12 December 2024
EMA/13310/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rytelo

International non-proprietary name: imetelstat

Procedure No. EMEA/H/C/006105/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

EPO	Erythropoietin
E-R	exposure-response
ESA	erythropoiesis-stimulating agent
ESMO	European Society for Medical Oncology
ET	essential thrombocytopenia
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-An	Functional Assessment of Cancer Therapy - Anaemia-Related Effects
FDA	Food and Drug Administration
hERG	human ether-à-go-go-related gene
Hgb	haemoglobin
HI-E	haematologic improvement-erythroid
HLA	human leukocyte antigen
HLM	human liver microsome
HPC	haematopoietic progenitor cell
HMA	hypomethylating agents
HR	hazard ratio
HSC	haematopoietic stem cell
HSCT	haematopoietic stem cell transplantation
hTERT	human telomerase reverse transcriptase
IPSS	International Prognostic Scoring System
IRC	independent review committee
IRR	infusion-related reaction
ITT	intent-to-treat
IV	intravenous(ly)
IWG	International Working Group
LFT	liver function test
LR MDS	lower-risk MDS
LS	least squares
LSC	leukemic stem cell
MAA	Marketing Authorization Application
mCR	molecular complete remission

MDS	myelodysplastic syndromes
MF	myelofibrosis
MK	megakaryocytes
MM	multiple myeloma
MPN	myeloproliferative neoplasm
NCA	Noncompartmental analysis
NDA	New Drug Application
NE	not estimable
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
PD	pharmacodynamic(s)
PDX	patient sample-derived xenograft
PFS	progression-free survival
PK	pharmacokinetic
PNH	paroxysmal nocturnal haemoglobinuria
popPK	population PK
PR	partial remission
PRO	patient-reported outcome
PY	person-year
PV	polycythaemia vera
qw	every week
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
QoL	quality of life
QUALMS	Quality of Life in Myelodysplasia Scale
RBC	red blood cell
RS	ring sideroblasts
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of product characteristics

t½	terminal elimination half-life
TA	telomerase activity
TEAE	treatment-emergent adverse event
TGI	tumour growth inhibition
TI	transfusion independence
TL	telomere length
Tmax	time to maximum plasma concentration
US	United States
VAF	variant allele frequency
TMDD	target-mediated drug disposition
UGT1A1	UDP-glucuronosyltransferase 1A1
VC	central volume of distribution
Vss	volume of distribution at steady state

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Geron Netherlands B.V. submitted on 8 September 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Rytelo, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

Rytelo, was designated as an orphan medicinal product EU/3/20/2305 on 27 July 2020 in the following condition: treatment of myelodysplastic syndromes.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Rytelo (imetelstat sodium) as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Rytelo

The applicant applied for the following indication: treatment of transfusion-dependent anaemia in adults with low- to intermediate-1 risk myelodysplastic syndromes (MDS) who have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMEA-C1-001910-PIP03-20-M01 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0517/2022 was completed.

The PDCO issued an opinion on compliance for the PIP P/0517/2022.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request for consideration

1.5.1. New active substance status

The applicant requested the active substance imetelstat contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
1 April 2016	EMA/H/SA/3259/1/2016/II	Jan Sjöberg and Odoardo Olimpieri
28 April 2016	EMA/H/SA/3259/2/2016/I	Armando Magrelli and Elmer Schabel
12 October 2017	EMA/H/SA/3259/3/2017/I	Martin Mengel and Jeanette McCallion
19 May 2022	EMA/SA/0000086595	Karri Penttila

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- The suitability of the pivotal study MDS3001 to demonstrate significant benefit and of the side-by-side comparison with the pivotal registrational study of luspatercept for the purposes of orphan designation maintenance
- The acceptability of the starting materials in the synthesis of imetelstat sodium drug substance and the overall analytical control strategy
- The acceptability of the absorption, distribution, metabolism, and excretion (ADME) studies of imetelstat in preclinical animal species to support registration
- The acceptability of the *in vitro* studies to characterise potential drug-drug interactions with concomitantly administered drugs cleared through CYP 2C8
- The fulfilment of the required non-clinical toxicology studies for a Marketing Authorisation Application for an anticancer pharmaceutical for patients with advanced cancer
- The need for nonclinical fertility, peri- and post-natal development, immunotoxicity, and carcinogenicity studies
- The unmet medical need in low/intermediate risk MDS patients who are transfusion dependent
- The suitability of the study eligibility criteria for the proposed target population and key study design elements of the pivotal study MDS3001

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Johanna Lähteenvuo

The application was received by the EMA on	8 September 2023

The procedure started on	28 September 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 December 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	3 January 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 January 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 January 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	15 August 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	24 September 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	3 October 2024
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	17 October 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	11 November 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	27 November 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Rytelo on	12 December 2024
The CHMP adopted a report on similarity of Rytelo with Reblozyl on (see Appendix on similarity)	12 December 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	12 December 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed therapeutic indication is:

Rytelo is indicated for the treatment of transfusion-dependent anaemia in adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) who have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA).

