REGIONE DEL VENETO
ULSS7 PEDEMONTANA
Via dei Lotti, n. 40
36061 Bassano del Grappa (VI)
Codice fiscale e partita IVA 00913430245

N. 2396 DEL 23/12/2022

DELIBERAZIONE
del

DIRETTORE GENERALE

Nominato con D.P.G.R. n. 26 del 26/02/2021

Coadiuvato dai sigg.:

DIRETTORE AMMINISTRATIVO dott.ssa MICHELA CONTE

DIRETTORE SANITARIO dr. ANTONIO DI CAPRIO

DIRETTORE DEI SERVIZI SOCIO – SANITARI dott.ssa ALESSANDRA CORO'

OGGETTO: RECEPIMENTO DEL VERBALE DEL COMITATO ETICO PER LE SPERIMENTAZIONI CLINICHE DELLA PROVINCIA DI VICENZA CONTENENTE LA PRESA D'ATTO DA PARTE DELLO STESSO RELATIVA ALLO STUDIO " EFFICACIA E SICUREZZA DEL LUSPATERCEPT IN PAZIENTI ADULTI AFFETTI DA ANEMIA TRASFUSIONE-DIPENDENTE DOVUTA A SINDROME MIELODISPLASTICA (MDS) CON SIDEROBLASTI AD ANELLO CON RISCHIO IPSS-R MOLTO BASSO, BASSO O INTERMEDIO CHE HANNO UNA RISPOSTA INSODDISFACENTE O CHE NON SONO ELEGGIBILI PER TRATTAMENTO CON ERITROPOIETINA RICOMBINANTE: UNO STUDIO RETROSPETTIVO MULTICENTRICO DELLA FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE (FISIM-ETS) E AUTORIZZAZIONE ALLA CONDUZIONE DEL MEDESIMO

IL DIRETTORE GENERALE
DELL'AZIENDA ULSS 7 PEDEMONTANA
dott. Carlo Bramezza

Documento informatico firmato digitalmente ai sensi del D. Lgs n. 82/2005, del T.U. n. 445/2000 e norme collegate, il quale sostituisce il documento cartaceo e la firma autografa; il documento informatico è conservato digitalmente negli archivi informatici dell'Azienda.

Proponente: UOC AFFARI GENERALI
Anno Proposta: 2022 Numero Proposta: 2675/22

Il Dirigente, Direttore dell'UOC Affari Generali, nonché Responsabile del procedimento, attesta che la presente proposta di deliberazione è stata regolarmente istruita nel rispetto della vigente normativa nazionale, regionale e regolamentare: f.to Cristiano Galizian

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Il Direttore dell'U.O.C. Affari Generali relaziona quanto segue.

Premesso che:

- con deliberazione n. 316 del 31/03/2017 si è provveduto ad istituire, ai sensi della deliberazione della Giunta Regionale del Veneto n. 2174 del 23/12/2016, recante "Disposizioni in materia sanitaria connesse alla riforma del sistema sanitario regionale approvata con L.R. 25 ottobre 2016 n. 19", il Nucleo per la Ricerca Clinica (N.R.C.) dell'Azienda ULSS7 Pedemontana;
- la citata DGRV n.. 2174/2016, Allegato L, richiama l'applicazione della disciplina regionale in materia di sperimentazione clinica (DGR n. 1066/2013 e DGR n. 925/2016), che prevede l'istituzione di un N.R.C. per ciascuna Azienda ULSS della Regione;
- la DGR n. 1066/2013 (Allegato B) prevede che il N.R.C. sia istituito preferibilmente " presso il Servizio di Farmacia Ospedaliera ovvero Servizio Farmaceutico territoriale ovvero Servizio di Farmacologia delle istituzioni sanitarie, fermo restando i criteri di indipendenza e di assenza di conflitti di interesse" e sia composto " da professionalità multidisciplinari appartenenti all'ambito sanitario, epidemiologico-statistico, etico-giuridico e organizzativo-gestionale";
- con deliberazione n. 1477 del 05/08/2022 è stato approvato, in aggiornamento della disciplina aziendale regolata con la deliberazione n. 453 del 28/05/2014, il Regolamento aziendale sulla gestione delle sperimentazioni cliniche profit e no-profit, comprensivo anche della regolamentazione dei fondi per la gestione della ricerca con determinazione delle quote dei fondi stessi e fissazione dei criteri per l'attribuzione dei compensi;
- con deliberazione n. 1684 del 09/09/2022 sono stati aggiornati i componenti del Nucleo per la Ricerca Clinica Aziendale (N.R.C.) ai sensi della DGRV n. 2174 del 23/12/2016.

Rilevato che:

- in data 30/05/2022, ns. prot. 50666 del 03/06/2022, il Presidente della Fondazione Italiana Sindromi Mielodisplastiche -ETS (FISiM-ETS) con sede in Bologna – via De' Poeti 1/7, dr. Carlo Finelli, ha trasmesso la documentazione relativa allo studio "*Efficacia e sicurezza del luspatercept in pazienti adulti affetti da anemia trasfusio ne-dipendente dovuta a sindrome mielodisplastica (MDS) con sideroblasti ad anello con rischio IPSS-R molto basso, basso o intermedio che hanno una risposta insoddisfacente o che non sono eleggibili per trattamento con eritropoietina ricombinante: uno studio retrospettivo multicentrico della Fondazione Italiana Sindromi Mielodisplastiche (FISiM-ETS)"* :

SCHEDA STUDIO CLINICO

Titolo	*"Efficacia e sicurezza del luspatercept in pazienti adulti affetti da anemia trasfusione-dipendente dovuta a sindrome mielodisplastica (MDS) con sideroblasti ad anello con rischio IPSS-R molto basso, basso o intermedio che hanno una risposta insoddisfacente o che non sono eleggibili per trattamento con eritropoietina ricombinante: uno studio retrospettivo multicentrico della Fondazione Italiana Sindromi Mielodisplastiche (FISiM-ETS)"*

Protocollo	FISiM-LUSPATERCEPT
Strutture interessate	U.O.C. Oncoematologia P.O. Bassano
Sperimentatori Principali	dr. Eros Di Bona – dirigente medico e Direttore dell'U.O.C. Oncoematologia del P.O. Bassano
Co sperimentatori	dr.ssa Anna Artuso - Dirigente medico dell'U.O.C. di Oncoematologia del P.O. Bassano dr.ssa Stefania Fortuna - Dirigente medico dell'U.O.C. di Oncoematologia del P.O. Bassano
Promotore	FISiM - Fondazione Italiana Sindromi Mielodisplastiche-ETS - Via De' Poeti, 1/7 – 40124 – Bologna
Centro Coordinatore	Ematologia dell'Humanitas Cancer Center di Rozzano – Prof. Matteo Giovanni Della Porta

- in data 25/05/2022, ns. prot. 50666 del 03/06/2022, il dr. Eros Di Bona, Direttore dell'U.O.C. di Oncoematologia del P.O. Bassano ha chiesto la valutazione e l'autorizzazione allo svolgimento dello studio presso la struttura citata.

