalassemia in sections 4.2 and 4.4. The SmPC is updated accordingly.

With respect to section 4.8, in clinical studies, with 1374 subjects exposed to luspatercept, there have been no EMH masses reported in subjects treated with luspatercept in non- β -thalassemia indications including MF and MDS. The overall post-marketing cumulative exposure to luspatercept through 24-Jun-2022, is estimated to be 21,615 patients from all geographic areas. There was one post-marketing spontaneous report in a patient treated for MDS, representing an estimated reporting rate of 0.004% (1/21,615).

Based on the clinical trial data to date, the Applicant agrees to include information regarding the risk of EMH in patients treated for β -thalassemia. However, at the current state of the evidence, given the inherent uncertainties, the Applicant does not consider one spontaneous report in MDS as a validated safety signal that should be communicated in the product information.

The risk of EMH will continue to be monitored across clinical studies and all indications as well as in the post-marketing setting and this question will be reassessed should the evidence change.

This has been applied also in the ongoing variation EMEA/H/C/004444/II/0009.

Assessment of the MAH's response:

The requested changes have been implemented in 4.2 and 4.4 of the SmPC.

Regarding the inclusion of a spontaneous case of EMH masses in a patient with MDS in section 4.8 of the SmPC, it is acknowledged that the occurrence of a single case in the post-marketing setting leaves inherent uncertainties. Hence, despite the very low frequency currently reported, the true frequency may be underestimated. Since the EMH event reoccurred on re-challenge after luspatercept was interrupted in response to the first EMH event in this patient, a causal relationship appears plausible. No additional data to invalidate this argument have been provided.

Conclusion:

Issue partially resolved.

The MAH is asked to list the single case of EMH mass in an MDS patient in the post-marketing setting in section 4.8 of the SmPC, as previously requested.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 8:

Currently, SmPC Section 4.4. (Special warnings and precautions for use) includes a recommendation not to use luspatercept in patients requiring treatment to control the growth of EMH masses. The MAH is asked to discuss why those patients should only be mentioned in Section 4.4. and not included as contraindication in Section 4.3.

Summary of the MAH's response:

The Applicant acknowledges the comment from the CHMP and agrees to remove the sentence "Luspatercept is not recommended for patients requiring treatment to control the growth of EMH masses." from section 4.4 of the SmPC and to include it as contraindication in Section 4.3 of the SmPC.

This has been applied also in the ongoing variation EMEA/H/C/004444/II/0009. The SmPC is updated accordingly.

Assessment of the MAH's response:

The requested change has been implemented in the respective sections of the SmPC.

Conclusion:

Issue resolved.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

10. Request for supplementary information

10.1. Major objections

None

10.2. Other concerns

1. The MAH is asked to include information in section 4.8 of the SmPC that EMH masses may also occur after extended treatment with luspatercept, i.e. after Week 96, for the first time.
2. The MAH is asked to list the single case of EMH mass in an MDS patient in the post-marketing setting in section 4.8 of the SmPC, as previously requested.

Rapporteur's conclusion:

After receiving the remaining change requests to the SmPC, the MAH submitted an updated SmPC including all outstanding amendments.