Myelodysplastic syndromes are a serious, life-threatening disease that constitute a heterogeneous group of hemopoietic clonal disorders characterized by ineffective hemopoiesis in which haematopoietic progenitor cells have a reduced ability to differentiate and an increased likelihood of apoptosis (Adès, 2014; Foran, 2012). This manifests in abnormal 'dysplastic' cell morphology in one or more haematopoietic cell lines and the development of peripheral cytopenias (Adès, 2014; Bejar, 2014; Foran, 2012)). Deletion of the long arm of chromosome 5, namely del(5q), is among the most recurrent cytogenetic aberrations in myelodysplastic syndromes (MDS), accounting for approximately 10–15% of all cases.

Clinical manifestations of MDS vary depending on subtype and the severity of cytopenias. Anaemia is the most common peripheral blood abnormality and leads to the majority of symptoms of MDS, occurring in approximately 80% to 85% of patients (Foran, 2012).

Lower-risk MDS are characterized by the presence of BM dysplasia, low BM blast percentage, low number and depth of cytopenia(s), and a variety of karyotypic and molecular abnormalities (Carraway, 2020).

Median survival in LR MDS ranges from 32.0 months to 56.1 months (based on SEER data from 2017; Zeidan, 2019). Patients with non-del(5q) LR-MDS who have failed ESA treatment, have a median OS of approximately 37 months (Kelaidi 2013).

2.1.2. Epidemiology

Myelodysplastic syndromes are among the most common haematologic malignancies in older people, with a median age at diagnosis of over 70 years old and less than 10% of patients being younger than 50 years old (Neukirchen, 2011; Fenaux, 2021). The incidence of MDS increases markedly with age, and the disease is most prevalent in individuals who are white and male (Ma, 2012; Neukirchen, 2011; Visser, 2012). Across identified studies in Europe, incidence of MDS ranged from 0.15 to 0.60 per 10,000 person-years (PY) (Avgerinou 2013; Bonadies 2017; Broccia 2014; Dinmohamed 2014; Dinmohamed 2015; HMRN 2022, Kontro 2022, Neukirchen 2011, RARECARENet 2022, Roman 2016, Solans 2022, Visser 2012). RARECARENet estimated that in 2013 there were 15,116 newly diagnosed cases of MDS in the EU28, based on a crude incidence rate of 0.25 per 10,000 PY identified between 2000-2007 (RARECARENet 2022). The age-adjusted incidence rate of MDS in the US in 2019 was estimated to be 3.6 cases per 100,000 persons, with an estimated 13,400 new cases of MDS annually (Zeidan, 2019; SEER Cancer Statistics Network). Prevalence of MDS in the EU, based on recent reviews of orphan designated medicines, is approximately 2 in 10,000 persons, well below the 5 in 10,000 criteria for orphan designation (European Commission: Community Register of orphan medicinal products).

2.1.3. Aetiology and pathogenesis

The cause of MDS is known only in 15% of cases (Ades, 2014; Fenaux, 2014). In approximately 30% of paediatric patients with MDS, the disease is due to an inherited predisposition, such as Down's syndrome, Fanconi anaemia, and neurofibromatosis (Ades, 2014; Fenaux, 2014). In adult patients without inherited predisposition, MDS may be attributed to a number of factors, including older age, prior treatment with chemotherapy agents or radiotherapy, and exposure to environmental irritants

(Ades, 2014; Fenaux, 2014; Foran, 2012). Advanced age is the single greatest risk factor (Sekeres, 2010).

Almost 80% of patients with MDS carry at least one mutation in one gene (Papaemmanuil, 2013). *SF3B1*, *TET2*, *SRSF2*, *ASXL1*, *DNMT3A*, and *RUNX1* are the most frequently mutated genes in at least 10% of patients who have MDS, with many additional genes that are mutated less frequently, and the number of driver mutations increases with time from diagnosis (Cazzola, 2020). Presence of certain mutations, for example *TP53* or *ASXL1*, *RUNX1*, *ETV6*, or *EZH2*, confers a higher risk of progression to AML independent of other more favourable mutations like *SF3B1* (Bejar, 2011; Thol 2011; Haferlach, 2014; Papaemmanuil, 2013; Liang, 2019). The *SF3B1* mutation is also significantly associated with lower haemoglobin (Hgb) values, consistent with a high degree of ineffective erythropoiesis, higher neutrophil and platelet counts, and lower bone marrow (BM) blasts in MDS patients (Malcovati, 2020). The number of mutations present in a karyotype correlates with the increased risk of disease and shorter OS, with lower-risk MDS (LR MDS) having fewer mutations than higher-risk MDS. The *SF3B1* mutation identifies a distinct subtype of MDS – MDS-RS+, that is characterized by ring sideroblasts (RS), ineffective erythropoiesis, and macrocytic anaemia. This condition has a relatively good prognosis, although most patients become transfusion dependent, and specific mutations or co-mutations may be associated with a worse outcome (Hasserjian, 2019; Cazzola, 2020; Janusz, 2021; Malcovati, 2015; Tang, 2019; Jafari, 2020).