Tenuto conto che:

- il Coordinatore del N.R.C. Aziendale in data 01/09/2022, ha verificato - considerata la regolarità della documentazione presentata dallo sperimentatore - la fattibilità locale della ricerca sopra citata;
- il Comitato Etico per le sperimentazioni Cliniche della Provincia di Vicenza (CESC) in occasione della seduta del 27/09/2022, ns. prot. 88649 dell'11/10/2022, ha preso atto dello studio di cui sopra;
- trattasi di uno studio no-profit, retrospettivo, osservazionale e multicentrico per raccogliere informazioni sull'efficacia e la sicurezza di Luspatercept in una popolazione *real world* italiana di pazienti adulti con anemia trasfusione-dipendente dovuta a SMD (sindromi mielodisplastiche) a rischio molto basso, basso e intermedio con sideroblasti ad anello, che hanno una risposta insoddisfacente o non sono idonei alla terapia a base di eritropoietina;
- vengono raccolti i dati di pazienti adulti con età >= 18 anni durante l'anno 2022;
- i dati di *real-word* ottenuti dai Centri Ematologici partecipanti in tutto il Paese saranno inseriti in una Piattaforma informatizzata REDCap ad hoc;
- per l'esecuzione dello studio non sono previsti costi aggiuntivi a carico dell'Azienda;
- non sono previsti compensi per gli sperimentatori;
- trattandosi di studio osservazionale senza procedure diagnostiche e/o terapeutiche divergenti dalla normale pratica clinica non è necessario stipulare specifica polizza assicurativa.

Per quanto sopra, il Direttore dell'U.O.C. Affari Generali, propone di recepire il verbale del Comitato Etico per le Sperimentazioni Cliniche della Provincia di Vicenza (CESC) dal quale risulta che lo stesso ha preso atto dello studio clinico dal titolo *" Efficacia e sicurezza del luspatercept in pazienti adulti affetti da anemia trasfusione-dipendente dovuta a sindrome mielodisplastica (MDS) con sideroblasti ad anello con rischio IPSS-R molto basso, basso o intermedio che hanno una risposta insoddisfacente o che non sono eleggibili per trattamento con eritropoietina ricombinante: uno studio retrospettivo multicentrico della Fondazione Italiana Sindromi Mielodisplastiche (FISiM-ETS)"* e di autorizzazione il dr. Eros Di Bona alla conduzione del medesimo presso l'U.O.C. di Oncoematologia del P.O. Bassano

IL DIRETTORE GENERALE

Vista la relazione e la proposta del Responsabile del procedimento;

Dato atto che il responsabile del Servizio competente ha attestato l'avvenuta regolare istruttoria della pratica, in ordine alla compatibilità con la vigente legislazione statale, regionale e regolamentare;

Visti:

- il decreto ministeriale 15/07/1997;
- la circolare del Ministero della Salute 02/09/2002 n. 6;
- il D.lgs 24/06/2003, n. 211;
- il decreto ministeriale 17/12/2004;
- la DGRV 28/12/2006, n. 4430;
- il decreto ministeriale 12/05/2006;
- il D.lgs 6/11/2007, n. 200;
- il decreto ministeriale 21/12/2007;
- la determinazione AIFA 20/03/2008;
- la DRGV 07/10/2008, n. 2855;
- la Legge 08/11/2012, n. 189 – Decreto Balduzzi;
- il decreto del Ministero della Salute 08/02/2013;
- la DRGV 28/06/2013 n. 1066;
- il D.M. 30/11/2021

Acquisito il parere favorevole del Direttore Amministrativo, Sanitario e dei Servizi Socio-Sanitari, per quanto di rispettiva competenza

DELIBERA

1. di recepire il verbale del Comitato Etico per le Sperimentazioni Cliniche della Provincia di Vicenza (CESC) che, nella seduta del 27/09/2022, ha preso atto dello studio " *Efficacia e sicurezza del luspatercept in pazienti adulti affetti da anemia trasfusione-dipendente dovuta a sindrome mielodisplastica (MDS) con sideroblasti ad anello con rischio IPPS-R molto basso, basso o intermedio che hanno una risposta insoddisfacente o che non sono eleggibili per trattamento con eritropoietina ricombinante: uno studio retrospettivo multicentrico della Fondazione Italiana Sindromi Mielodisplastiche (FISiM-ETS)"* come da documentazione agli atti del presente provvedimento;
2. di autorizzare, per quanto in premessa illustrato, lo svolgimento dello studio presso l'U.O.C. di Oncoematologia del P.O. Bassano sotto la diretta Responsabilità del dr. Eros Di Bona, Direttore della struttura citata;
3. di dare atto che il dr. Eros Di Bona e i Co-sperimentatori dr.ssa Anna Artuso e la dr.ssa Stefania Fortuna, dirigenti medici della struttura sopra citata, sono autorizzati a svolgere l'attività di ricerca al di fuori l'attività istituzionale;
4. di stabilire che lo studio clinico dovrà essere eseguito secondo quanto previsto dal protocollo di studio, dalla normativa vigente in ambito di sperimentazioni e dalle norme di buona pratica clinica (GCP) e che allegato alla presente deliberazione ne costituisce parte integrante e sostanziale;
5. di dare atto che ai sensi dell'art.8 del Regolamento aziendale sulla gestione delle sperimentazioni cliniche (deliberazione n. 1477/2022):
   a) il Responsabile della Sperimentazione durante il corso dello studio è tenuto a comunicare al CESC, per il tramite del NRC, le informazioni necessarie a consentire il periodico

aggiornamento sull'andamento della ricerca, ogni evento o reazione avversa, l'interruzione anticipata di uno studio, con l'indicazione dettagliata dei motivi e degli eventuali risultati parziali ottenuti

b) lo Sperimentatore si impegna a fornire annualmente al CESC un rapporto scritto sullo stato di avanzamento dello studio (monitoraggio periodico) e una relazione analitica alla conclusione dello studio e pubblicazione se previsto;

6. di dare atto che dall'esecuzione del predetto studio non deriverà nessun onere aggiuntivo di spesa in capo all'Azienda ULSS7 Pedemontana;

7. di dare atto che il presente provvedimento è soggetto a pubblicazione ai sensi dell'art. 23, lettera d) del D.L.vo 14 marzo 2013 n. 33;

8. di dare atto che la presente deliberazione viene pubblicata all'albo del sito istituzionale dell'Azienda per 10 gg. continuativi, inviata contestualmente al Collegio Sindacale e diventa esecutiva il giorno stesso della sua pubblicazione come da norma regolamentare approvata con deliberazione n. 1386 del 22/07/2022.

Protocol cover page

PROTOCOL TITLE:

EFFICACY AND SAFETY OF LUSPATERCEPT IN ADULT PATIENTS WITH TRANSFUSION-DEPENDENT ANEMIA DUE TO VERY LOW-, LOW- AND INTERMEDIATE-RISK (IPSS-R) MYELODYSPLASTIC SYNDROME (MDS) WITH RING SIDEROBLASTS, WHO HAD AN UNSATISFACTORY RESPONSE TO OR ARE INELIGIBLE FOR ERYTHROPOIETIN-BASED THERAPY: A RETROSPECTIVE MULTICENTER STUDY BY FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE (FISiM-ETS)

PROTOCOL NAME: FISiM-LUSPATERCEPT

PROTOCOL VERSION 1.0 DATE 27/01/2022

CONFIDENTIALITY STATEMENT

The information contained in this document is the property of Fondazione Italiana Sindromi Mielodisplastiche-ETS (FISiM-ETS) and therefore is provided to you in confidence for review by you, your staff, an applicable Ethics Committee/Institutional Review and regulatory authorities. It is understood that the information will not be disclosed to others without prior written approval from the Fondazione Italiana Sindromi Mielodisplastiche ETS (FISiM-ETS), except to the extent necessary to obtain informed consent from those persons to whom the medication may be administered

Contact addresses

Investigator sponsor	***FISiM Fondazione Italiana Sindromi Mielodisplastiche-ETS*** Via De' Poeti, 1/7 - 40124 Bologna, Italy
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Steering Committee:	Lorenza Borin, Daniela Cilloni, Matteo G Della Porta, Bruno Fattizzo, Pellegrino Musto, Esther Oliva, Marta Riva, Prassede Salutari, Maria Teresa Voso, Valeria Santini
Writing Committee:	Marta Riva, Bruno Fattizzo, Lorenza Borin
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Statistician:	Laura Giordano e-mail: laura.giordano@humanitas.it

Signatures Page

STUDY COORDINATOR SIGNATURE *(where applicable)*

Printed name

Role & Department

Signature Date

CENTRE SIGNATURE – PRINCIPAL INVESTIGATOR

I have read this Protocol of study entitled "*EFFICACY AND SAFETY OF LUSPATERCEPT IN ADULT PATIENTS WITH TRANSFUSION-DEPENDENT ANEMIA DUE TO VERY LOW-, LOW- AND INTERMEDIATE-RISK (IPSS-R) MYELODYSPLASTIC SYNDROME (MDS) WITH RING SIDEROBLASTS, WHO HAD AN UNSATISFACTORY RESPONSE TO OR ARE INELIGIBLE FOR ERYTHROPOIETIN-BASED THERAPY: A RETROSPECTIVE MULTICENTER STUDY BY FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE (FISiM-ETS)*" and I agree to conduct the study as detailed herein and in compliance with guidelines for Good Clinical Practice and applicable regulatory requirements. I will provide all study personnel under my supervision with all information provided by the Sponsor and I will inform them about their responsibilities and obligations.

_____

Printed name

_____

Role & Department

_____

Address

_____ _____

Signature Date

Glossary of abbreviations

IEC	Independent ethics committee
ICH/ GCP	International Conference on Harmonisation (ICH) /Good Clinical Practice standard
MoH	Ministry of Health

INDEX

1 Summary

(limit to 1-2 pages)

Title

EFFICACY AND SAFETY OF LUSPATERCEPT IN ADULT PATIENTS WITH TRANSFUSION-DEPENDENT ANEMIA DUE TO VERY LOW-, LOW- AND INTERMEDIATE-RISK (IPSS-R) MYELODYSPLASTIC SYNDROME (MDS) WITH RING SIDEROBLASTS, WHO HAD AN UNSATISFACTORY RESPONSE TO OR ARE INELIGIBLE FOR ERYTHROPOIETIN-BASED THERAPY: A RETROSPECTIVE MULTICENTER STUDY BY FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE (FISiM-ETS)

Investigator sponsor FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE (FISiM-ETS)
Study coordinator Matteo G Della Porta

Protocol name FISiM-LUSPATERCEPT
Protocol version and date v. 1.0 27/01/2022

Background and rationale	*Myelodysplastic syndromes (MDS) are a group of malignancies characterized by reduced differentiation and increased apoptosis of hematopoietic progenitor cells, leading to ineffective hematopoiesis. Treatment of MDS varies according to prognosis. Patients with low IPSS-R risk have a low probability of progression to acute myeloid leukemia (AML) and the treatment is aimed at controlling cytopenia and improving quality of life (QOL). Anemia is the most common disease feature, occurring in 80%–85% of low-risk patients, 40% of whom eventually become RBC transfusion-dependent (TD).* *Luspatercept is a recombinant fusion protein that selectively binds to ligands belonging to the transforming growth factor-beta (TGF-beta) superfamily. Luspatercept binds to GDF11, GDF8, activin B, and other ligands. This binding leads to inhibition of Smad2/3 signaling, which is abnormally high in disease models of ineffective erythropoiesis such as MDS, resulting in erythroid maturation and differentiation.* *Luspatercept is now approved for the treatment of adult patients with TD anemia due to very low-, low-, and intermediate-risk MDS with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.* *FISiM (Fondazione Italiana Sindromi Mielodidplastiche) promotes a multicenter, retrospective observational study to collect information on the efficacy and safety of luspatercept in a real world Italian population of adult patients with transfusion-dependent anemia due to very low- and intermediate-risk MDS with ring sideroblasts*
Population and patient selection criteria	*- Adult patients (i.e. aged >=18 years) with diagnosis of MDS according to WHO 2016 classification that met IPSS-R criteria for very low, low, or intermediate-risk MDS along with the following additional criteria:* *- Ring Sideroblasts (RS) ≥15% of erythroid precursors in bone marrow in the absence of SF3B1 mutation, or ≥5% in the presence*

	of SF3B1 mutation; *-Refractory or intolerant to, or ineligible for prior therapy with erythropoiesis stimulating agents (ESA).* *-Required red blood cell (RBC) transfusions per the following criteria:* - *Mean RBC transfusion requirement ≥2 units/8 weeks in the 16 weeks before the start of luspatercept treatment* - *No consecutive 56-day period free from RBCTs in the 16 weeks before the start of luspatercept treatment* *- Treatment with luspatercept*
Study design	*Multicenter, retrospective observational trial (expected study population: 215 patients)*
Objectives	*The general objective of the study is to define the efficacy and safety of luspatercept in a real world Italian population of adult patients with transfusion-dependent anemia due to very low- and intermediate-risk MDS with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.* . *End-points.* *The primary end point is transfusion independence for 8 weeks or longer during weeks 1 through 24* *The key secondary end point is transfusion independence for 12 weeks or longer, assessed during both weeks 1 through 24 and weeks 1 through 48.* *Other secondary end points include erythroid response (also called hematologic response–erythroid; defined by the IWG 2006 and 2018 criteria), longest duration of primary response, mean increase in hemoglobin levels of at least 1.0 g per deciliter, progression to acute myeloid leukemia, mean change in the serum ferritin level, and safety analyses.* *Subgroup analyses will be performed as exploratory end points.*
Statistical methods, data analysis	*Data will be summarised as frequencies and proportions or as medians and range and differences will be estimated by the chi square test (the Fisher exact test when appropriated) or the t test (the Wilcoxon Mann Whitney U test and the ANOVA model when appropriated based on patients' characteristics distribution)* *Survival curves will be estimated by Kaplan Meier method and differences between groups will be evaluated by the log-rank test. Hazard ratio and their corresponding 95% confidence intervals will be calculated by the Cox Regression Hazard model. All analyses will be performed using SAS version 9.4.*
Ethical considerations	*The responsible investigator ensures that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) or the laws and regulations of the country. The protocol has been written, and the study will be conducted according to the ICH Guideline for Good Clinical Practice*
Study time table	*Data collection period: January 2022 – December 2022* *May 2022: data of planned interim analysis* *January 2023: expected final report data*

2 Background and introduction

Myelodysplastic syndromes (MDS) are a group of malignancies characterized by reduced differentiation and increased apoptosis of hematopoietic progenitor cells, leading to ineffective hematopoiesis. The incidence of MDS ranges from 1.5 to 4 cases per 100,000 individuals per year. Prognosis is determined by a number of factors, including age, cytogenetic abnormalities, and cytopenia as determined by the Revised International Prognostic Scoring System (IPSS-R), but also by the occurrence of molecular aberrations (eg, gene mutations) and red blood cell (RBC) transfusion dependence.