2.1.4. Clinical presentation, diagnosis

Chronic anaemia is the major presentation of LR MDS, leading to red blood cell (RBC) transfusion dependency in approximately 40% of patients (Zeidan, 2013; Adès, 2014). Patients with chronic transfusion-dependent anaemia are highly symptomatic and suffer from exhaustive fatigue, shortness of breath and palpitations. Frequent RBC transfusions can lead to alloimmunization and difficulty in identifying a matched donor supply to support the continuous need for transfusions. The need for frequent transfusions results in increased utilization of healthcare resources and overall represents an economic burden to the healthcare system (De Zern, 2017). Over time patients develop end organ dysfunction not only due to chronic anaemia but also because of iron overload from numerous and frequent transfusions (Singhal, 2017; Germing, 2019; De Swart, 2020; Platzbecker, 2021). Additionally, comorbid conditions such as heart disease, mainly congestive heart failure, affect 18% and 25% of younger and older LR MDS patients, respectively (Castelli, 2018). These factors result in impaired QoL and most importantly shortened progression free survival (PFS) and OS (De Swart, 2020; Castelli, 2018; Platzbecker, 2021).

2.1.5. Management

Currently, allogeneic haematopoietic stem cell transplantation (HSCT) is the only potentially curative therapy for MDS and comes with a high risk of morbidity and mortality, especially in the older MDS patients who often have other complicating comorbidities. Non-relapse mortality following HSCT represents a limiting factor especially in LR MDS, and the survival rate differs significantly depending on age, disease risk, comorbidities, conditioning intensity, and type of donor (Robin, 2020).

According to the European Society for Medical Oncology (ESMO) Guidelines for MDS (Fenaux, 2021), the aim of therapy in LR MDS is to improve cytopenias, mainly anaemia (usually the predominant cytopenia), and improve QoL. In patients with mild and asymptomatic cytopenias, the approach is generally watchful observation. Eventually, as mentioned above, ~40% of LR MDS patients will become transfusion dependent.

Therapies for lower-risk myelodysplastic syndromes

Erythropoiesis-stimulating agents

In the LR MDS setting, ESA use results in an overall ≥ 8-week TI rate of 20% to 40% and rates tend to be higher in those with low baseline serum erythropoietin (EPO) levels (< 500 U/L, ideally < 100 U/L) and minimal or no RBC transfusion needs. However, responses to ESA therapies tend to be transient (duration of response between 18 and 24 months) and most patients eventually lose response or become refractory. In addition, there is a proportion of patients with high endogenous EPO levels who are ineligible for and would not derive benefit from ESA therapy. Absence of response or short response to ESAs in LR MDS is associated with a higher risk of AML transformation and poorer survival (median of 36.7 vs. 54.3 months in patients with longer response to ESA) (Kelaidi, 2013). Ultimately, with or without ESA treatment, patients become dependent on RBC transfusions to maintain minimum acceptable Hgb levels, at which point remaining therapeutic options are limited (Hellström-Lindberg, 2003; Sekeres, 2019), and currently available treatments have not been developed with intent to modify the underlying disease pathology.

Lenalidomide

Lenalidomide (Revlimid) is approved as a treatment of lower-risk patients with MDS with del(5q), which is observed in 10% to 15% of patients with MDS and is associated with a more favourable prognosis (List, 2006). Lenalidomide is not currently approved to treat MDS patients who are non-del(5q).

Treatment with lenalidomide results in TI in approximately two-thirds of del(5q) patients with a median TI duration of 2 to 3 years, and cytogenetic responses in 50% to 70% of patients (Fenaux, 2013; Ades, 2014). While some LR MDS non-del(5q) patients do respond to lenalidomide, the rate and duration of RBC TI is not as robust as that in the del(5q) patients (List, 2006; Santini 2016).

Luspatercept

Luspatercept (Reblozyl) is approved in the EU for the treatment of patients with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS. In the pivotal registration study (MEDALIST), treatment with luspatercept resulted in ≥ 8-week TI rate of 38% with a median duration of 30.6 weeks (Fenaux, 2020a). Less than half of the subjects (43%) in the MEDALIST study had RBC transfusion burden of ≥ 6 units/8 weeks at baseline. Luspatercept was more efficacious in subjects with a lower transfusion burden. The ≥ 8-week RBC TI rate was 80% in subjects who received < 4 units/8 weeks vs. 40% with placebo, 37% in subjects who received 4 to < 6 units/8weeks vs. 4% with placebo and 9% in subjects who received ≥ 6 units/8weeks vs. 3% with placebo (Fenaux, 2020a).

Azacitidine

In the EU, hypomethylating agents (HMAs), specifically azacitidine, are primarily used in patients with higher risk MDS, (intermediate 2 and high risk per IPSS). Whilst some HMAs may be used off-label in MDS, given the limited benefit observed in LR MDS, HMAs are generally not recommended as standard of care for this patient population (Fenaux 2021).