Treatment of MDS varies according to prognosis. Patients with low IPSS-R risk have a low probability of progression to acute myeloid leukemia (AML) and the treatment is aimed at controlling cytopenia and improving quality of life (QOL), whereas patients with high-risk disease have a shorter life expectancy and treatment is aimed at modifying the natural course of the disease.

Anemia is the most common disease feature, occurring in 80%–85% of low-risk patients, 40% of whom eventually become RBC transfusion-dependent (TD).

Besides lenalidomide, which is exclusively approved for patients with deletion of chromosome 5q, erythropoiesis-stimulating agents (ESAs) constitute the first option for patients with low risk disease. Patients who do not respond to ESAs have very limited options and ultimately require long-term RBC transfusions. Chronic transfusions lead to secondary iron overload and have a deleterious effect on the patient's QOL.

On April 26, 2019, Celgene Europe BV applied for a marketing authorization via the European Medicines Agency (EMA) centralized procedure for luspatercept (trade name Reblozyl). Luspatercept is a recombinant fusion protein that selectively binds to ligands belonging to the transforming growth factor-beta (TGF-beta) superfamily. Luspatercept binds to GDF11, GDF8, activin B, and other ligands. This binding leads to inhibition of Smad2/3 signaling, which is abnormally high in disease models of ineffective erythropoiesis such as MDS, resulting in erythroid maturation and differentiation.

The review of the benefit–risk balance was conducted by the Committee for Medicinal Products for Human Use (CHMP), and the positive opinion was issued on April 30, 2020. The indication approved in the EU is as follows: "Reblozyl is indicated for the treatment of adult patients with TD anemia due to very low-, low-, and intermediate-risk MDS with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.

The clinical development program for luspatercept in MDS consists of 3 clinical trials, including the phase 3, randomized, double-blind, placebo-controlled study ACE-536-MDS-001 (MEDALIST) and 2 supportive phase 2, open-label, single-arm trials (A536-03 and A536-05).

In the MEDALIST trial, adult patients with very low, low, or intermediate IPSS-R risk MDS with ring sideroblasts who required RBC transfusions were randomized 2:1 to luspatercept (1mg/kg) or placebo by the SC route every 3 weeks.16 In both treatment groups, best supportive care could be used when clinically indicated, including RBC transfusions or iron chelation therapy, but excluding ESAs or other MDS-directed agents. The primary endpoint of the trial was the proportion of subjects who were RBC transfusion-independent (RBC-TI) over any 56-day period from week 1 to week 24.

In the MEDALIST trial, 229 subjects very low, low or intermediate IPSS-R risk MDS with ring sideroblasts were randomized: 153 to luspatercept and 76 to placebo (ITT population). Forty-nine (21.4%) patients discontinued from the study, with no differences between arms. Patients' baseline characteristics and prior medication use were well balanced across treatment arms. The percentage of responders (RBC-TI during 56 d through week 24) was 37.91% versus 13.16% ($P < 0.0001$) for

patients receiving luspatercept versus placebo, respectively (Table 1). When the assessment period was extended to 84 days, the proportion of responders was 33.33% versus 11.84% through week 48 and 28.10% versus 7.89% through week 24.

The safety database comprised 571 subjects who received luspatercept. The mean luspatercept treatment duration was 49 weeks (median 45.6). Treatment emergent adverse events (TEAEs) were documented in 95.3% of patients in the pooled luspatercept group, compared to 91.2% of patients in the placebo group. Incidence rates of serious TEAEs (23.8% versus 15.0%), grade ≥3 TEAEs (34.9% versus 25.9%) and TEAEs leading to permanent drug discontinuation (8.8% versus 3.6%) were higher in the pooled luspatercept group. In the MDS cohort, the most frequent TEAEs leading to discontinuation were progression to high-risk MDS, transformation to AML, general physical deterioration and sepsis. Fatal TEAEs were observed in 1.8% versus 2.6% of patients receiving luspatercept versus placebo. The most frequently reported TEAEs (≥15%) in the MDS group were fatigue, diarrhea, nausea, cough, dizziness, hypertension, peripheral edema, headache, viral upper respiratory tract infection, and back pain.

Overall, luspatercept significantly reduced red blood cell (RBC) transfusion requirements in patients with MDS with ring sideroblasts and had a generally manageable tolerability profile in clinical trials. Thus, luspatercept is an emerging treatment option in adults with transfusion-dependent anaemia due to MDS.

3 Rationale of the study

Despite that luspatercept is approved based on data of safety and efficacy from a large randomized clinical trial, we know that especially for human diseases arising in elderly people, features of subjects included in those randomized trials often do not reflect those of the population in which a therapy is intended to be used. Compliance to treatment and safety in clinical trials can also differ from real world settings. Consequently, in order to drive clinical decision-making process, data from randomized clinical trials should be integrated with evidence generated in a real world setting.

To date, no information is available on the efficacy and safety luspatercept in the treatment of MDS in real world populations. FiSIM (Fondazione Italiana Sindromi Mielodisplastiche) promotes a multicenter, retrospective observational study to collect information on the efficacy and safety of luspatercept in a real world Italian population of adult patients with transfusion-dependent anemia due to very low- and intermediate-risk MDS with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy

4 Objectives of the study

The general objective of the study is to define the efficacy and safety of luspatercept in a real world Italian population of adult patients with transfusion-dependent anemia due to very low- and intermediate-risk MDS with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.

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4.1 End-points

4.1.1 Primary endpoint

The primary end point is transfusion independence for 8 weeks or longer during weeks 1 through 24

4.1.2 Secondary endpoint

The key secondary end point is transfusion independence for 12 weeks or longer, assessed during both weeks 1 through 24 and weeks 1 through 48.

Other secondary end points include erythroid response (also called hematologic response–erythroid; defined by the IWG 2006 and 2018 criteria, see ***ANNEX 1***), longest duration of primary response, mean increase in hemoglobin levels of at least 1.0 g per deciliter, progression to acute myeloid leukemia, mean change in the serum ferritin level, and safety analyses.

Subgroup analyses will be performed as exploratory end points.

5 Patient selection criteria

5.1 Inclusion criteria

- Adult patients (i.e. aged >=18 years) with diagnosis of MDS according to WHO 2016 classification that met IPSS-R criteria for very low, low, or intermediate-risk MDS along with the following additional criteria:
    - Ring Sideroblasts (RS) ≥15% of erythroid precursors in bone marrow in the absence of SF3B1 mutation, or ≥5% in the presence of SF3B1 mutation;
    - Bone marrow blasts <5%;
    - Peripheral white blood cell count <13,000/μL;
    - ECOG PS 0-2;
- Refractory or intolerant to, or ineligible for prior ESA therapy.*
- Required RBC transfusions per the following criteria:
    - Mean RBC transfusion requirement ≥2 units/8 weeks in the 16 weeks before the start of luspatercept treatment
    - No consecutive 56-day period free from RBCTs in the 16 weeks before the start of luspatercept treatment
- Treatment with luspatercept

* Definition of Refractory or intolerant to, or ineligible for prior ESA therapy: Refractory to ESA therapy was defined as non-response or loss of response to recombinant human EPO (≥40,000 U/week for ≥8 doses or equivalent) or darbepoetin-alpha (≥500 μg q3w for ≥4 doses or equivalent) as a single agent or combination therapy (eg, with G-CSF). Intolerant to ESA therapy was defined as discontinuation to an ESA-containing regimen due to intolerance or an AE. ESA ineligible was defined as low change of response due to endogenous serum EPO levels >200 u/L in patients naïve to ESAs.

5.2 Exclusion criteria

- Any prior treatment with the following therapies:

- Prior therapy with disease modifying agents for MDS including immunomodulatory drugs (eg, lenalidomide), hypomethylating agents (eg, azacitidine or decitabine), and immunosuppressive therapy.

- Presence of the following conditions:

  - Pregnancy

  - The following blood and laboratory parameters: ANC <500/μL and Platelets <50,000/μL

6 Study Design

This is a multicenter, retrospective observational trial

7 Statistical considerations

7.1 Sample size

All patients treated with luspatercept in Italy between November 2020 and January 2022 will be included in this study (i.e., around 215 subjects). With this sample size, considering a proportion of subjects who were RBC transfusion-independent of 38% we can ensure a confidence interval of a predetermined width of 13 points (CI 95%: 32;45%). In case of the proportion estimated should be of 30%, (CI 95%:24;37%) or of 50% (CI 95%:44;57%) the same width for the CI could be ensured. All results will be reported with their corresponding 95% confidence intervals.

7.2 Analysis

Data will be summarised as frequencies and proportions or as medians and range and differences will be estimated by the chi square test (the Fisher exact test when appropriated) or the t test (the Wilcoxon Mann Whitney U test and the ANOVA model when appropriated based on patient characteristics distribution)
Survival curves will be estimated by Kaplan Meier Method and differences between groups will be evaluated by the log-rank test. Hazard ratio and their corresponding 95% confidence intervals will be calculated by the Cox Regression Hazard model. All analyses will be performed using SAS version 9.4.

Primary Outcome Measures:
- Percentage of patients who achieved RBC Transfusion Independence (RBC-TI) ≥ 8 weeks from week 1 to week 24 [Time Frame: from week 1 through week 24 of treatment]. RBC-TI response is defined as the absence of any RBC transfusion during any consecutive 56-day (8-week) period (ie, Days 1 to 56, Days 2 to 57, Days 3 to 58, etc.) during the first 24 weeks of study treatment. Patients had to have at least 56 days (≥ 8 weeks) of transfusion independence prior to (and including) the Week 24 date to qualify as a responder. Patients who failed to achieve RBC-TI at least 56 days prior to or on the cut-off date were counted as non-responders.

Secondary Outcome Measures:
- Percentage of patients who achieved RBC-TI ≥ 12 weeks from week 1 to week 24 [Time Frame: From Week 1 through Week 24 of treatment]. RBC-TI Response is defined as the absence of any RBC transfusion during any consecutive 84-day (12-week) period (ie, Days 1 to 84, Days 2 to 85, Days 3 to 86, etc.) during the first 24 weeks of treatment.

- Percentage of patients who achieved RBC-TI ≥ 12 Weeks from Week 1 to week 48 [Time Frame: From Week 1 through Week 48 of treatment]. RBC-TI Response is defined as the absence of any RBC transfusion during any consecutive 84-day (12-week) period (ie, Days 1 to 84, Days 2 to 85, Days 3 to 86, etc.) during the first 48 weeks of treatment.

-Percentage of patients who achieved RBC-TI ≥ 8 Weeks from week 1 through week 48 [Time Frame: From Week 1 through Week 48 of treatment]. RBC-TI response is defined as the absence of any RBC transfusion during any consecutive 56-day (8-week) period (ie, Days 1 to 56, Days 2 to 57, Days 3 to 58, etc.) during Week 1 through Week 48. Patients had to have at least 56 days (≥ 8 weeks) of transfusion independence prior to (and including) the Week 48 cut-off date to qualify as a responder. Patients who failed to achieve RBC-TI at least 56 days prior to Week 48 were counted as non-responders.

-Change from baseline in RBC Units Transfused over fixed 16-week Period [Time Frame: At Baseline (16 weeks prior to first dose of study treatment) and Weeks 9 to 24 or Weeks 33 to 48]
Mean change in total number of RBC units transfused over a fixed 16-week period (Week 9-24 or Week 33-48) from the total number of RBC units transfused in the 16 weeks immediately on or prior to first dose of study treatment.

-Percentage of patients who achieved an Hematologic Erythroid Response (HI-E) over any consecutive 56-Day Period [Time Frame: Week 1 through 24 or Week 1 Through Week 48]
A modified HI-E response was defined as the percentage of participants meeting the modified HI-E per the International Working Group (IWG 2018) sustained over 56-day consecutive period during the Treatment period. For patients with a baseline RBC transfusion burden of ≥ 4 units/8 weeks, a HI-E is defined as a reduction in RBC transfusion of at least 4 units/8 weeks; for patients with baseline RBC transfusion burden of <4 units/8 weeks, HI-E is defined as a mean increase in hemoglobin of ≥ 1.5 g/dL for 8 weeks in the absence of RBC transfusions.

-Percentage of patients who achieved a Mean Hemoglobin (Hgb) Increase of at Least 1.0 g/dL over any consecutive 56-Day period in absence of RBC Transfusions [Time Frame: Week 1 though Week 24 and Week 1 through 48]. A mean hgb increase of ≥ 1.0 g/dL is analyzed as the percentage of patients with a hgb increase ≥1.0 g/dL compared with baseline (after applying the 14/3 day rule) that is sustained over any consecutive 56-day (8-week) period in the absence of RBC transfusions during the treatment period. (Week 1 through Week 24 and Week 1 through Week 48).

-Duration of Red Blood Cell Transfusion Independence (RBC-TI) - Week 1 Through Week 24 [Time Frame: From start of study treatment to 16 weeks after last dose, up to approximately 93 weeks]. Duration of RBC-TI is defined as the longest duration of response for patients who achieved RBC-TI of ≥ 8 weeks during the treatment period Week 1 through Week 24. Patients who maintained RBC-TI through the end of the treatment period were censored at the date of discontinuation or death, whichever occurred first. Median was estimated from unstratified Kaplan Meier method.

-Duration of Red Blood Cell Transfusion Independence (RBC-TI) - Week 1 Through Week 48 [Time Frame: From start of study treatment to 16 weeks after last dose, up to approximately 93 weeks] Duration of RBC-TI is defined as the longest duration of response for participants who achieved RBC-TI of ≥ 8 weeks during the treatment period Week 1 through Week 48. Patients who maintained RBC-TI through the end of the treatment period were censored at the date of discontinuation or death, whichever occurred first. Median was estimated from unstratified Kaplan Meier method.