Anti-Thymocyte Globulin (ATG) +/- Cyclosporine (CSA)

Anti-thymocyte globulin (ATG) with or without cyclosporine (CSA) is used for the treatment of patients without del(5q) who failed ESA. ATG ± CSA, can yield an erythroid response (associated with response of other cytopenias, especially thrombocytopenia) in 25%-40% of patients. Anti-thymocyte globulin results are better in relatively young (< 65 years), LR MDS patients with a recent RBC transfusion history, normal karyotype (or possibly trisomy 8), no excess blasts and HLA DR15 genotype, and in patients with thrombocytopenia, a small paroxysmal nocturnal haemoglobinuria (PNH) clone or with

marrow hypocellularity. Therefore, this treatment is generally proposed to a minority of patients and is not approved for use in several territories (Fenaux 2021).

2.2. About the product

Imetelstat is a 13-nucleotide (13-mer) oligonucleotide with a covalently bound lipid tail. Imetelstat is a first in class telomerase inhibitor that specifically targets malignant cells characterized by the abnormal elevation of telomerase activity (TA). Imetelstat has a nucleotide sequence that is complementary to, and specifically binds with high affinity to the template region of the RNA component of human telomerase, which lies in the active or catalytic site of the telomerase reverse transcriptase (hTERT), resulting in competitive inhibition of hTERT enzymatic activity, which prevents telomere binding. While there may be some structural similarities between imetelstat and other oligonucleotide classes, the mechanism of action for imetelstat is not antisense based, as it does not target mRNA of any gene, and does not activate RNase-H-based degradation of its target sequence; instead, it behaves like a classical active site enzyme inhibitor. The structure of imetelstat allows for high sequence-specific binding and enhanced entry into cells to increase the inhibition of TA (Asai, 2003; Herbert, 2005).

Nonclinical studies have indicated that inhibition of TA by imetelstat results in inhibition of cell proliferation of several cancer cell lines and human tumours in mouse xenograft models (Hochreiter, 2006; Shammas, 2008; Marian, 2010a; Marian 2010b; Ouellette, 2011). Moreover, imetelstat also inhibits proliferation and induces apoptosis of cancer stem cells (Joseph, 2010; Bruedigam, 2014). Telomerase inhibition by imetelstat leads to the loss of a cancer cell's ability to maintain telomere length (TL), which results in broad antitumor activity as demonstrated by inhibition of proliferation, reduction in colony formation and induction of apoptosis/senescence in different cancer cell lines, and patient derived samples (Wang, 2004; Herbert, 2005; Shammas, 2008; Hochreiter, 2006; Brennan, 2010; Joseph, 2010; Marian, 2010a; Marian 2010b; Frink, 2016).

2.3. Type of application and aspects on development

The imetelstat clinical development program includes studies in haematological and solid tumour malignancies, as monotherapy or in combination with other drugs. The efficacy and safety of imetelstat as treatment for transfusion dependent LR MDS that is relapsed after, refractory to or ineligible for ESA therapy, are supported by the pivotal Phase 2/3 study (Study MDS3001; IMerge), with a focus on the Phase 3 portion, which is randomized, double-blinded, and placebo-controlled. This was a global study conducted at 77 study sites in 17 countries, including the EU and the US. The Phase 3 part of Study MDS3001 is the pivotal study in support of registration in support of the clinical benefit of imetelstat in transfusion dependent LR MDS. The Phase 2 part of Study MDS3001 provides supportive evidence of efficacy and safety for the Marketing Authorisation Application (MAA).

Four additional studies in haematological malignancies indications, including MDS, myelofibrosis (MF), essential thrombocytopenia (ET) or polycythaemia vera (PV) and multiple myeloma (MM), are included in support of safety.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a lyophilised powder for concentrate for solution for infusion containing 47 mg or 188 mg of imetelstat as active substance.

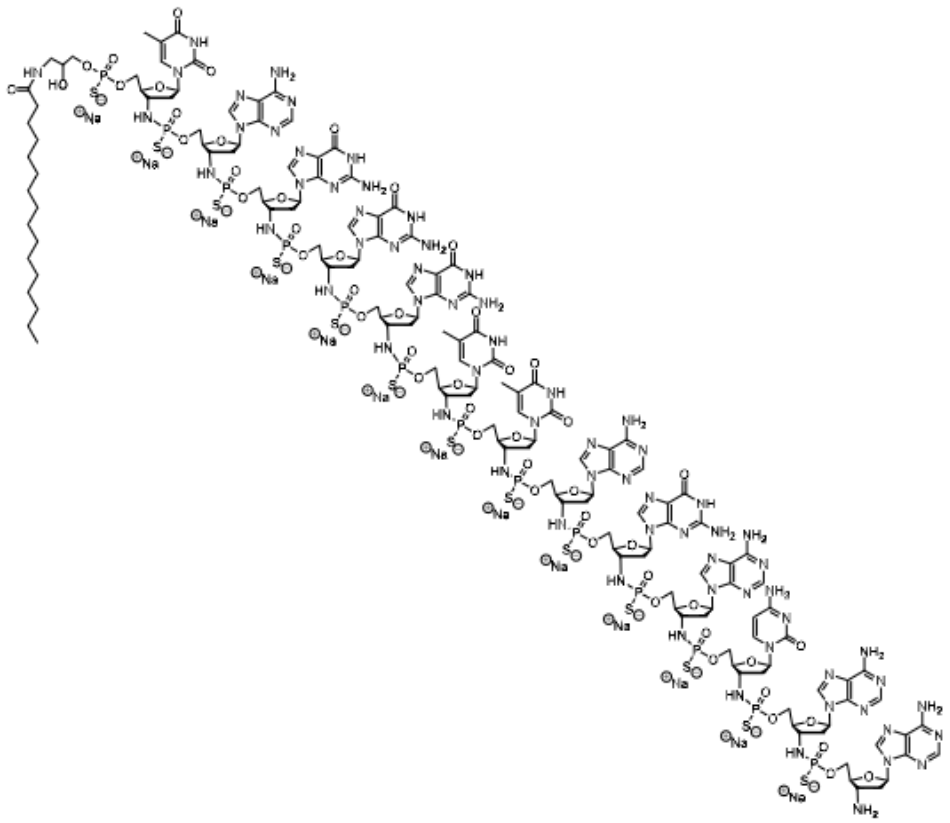
Other ingredients are: sodium carbonate (for pH-adjustment), hydrochloric acid (for pH-adjustment).