-Percentage of patients who achieved a Hematologic Improvement in Neutrophil Response (HI-N) Over Any Consecutive 56-day Period [Time Frame: Week 1 through Week 24 or Week 1 Through Week 48 of study treatment]. Percentage of patients who achieved a hematologic improvement in neutrophil response (HI-N) per IWG criteria sustained over any consecutive 56-day (8-week) period, during the treatment period (Week 1 to Week 24 and Week 1 to Week 48) HI-N was defined as at least a 100% increase and an absolute increase > 0.5 X 10^9/L.

-Percentage of patients who achieved a Hematologic Improvement in Platelet Response (HI-P) Over Any Consecutive 56-day Period [Time Frame: Week 1 through Week 24 or Week 1 Through Week 48 of study treatment]. Percentage of patients who achieved a hematologic improvement platelet response (HI-P) was defined as the percentage of participants meeting the HI-P criteria per the IWG sustained over any consecutive 56-day (8-week) period (Week 1 to Week 24 and Week 1 to Week 48) during the treatment period. HI - P response was defined as: Absolute increase of ≥ 30 X 10^9/L in platelets for participants starting with > 20 X 10^9/L platelets; Increase in platelets from < 20 X 10^9/L to > 20 X 10^9/L and by at least 100%

- Change From Baseline in Mean Serum Ferritin [Time Frame: Baseline and Week 9 through Week 24 and Week 33 through Week 48]. Mean change from baseline in mean serum ferritin was calculated as the difference of postbaseline mean serum ferritin (averaged over the specified timepoints) and baseline mean serum ferritin.

-Time to Red Blood Cell Transfusion Independence (RBC-TI) - Week 1 Through Week 24 [Time Frame: From first dose to Week 24 of treatment]. Time to RBC-TI is defined as the time between first dose date and the date of onset of RBC-TI first observed for participants who achieved RBC-TI of ≥ 8 weeks during Week 1 through Week 24

-Time to Red Blood Cell Transfusion Independence (RBC-TI) - Week 1 Through Week 48 [Time Frame: From first dose to Week 48 of treatment]. Time to RBC-TI is defined as the time between first dose date and the date of onset of RBC-TI first observed for participants who achieved RBC-TI of ≥ 8 weeks during Week 1 through Week 48

-Percentage of patients who progressed to Acute Myeloid Leukemia (AML) [Time Frame: From randomization to study completion (up to approximately 57 months)]. Percentage of participants progressing to AML throughout the course of the study

-Time to Acute Myeloid Leukemia (AML) Progression [Time Frame: From randomization to study completion (up to approximately 57 months)]. Time to AML progression is defined as the time between randomization date and the first diagnosis of AML as per World Health Organization (WHO) classification of ≥ 20% blasts in peripheral blood or bone marrow. Participants with a diagnosis of AML were considered to have had an event, participants who did not progress to AML at the time of analysis were censored at the last assessment date which did not indicate progression to AML.

-Overall Survival [Time Frame: From randomization to study completion (up to approximately 57 months)]. Overall Survival is defined as the time from the date of study drug randomization to death due to any cause. Overall survival was censored at the last date that the participant was known to be alive for participants who were alive at the time of analysis and for those who discontinued from the study or were lost to follow-up.

-Number of patients with Treatment Emergent Adverse Events (TEAEs) [Time Frame: From date of first dose up to 42 days after the last dose (up to approximately 83 weeks)]. The outcome measure describes the number of participants who experienced different types of Treatment-emergent adverse events (TEAEs). TEAEs were defined as Adverse Events (AEs) that started on or after the day of the first dose and on or before 42 days after the last dose of luspatercept. The investigator will determine the relationship of an AE to study drug based on the timing of the AE relative to drug administration and whether or not other drugs, therapeutic interventions, or underlying conditions could provide a sufficient explanation for the event. The severity of an AE is evaluated by the investigator according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (Version 4.0) where Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-threatening and Grade 5 = Death

8 Withdrawal of subjects

Subjects may always and without specification of reasons withdraw their informed consent, and as corollary, terminate the observational study.

Documentation of the withdrawal in the patient's medical record and in the CRF should be provided by the investigator.

9 Forms and procedures for collecting data and data managing

The study contemplates the collection of clinical and biological data in an ad-hoc CRF. A copy of the CRF is attached as ***Annex 2*** in the protocol. CRF is the primary data collection instruments for the study. All data requested on the CRF must be recorded, and any missing data must be explained

After the conclusion of the research, data shall be kept for 20 years after which the data will be destroyed.

In this study, we will use as resource data an electronic CRF (provided by REDCAP FISiM registry)

10 Ethical considerations

10.1 Patient protection

The responsible investigator ensures that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) or the laws and regulations of the country. The protocol has been written, and the study will be conducted according to the ICH Guideline for Good Clinical Practice. The protocol and its annexes are subject to review and approval by the competent Independent Ethics Committee(s) ("IEC").

10.2 Subject identification – Personal Data protection

All records identifying the subject must be kept confidential and, to the extent permitted by the applicable laws and/or regulations, not be made publicly available. The name of the patient will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the study. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patient initials and date of birth will also be reported on the case report forms.

Any and all patient information or documentation pertaining to a clinical trial, to the extent permitting, through a "key" kept anywhere, regardless of whether such key is supplied along with the information or documentation or not, must be considered as containing sensitive personal data of the patient, and is therefore subjected to the provisions of applicable data protection ("privacy") regulations. Breach of such regulations may result in administrative or even criminal sanctions.

Particularly, an information sheet prepared according to such regulations and a form to evidence the consent of patients to the processing of such data must therefore accompany the informed consent administered to the patient (see paragraph 14.3 below). Such information must (i) identify the roles of the holder ("*titolare*") and processor ("*responsabile*", appointed by the holder) of the patient personal data (also if not directly identifying the patient), as well as the purposes of the personal data collection and processing (medical treatment and related/unrelated scientific research), (ii) adequately describe the flows of communication involving them, particularly if third parties should become involved, and (iii) seek the patient's prior and specific consent to such processing.

Patient information or documentation may be considered "anonymous", and as such not subject to privacy regulations, only when no key whatsoever, permitting the identification of the patient, is any longer available

10.3 Informed consent

All patients will be informed of the aims of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered at the Data Center. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

11 Conflict of Interest

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest.

12 Data ownership

According to the ICH Guidelines on Good Clinical Practice the sponsor of a study is the owner of the data resulting therefrom. All centers and investigators participating in the study should be made aware of such circumstance and are invited not to disseminate information or data without the Institution's prior express consent.

FISiM is the Sponsor of the Study, it shall obtain all the approvals which are deemed to be necessary for the performance of the research, including all the regulatory approvals, as provided by legislation in force (EC approval and so on). The Sponsor, also by means of the Principal Investigator, undertakes to comply with Good Clinical Practices (Ministerial Decree 15 July 1997),

the EC Directive 2001/20/CE (as acknowledged in Italy through the Legislative Decree 211/2003), as well as the relevant rules on patients' data protection (General Data Protection Regulation 2016/679).

Data and results could not be used for drug industrial development, for the issuance of trial drug market authorization or, in any case, for profitable purposes. All centers and investigators participating in the study should be made aware of such circumstance and invited not to disseminate information or data without the Institution's prior express consent.

13 Publication Policy

After completion of the study, the project coordinator together with Steering Committee will prepare a draft manuscript containing final results of the study on the basis of the statistical analysis. The manuscript will be derived to the co-authors for comments and after revision will be sent to a major scientific journal.

All publications, abstracts, presentations, manuscripts and slides including data from the present study will be submitted to and reviewed by the Study Coordinator and Steering Committee for coordination and homogeneity purposes: specific advance periods for submission and review may be specified in the protocol. Authorship will be defined on the basis of individual contribution of any single center in terms of number of patients enrolled. The timing of publications (in the event several Centers should be participating in the Study) may be coordinated, and publication delayed if patentable inventions should be involved (for the time required in order to file the relevant patent applications); otherwise, according to the MoH's Decree of May 12, 2006, investigators cannot be precluded from or limited in publishing the results of their studies (IECs must verify that no excessive restriction is contained in the protocols submitted to their review and approval).

14 Study time table

Data collection period: January 2022 – December 2022

May 2022: data of planned interim analysis

January 2023: expected final report data

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List of annexes to be included with the protocol

ANNEX1

IWG 2006 and 2018 HI-E criteria for response evaluation

Item	IWG 2018 criteria	IWG 2006 criteria
Baseline criteria		
Definition of transfusion-burden categories	3 groups: NTD (0 RBCs in 16 wk)* LTB (3-7 RBCs in 16 wk in at least 2 transfusion episodes, maximum 3 in 8 wk)* HTB (≥8 RBCs in 16 wk, ≥4 in 8 wk)	2 groups: TD (at least 4 U of RBC with 8 wk for Hb < 9 g/dL) TID (<4 U of RBC with 8 wk for Hb < 9 g/dL)
Pretreatment RBC transfusion policy	Transfusion policy for the individual patient prior to therapy should be maintained on treatment‡	Transfusion threshold of 9 g/dL, no exception for clinical indication
Response evaluation criteria: HI-E		
NTD (0 RBCs in 16 wk)*	At least 2 consecutive Hb measurements ≥1.5 g/dL for a period of minimum 8 wk in an observation period of 16 to 24 wk compared with the lowest mean of 2 Hb measurements (apart from any transfusion) within 16 wk before treatment onset‡; only a response duration of at least 16 wk, however, is considered clinically meaningful	Hb increase by 1.5 g/dL and/or relevant reduction of U of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk; only RBC transfusions given for an Hb of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation
LTB (3-7 RBCs in 16 wk in at least 2 transfusion episodes, maximum 3 in 8 wk)*	HI-E in LTB patients corresponds to transfusion independence, defined by the absence of any transfusions for at least 8 wk in an observation period of 16-24 wk with the same transfusion policy (defined below) compared with 16 wk prior to treatment; only a response duration of at least 16 wk, however, is considered clinically meaningful	
HTB (≥8 RBCs in 16 wk, ≥4 in 8 wk)	Major response: Major HI-E response in HTB patients corresponds to transfusion independence, defined by the absence of any transfusions over a period of minimum 8 wk in an observation period of 16-24 wk with the same transfusion policy (defined below) compared with 16 wk prior to treatment; only a response duration of at least 16 wk, however, is considered clinically meaningful Minor response: Minor HI-E response in HTB patients is defined as a reduction by at least 50% of RBCs over a minimum of 16 wk with the same transfusion policy (defined below) compared with 16 wk prior to treatment	
On-treatment RBC transfusion policy§	Transfusion policy for the individual patient prior to therapy should be maintained on treatment if not otherwise clinically indicated (documentation by the treating physician required); we suggest a maximum variation between pre- and on-study practice of 1 g/dL (or 0.6 mmol/L) in terms of transfusion threshold	Transfusion threshold of 9 g/dL, no exception for clinical indication
Dose adjustment thresholds for high Hb levels	If the drug under investigation is stopped or its dose reduced in a responding patient for protocol-defined reasons leading to a loss of response, this should not be counted as such if reintroduction at the same or lower dose of the drug induces a new response; if reintroduction of the drug at a lower dose does not reinduce a response, this should be documented as such	NA

Abbreviations.

*
The coauthors did not fully agree on whether patients who received only 1 or 2 RBC concentrates during the 16-wk screening period should be categorized in the NTB or LTB group. If such patients are included in clinical trials evaluating HI-E, it is recommended that HI-E achievement requires not only transfusion independence but also an increase of Hb by at least 1.5 g/dL (= 0.9 mmol/L).

†
As in IWG 2006 criteria, only RBC transfusions administered for an Hb level below 9 g/dL are taken into account. Exceptions to this rule may be accepted in cases of well-documented moderate or severe angina pectoris, cardiac or pulmonary insufficiency, or ischemic neurologic diseases. In these cases, a higher transfusion trigger level may be established for an individual patient. These patients may require special attention when analyzing responses within clinical trials. Transfusions for intercurrent diseases (bleeding, surgical procedure, etc) are not considered.

‡
Oscillations (eg, natural or due to drug intervals) within this period are accepted as long as the patient remains off any transfusions and the same transfusion policy has been maintained. We suggest accepting 1 drop to an increase of between 1.0 and 1.5 g/dL over a period of 8 wk. We recommend that intervals between blood counts do not exceed 2 wk.

§
Exceptions to this rule may be accepted in cases of well-documented moderate or severe angina pectoris, cardiac or pulmonary insufficiency, or ischemic neurologic diseases. In these cases, a higher transfusion trigger level may be established for an individual patient. These patients may require special attention when analyzing responses within clinical trials. Transfusions for intercurrent diseases (bleeding, surgical procedure, etc) should not be taken into account.

IWG 2006 and 2018 HI-N and HI-P criteria for response evaluation

IWG 2018 criteria		**IWG 2006 criteria**	
Type of response	**Criteria**	**Type of response**	**Criteria**
Platelet response (pretreatment, <100 × 10^9/L), HI-P	• Absolute increase of 30 × 10^9/L for patients starting with >20 × 10^9/L PLTs or • Increase from <20 × 10^9/L to >20 × 10^9/L and by at least 100% In addition, • Evolution of bleeding symptoms is to be taken into account • Increments of platelets also for patients with a pretreatment PLT count of >100 × 10^9/L are to be reported	Platelet response (pretreatment, <100 × 10^9/L), HI-P	• Absolute increase of 30 × 10^9/L for patients starting with >20 × 10^9/L PLTs or • Increase from <20 × 10^9/L to >20 × 10^9/L and by at least 100%
Dose-adjustment policy for PLT counts on treatment	• If the drug under investigation is being stopped or its dose is being reduced in a responding patient for protocol-defined reasons leading to a loss of response, this should not be counted as such, if reintroduction at the same or lower dose of the drug induces a new response • When the investigational drug is stopped or reduced in dose, weekly blood counts are required to monitor the PLT levels • 2 subsequent PLT counts >450 × 10^9/L are a sufficient reason for treatment discontinuation in the case of treatment with TPO agonists		None
Neutrophil response (pretreatment, all patients), HI-N	At least 100% increase and an absolute increase >0.5 × 10^9/L (pretreatment, <1.0 × 10^9/L) Increments of neutrophils also for patients with a pretreatment ANC of >1.0 × 10^9/L are to be reported	Neutrophil response (pretreatment, <1.0 × 10^9/L), HI-N	At least 100% increase and an absolute increase >0.5 × 10^9/L

ANC, absolute neutrophil count; PLT, platelet; TPO, thrombopoietin.