The product is available in a clear, Type 1 glass vial with a chlorobutyl rubber stopper and an aluminium flip-off seal with a dark green plastic cap (47 mg) or royal blue plastic cap (188 mg). Pack size: 1 vial.

2.4.2. Active substance

2.4.2.1. General information

Imetelstat sodium is a synthetic 13-mer oligonucleotide carrying a palmitoyl residue attached via an aminoglycerol linker. Its molecular formula is $C_{148}H_{198}N_{68}O_{53}P_{13}S_{13}Na_{13}$ (as sodium salt) and molecular weight is 4896 g/mol (as sodium salt 1:13). The molecular structure is presented below in **Figure 1**.



DNA, d(3′-amino-3′-deoxy-P-thio) (T-A-G-G-G-T-T-A-G-A-C-A-A), 5′-[O-[2-hydroxy-3-(hexadecanoyl-amino)propyl]phosphorothioate], sodium salt (1:13)

Figure 1 Imetelstat molecular structure

Imetelstat sodium is a white to off-white or slightly yellow powder. Polymorphism has not been observed. It exists as an amorphous solid. It is relatively hygroscopic and is highly soluble in aqueous solutions.

With respect to stereochemistry, imetelstat sodium contains 12 internucleoside N3′ →P5′ -thio-phosphoramidate groups, plus one 5′ -terminal phosphorothioate group, connecting the palmitoylated aminoglycerol linker to the oligonucleotide. Each internucleoside N3′ →P5′ -thio-phoshoramidate group in the active substance represents a stereogenic center, resulting in a mixture of Rp- and Sp-isomers. In the imetelstat sodium molecule, the total number of possible stereoisomers resulting from phosphorus stereoisomers and the presence of the racemic C in the amido-propanediol fragment of the starting material is 2^{14} = 16384, based on the potential permutations of Rp- and Sp-isomers, and the R and S isomers of the racemic C.

2.4.2.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The active substance is manufactured by one manufacturing site.

Imetelstat sodium is manufactured by solid-phase synthesis followed by purification, ultrafiltration and diafiltration for salt exchange and concentration, and finally bulk lyophilization, homogenisation and packaging.

Process parameters and amounts of all materials, reagents and solvents are laid down in the process description with set points or ranges justified by process development. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

During the procedure, major objections were raised requesting additional information on control of the purification and ultrafiltration steps, and requesting a more clear and logical description of the process controls for all steps. In response, revised criticality assessments were provided for purification and ultrafiltration steps and critical in process controls (IPCs) were identified. The dossier was revised for all steps to provide a focussed, stepwise presentation of the various process controls performed. In addition, process intermediates have been formally defined in the imetelstat sodium manufacturing process.

During the procedure, a major objection was raised on the lyophilisation step as the adequate closure of the primary container was not identified as a critical step. In response the applicant confirmed that the primary container is closed manually by trained staff and has been redefined as a critical process parameters (CPP). This was considered acceptable and it was noted that the applicant commits to finalise the introduction of a torque-assisted closing procedure for the active substance primary container during 2025 as planned, and thereafter submit an appropriate variation application to implement it in the active substance manufacturing process (REC1).

The proposed hold times are acceptable based on presented data.

Control of materials

Five starting materials are defined for the process including the nucleoside phosphoramidites (amidite A^{dmf}, amidite C^{Bz}, amidite G^{iBu}, and amidite T) and the palmitoylated aminoglycerol linker loaded on a polymeric solid support (LLPS).

The applicant has described the rationale behind the selection of the starting materials. The proposed phosphoramidite starting materials and the LLPS are adequately justified with reference to ICH Q11 expectations: they are well-characterized, stable solids incorporated in imetelstat sodium as significant

structural fragments, their impact on active substance is understood and controlled, their impurity profiles are well-defined, and their quality can be controlled by specifications. Based on available documentation, it is agreed that suitable starting materials have been selected. They are also in line with the overall conclusions of two scientific advices (BfArM 2016, EMA/CHMP/SAWP/643024/2017).

The specifications for the starting materials are acceptable after changes implemented during the procedure. The questions that were raised concerned improved impurity control in all five starting materials, which has been achieved through tightened limits.

Regarding other process materials used in the imetelstat sodium manufacturing process, acceptable specifications have been presented.

Manufacturing process development

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The development is described, starting from early phases, and ending in commercial process characterization studies in five stages, during which QbD/DoE approaches were used.

During the procedure, a major objection was raised as it was unclear if the applicant applied for one or more design spaces or not. With the clarifications provided in response, it has been possible to conclude that the process is adequately controlled. No design spaces are implemented for the manufacture of imetelstat and the applicant has confirmed full compliance with the conditions and expectations specified in the EMA document EMA/CHMP/CVMP/QWP/354895/2017, i.e., "Questions and answers: Improving the understanding of NORs, PARs, DSp and normal variability of process parameters".

Characterisation

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Imetelstat sodium was characterized by MALDI-TOF-MS, ^{31}P-NMR, ^{1}H-NMR, ^{13}C-NMR, and 2D techniques (COSY, TOCSY, NOESY, HSQC, HMBC and JMOD), FT-IR, UV, circular dichroism, XRPD, differential scanning calorimetry, and thermogravimetric analysis.

In addition, sodium content, hygroscopicity, and isomerism was studied as described above. No commercially suitable synthesis method is available for the stereo-selective formation of internucleoside thio-phosphoramidate linkages, thus the product throughout nonclinical and clinical development has been a mixture of Rp- and Sp-isomers.

Potential and actual impurities were discussed and characterised, with reference to expected impurities arising from the coupling/solid phase process and known side-processes. Although the active substance is fully synthetic, ICH Q6B is referenced for classification of impurities as either product related substances or product related impurities. Possible routes for formation of both process-related impurities and degradation products are described. Forced degradation studies have been performed. Acceptable justifications have been presented for using finished product batch data in the characterization of the active substance. The issues raised on different aspects of impurity characterization have been acceptably resolved.

The primary container closure for imetelstat sodium consists of a 4-litre high density polyethylene (HDPE) bottle with a polypropylene (PP) screw cap, fitted with a tamper-evident seal. The secondary packaging is a low-density polyethylene (LDPE) laminated foil (White PET/ALU foil/LDPE) bag which is heat-sealed. The laminated bottle is bubble-wrapped before being placed in a dry-ice shipping container (2 bottles per container). Technical drawings, including dimensions, are provided and supplier's CoAs are included in the dossier. Specifications for the primary container closure system components are provided and compliance with relevant EU/Ph. Eur. standards are declared.

2.4.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

The active substance specification includes tests for appearance (solid), appearance (reconstituted solution), identification (LC-UV/MS, RP-HPLC-UV, 31P-NMR), oligonucleotide content (UV), purity and impurities (HPLC/UV), chromatographic assay, purity & product related substance (LC-UV/MS), sodium content (ICP-OES), water content (Ph. Eur.), pH (Ph. Eur.), residual solvents (GC-FID), elemental impurities (ICP-MS), microbial limit test (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The specification is acceptable after tightening of assay and certain impurity limits during the procedure. Relevant justifications of specification limits have been presented and are considered acceptable. The claimed toxicologically qualified levels for impurities are in many cases higher than what is relevant for control of impurities in the active substance considering a reasonable assay limit. Therefore, the primary aim of setting specification limits has been to ensure that the manufacturing process delivers active substance of consistent and reproducible quality, i.e. a robust process. While stability data and analytical method variability should be taken into account in setting specifications, limits proposed to accommodate obvious outliers, neither batches nor individual data points, have not been accepted. Acceptable control of benzene as a potential impurity in process solvents has been demonstrated.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

A comparatively large number of active substance batches are presented in the dossier, including six commercial process batches manufactured during 2024 and five manufactured during 2023, and four PPQ batches manufactured in 2020–2022. All results comply with specification limits. There appears to be an overall trend towards higher purity with later process versions, and results are comparable between batches made using the same process version.

The primary container closure for imetelstat sodium consists of a 4-litre high density polyethylene (HDPE) bottle with a polypropylene (PP) screw cap, fitted with a tamper-evident seal. The secondary packaging is a low-density polyethylene (LDPE) laminated foil (White PET/ALU foil/LDPE) bag which is heat-sealed. The laminated bottle is bubble-wrapped before being placed in a dry-ice shipping container (2 bottles per container). Technical drawings, including dimensions, are provided and supplier's CoAs are included in the dossier. Specifications for the primary container closure system components are provided and compliance with relevant EU/Ph. Eur. standards are declared.

2.4.2.4. Stability

Stability studies were conducted according to ICH Q1A (R2) recommended storage conditions and test frequencies. The primary stability batches were made to production scale and are packed in a smaller-volume bottle than described for the commercial use, though otherwise representative for the proposed primary container.

Based on the results for the six primary stability batches, stored at long term (-20 °C) and at accelerated (5 °C) conditions for up to 60 months, imetelstat sodium appears to be stable. There is some variability in results, but no obvious trends in batch-to-batch comparisons.. All results remain within specification limits.