ANNEX2- CRF copy

PATIENT EVALUATION BEFORE STARTING LUSPATERCEPT TREATMENT

Patient Characteristics		
*Patient Initials/Identifier (limit of 3 characters):		
* Disease/Indication to be Treated:		
* Date of Diagnosis (MM/YYYY, if known):		
*Age of Patient (Years):		
*Gender of Patient:		
*Race of Patient:		
*Weight of Patient (kg):		
*Height of Patient (cm):		
*Medical History: Provide patient medical history/current physical condition/ rationale for request (including a detailed summary of disease):		
*Patient Medications: List patient's current treatment(s), concomitant medication(s)		

*Is patient older than 18?	YES/NO
*Does the patient have documented diagnosis of very low, low and intermediate risk MDS according to International Prognostic Scoring System-Revised (IPSS-R)?	YES/NO
*Does the patient has RS ≥15% of erythroid precursors in bone marrow in the absence of SF3B1 mutation, or ≥5% in the presence of SF3B1 mutation?	YES/NO (specify presence of SF3B1 mutation)
*Has the patient received prior ESA therapy and is refractory or intolerant to? Refractory to ESA therapy is defined as non-response or loss of response to recombinant human EPO (≥40,000 U/week for ≥8 doses or equivalent) or darbepoetin-alpha (≥500 μg q3w for ≥4 doses or equivalent) as a single agent or combination therapy (eg, with G-CSF). Intolerant to ESA therapy was defined as discontinuation to an ESA-containing regimen due to intolerance or an AE.	YES/NO (please specify agent used)
*Is patient ineligible for ESA therapy? ESA ineligible is defined as low chance of response due to endogenous serum EPO levels >500 u/L in patients naïve to ESAs	YES/NO (if yes, specify sEPO level)
*Does patient need regular transfusion support (defined as ≥2 units/8 weeks in the 16 weeks prior the treatment with luspatercept)?	YES/NO (If yes please, specify number of units)
*What is the patient's ECOG performance status?	0-1-2-3
*Has the patient a diagnosis of MDS with del(5q) or secondary MDS	YES/NO
*Has the patient received prior therapy with *disease modifying agents* for MDS, such as immunomodulating agents (i.e. lenalidomide), hypomethilating agents (azacitidine and decitabine) and immunosuppressive therapy?	YES/NO
*Has the patient a prior history of MDS or other onco-hematologic malignancy?	Yes/NO (If YES, please specify)
*Does the patient have any history of testing positive for human immunodeficiency virus (HIV) or known AIDS?	Yes/NO
*Does the patient have any positive test result for hepatitis B virus indicating acute infection?	Yes/NO

*Does the patient have any positive test result for hepatitis C virus indicating acute infection?	Yes/ NO

CLINICAL ASSESSMENT AND LABORATORY TESTS REQUIRED BEFORE STARTING LUSPATERECPT TREATMENT

BLOOD COUNT	**Value**	**Units**	**Range**	**Not Done**	**Date of asessment**
*16-weeks Hemoglobin level #		g/dL			.
*Hematocrit					
*Reticulocytes					
*MCV		fl			
*Red Cell Count					
*White Cell Count		$10^3/mm^3$			
*% Neutrophils		%			
*% Eosinophils		%			
*% Basophils		%			
*% Lymphocytes		%			
*% Monocytes		%			
*Platelets					
*Absolute Neutrophil Count (ANC)					

* # Median of all pre-transfusional Hb values documented in the of last 16 weeks before program inclusion

*Microscopic examination of peripheral blood	Blast YES/NO (if yes specify %)

LAB VALUES	**Value**	**Units**	**Range**	**Date of Assessment**	**Not Done**
*Serum Ferritin					
*sEPO (after 7 days of last RBC transfusion)					

***Bone marrow aspiration and biopsy**	**Result**		**Date of Assessment**	**Not Done**
BM Aspiration:Blasts %				
BM Biopsy Qualitative description e.g. features and elements				
Ring sideroblasts %				
***Cytogenetic/Mutational test**	**results**	**Method**	**Date of Assessment**	**Not done**
Karyotype Qualitative description e.g. features				

Mutation SF3B1 status				
*DIAGNOSIS (specify according to WHO 2016)				
*IPSS-R score calculation	Select one of these options (very low, low, intermediate, high-risk, very high risk)			
*RBC transfusion burden: units of RBC transfused/8 weeks in the 16 weeks prior to program inclusion				

LUSPATERCEPT TREATMENT FORM

Assessment of Treatment with LUSPATERCEPT
*First Luspatercept dose administered: mg *Date:

Assessment of disease and clinical work-up during treatment phase	
*Number of cycles administered with luspatercept	
*Date of last cycle	Insert date
*Days between the last two doses of luspatercept	
*Last dose of luspatercept administered (mg/kg)	__ Mg/kg
- Disease progression If yes, specify reason and date	
- Discontinuation (consent withdrawn / lack of efficacy / pregnancy) - If yes, specify reason and date	
- Death - If yes, specify reason and date	
- If response evaluation not available, please specify reason:	
*Dose Delay/Dose reduction/Drug Discontinuation (specify one)	YES/NO. If yes, specify reasons (I.e. consent withdrawn, lack of efficacy, Hb level > 11.5 g/dL, pregnancy etc)
*Hb level pre-luspatercept dose (assessed before last dose administered)	
*Number of RBC units transfused between the last dose of luspatercept:	
*Hb pre-transfusion value before last transfusion event:	
* Luspatercept dose required for the next cycle	Specify dose required for next cycle: ☐ 0.8 mg/kg ☐ 1.0 mg/kg ☐ 1.33 mg/kg ☐ 1.75 mg/kg
* Expected data for the next luspatercept cycle	
* If a dose modification has been applied, please specify reason and new dose assumed:	

*Adverse Events reporting (to report an AE, please use modules and address specified in the LoA) Please specify: date of onset, date of resolution, type of AE, CTC grade, relation to study drug, action taken, outcome and treatment required .	
■ Date of onset	
■ Date of resolution	
■ CTC grade	
■ Relation to study drug	
■ Action taken regarding study drug	
■ Treatment required	
■ Outcome	

BLOOD COUNT	**Value**	**Units**	**Range**	**Not Done**	**Not Done Date of Assessment**
* Hemoglobin value pre-luspatercept dose (last dose)		g/dL			
*Hematocrit					
*Reticulocytes					
*MCV		Fl			
*Red Cell Count					
*White Cell Count		$10^3/mm^3$			
*% Neutrophils		%			
*% Eosinophils		%			
*% Basophils		%			
*% Lymphocytes		%			
*% Monocytes		%			
*Platelets					
*Serum ferritin					
Other (specify)					