The stability results were obtained by testing the list of parameters defined in the specification and using the validated analytical methods described in the dossier. Stability data is presented for some of

the supportive batches, testing was either not complete (certain parameters not evaluated) or not completed according to ICH testing frequency.

The ongoing stability studies will continue to completion according to protocol presented in the dossier.

It is agreed that available results, including the supportive batches for which up to 60 months data is included for up to eight batches, support the claimed retest period of 48 months. The approved retest period for imetelstat sodium active substance is 48 months when stored at the recommended storage temperature of -20 ± 5 °C in the proposed primary container closure system described above.

2.4.3. Finished medicinal product

2 . 4 . 3 . 1 . Description of the product and pharmaceutical development

The Rytelo finished product is a lyophilised powder for reconstitution which is provided in a single-dose borosilicate glass vial with elastomeric stopper, and aluminium seal with flip-off plastic cap.

Each vial contains a target fill of imetelstat sodium which reflects the excess volume, or overfill, that is added to each vial during manufacturing to ensure that extraction of not less than 200 mg or 50 mg of imetelstat sodium (equivalent to 188 mg or 47 mg of imetelstat) can be achieved following reconstitution with the specified volume of sodium chloride 0.9% solution.

Reconstitution with 6.3 ml or 1.8 ml 0.9% sodium chloride solution for injection provides a concentration of 33.33 mg/ml imetelstat sodium (31.39 mg/ml imetelstat base), which gives a maximum deliverable volume of 6 ml or 1.5 ml. The required dosing volume is further diluted in the infusion bag of 0.9 % sodium chloride solution for injection prior to administration via an intravenous infusion.

The two strengths 188 mg and 47 mg imetelstat were selected to provide flexibility to achieve the target dose based on patient body weight whilst minimising wastage or potential for re-use.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. Water for injection (WFI) is a processing agent that is removed during the lyophilisation. No other excipients or bulking agents were added as the active substance alone provides enough structure to the lyophilised cake, with a good appearance, reconstitution time and low moisture content.

The quality target product profile for Rytelo finished product is based on the properties of the active substance, the intended use, the characterization of the finished product and the intended patient population.

Pharmaceutical development studies assessing pH, solubility, and viscosity evaluated the feasibility of a liquid formulation and ultimately led to the development of a stable lyophilised formulation without bulking agents or other excipients.

A robust lyophilisation cycle was developed with temperature and pressure range suitable for the large scale lyophiliser in the manufacturing facility.

During the procedure a major objection was raised, requesting further details of the choice of sterilisation process chosen for the commercial product. A feasibility study was conducted to evaluate the suitability of terminal sterilisation, i.e., gamma irradiation and steam sterilisation. Data demonstrate that both gamma irradiation and steam sterilisation reduce the purity of the active substance. It was also clearly shown that terminal sterilization by dry heat is not viable for the finished product due to impact on purity of the active substance. The milder steam sterilisation was initially

chosen, but data shows that it also does not work as a sterilisation method for the product due to degradation and loss of purity. The conclusion is therefore that aseptic processing utilising sterile filtration for the finished product is justified as the terminal sterilisation processes resulted in finished product of inferior quality.

No preservative is included in the finished product. The finished product is sterile-filtered and aseptically filled using validated processes. The sterilising filtration is conducted by two in-line filters, which are tested for integrity before and after use with a validated test method. In addition, microbial in-use stability studies have been conducted to support the post reconstitution/dilution times from a microbiology product quality perspective during DP preparation for administration to the patient.

Compatibility studies were conducted to support the instructions for use and handling in the SmPC, i.e., a maximum in use storage period of 48 hours when stored refrigerated at 2 to 8°C, and 18 hours when stored at room temperature at 20ºC to 25ºC, from the time of reconstitution to completion of the infusion.

Container closure system

The primary container closure system is composed of type I borosilicate glass vials that are washed and depyrogenated and closed with rubber stoppers that can be washed and sterilised using validated processes or purchased sterile ready-to-use. Aluminum seals with plastic caps are used to ensure adequate closure of the container closure system. A number of container closure integrity testing studies have been performed to demonstrate that the primary container closure system is able to preserve the integrity and hence sterility of the product. In addition, sterility testing is conducted annually and at expiry during long term stability studies to demonstrate that the selected container closure system is able to protect the finished product from any potential microbial ingress throughout its proposed shelf life.

The applicant has presented data from an ongoing long-term leachables study of the product in the commercial container closure system with the proposed chlorobutyl stopper used for the 200 mg finished product. Currently there are no product-specific leachables data for the proposed stopper. However, the applicant commits to conducting a simulated extractables study to identify any potential extractables from the stopper using a validated analytical method. The applicant will include the results in the MA dossier as a post approval submission when the final study results are available (any unexpected findings of concern would also be communicated to the Agency whilst the study is on-going) **(REC2)**.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured at two manufacturing sites (one site for each strength) . Satisfactory proof of GMP compliance has been documented for all finished product manufacturing, testing and packaging sites.

The manufacturing process consists of seven main steps . These include thawing of active substance, addition of active substance to WFI, adjusting of pH if needed (Na_2CO_3 or HCl), sterile filtration and aseptic filling in washed, depyrogenated and sterilised vials, followed by lyophilising, stoppering, capping and tray loading. Relevant process parameters justified by the pharmaceutical development and/or the process validation are presented. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Major steps of the manufacturing process have been validated by a number of studies. A batch size range has been proposed and accepted for each finished product strength. Validation of the commercial processes for the production of finished product have been completed at both sites on

three PPQ batches per finished product strength covering the minimum and maximum proposed batch sizes. In-process hold times were challenged and testing of samples from the process showed consistent product quality.

Filter validation and media fill validation have been performed. Filtration and filling duration is supported by media fill data.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form; appearance (visual, solid & reconstituted solution), clarity and degree of opalescence (Ph. Eur.), colour of solution (PH. Eur.), reconstitution time, identification (RP-HPLC/UV, LC-UV/MS), oligonucleotide content assay (UV), purity and impurities (RP-HPLC/UV), chromatographic assay, purity & product related substance (LC-UV/MS), osmolality (Ph. Eur.), uniformity of dosage units (content uniformity) (Ph. Eur.), water content (Ph. Eur.), pH (Ph. Eur.), particulate matter (Ph. Eur.), elemental impurities (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

During the procedure a major objection was raised due to an incomplete risk assessment concerning the potential presence of nitrosamine impurities in the finished product. In response, an updated risk assessment has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

Batch analysis data from several batches, including commercial and clinical batches, are provided. PPQ batches, manufactured according to the intended commercial manufacturing process, are tested according to the proposed commercial release specification. All parameters comply with the suggested acceptance criteria.

2.4.3.4. Stability of the product

Stability studies have been performed on both strength presentations at long-term conditions (5°C±3°C), accelerated conditions (25°C±2°C / 60%±5% RH) in accordance with ICH Q1A(R2).

The parameters tested were the same as release and tested with the validated analytical test methods. For the 188 mg presentation, 24 months primary stability data from three process performance qualification (PPQ) batches stored at long-term conditions were provided, as well as 24-72 months stability data from three batches manufactured by similar processes to the validated commercial process. Moreover, data for six supporting stability batches were presented: one batch, 24 months; two batches, 48 months (one batch with data points OOS); one batch, 60 months (one batch with data points OOS) and two batches 72 months.

For 47 mg presentation, 12 months, primary stability data from three PPQ batches stored at long-term conditions were provided, as well as 24 months primary stability data from one batch used for clinical studies (commercial process).

For both product strengths, all results for time points tested up to date for the primary batches were within the proposed commercial specifications. Moreover, 60 months data for three supporting stability batches from the 188 mg strength were presented with results within the specifications.

Batches from each product strength were also exposed to stressed conditions (40°C±2°C). The results show comparable stability trends for primary and supporting stability batches with several OOS results, e.g., purity as well as unlipidated species by RP-HPLC/UV.

Photostability studies have been performed on one supporting stability batch per strength in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Results indicate stability under these conditions.

Forced degradation studies were conducted on finished product batches and a single active substance batch. These showed moderate to significant degradation occurs under acidic conditions, moderate degradation occurs under neutral and basic conditions, significant degradation occurs under oxidative conditions and significant degradation occurs if exposed to heat and humidity in the solid state, and moderate degradation occurs in dry heat.

It is acknowledged that, except for total fill content and container closure dimensions, the 188 mg and 47 mg presentations are equivalent with regard to the active and inactive ingredients. The stability data available for 188 mg presentation are considered to be supportive of the proposed shelf life of 48 months assigned to both strengths.

Based on the stability data provided and the compatibility studies mentioned above, the following shelf-life and storage conditions are considered appropriate for both strength presentations of Rytelo finished product when stored in the primary container closure system:

- Shelf life (unopened): Up to 48 months when stored at the recommended storage temperature of 5°C ± 3°C. Do not freeze.
- In-use period (once reconstituted and diluted): Up to 48 hours when stored at 2-8°C or up to 18 hours at room temperature (20-25°C) which is supported by microbial challenge and physico-chemical compatibility data.

2.4.3.5. Post approval change management protocol(s)

Not applicable.

2.4.3.6. Adventitious agents

Not applicable

2.4.4. Discussion on chemical and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the procedure, major objections were raised on the active substance relating to the purification and ultrafiltration steps, the description of manufacturing process and controls, the control of container closure following lyophilisation and the link between development studies and overall control strategy.

Major objections were raised on the finished product relating to the choice of sterilisation process and the absence of a risk assessment relating to potential nitrosamines formation. The applicant addressed all of the issues raised in the initial assessment and updated the relevant dossier sections accordingly.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant is recommended to finalise the introduction of a torque-assisted closing procedure for the active substance primary container during 2025 as planned, and thereafter submit an appropriate variation application to implement it in the active substance manufacturing process.
2. The applicant is recommended to initiate extractable and leachable studies for the stopper followed by a long-term leachables study for up to 72 months to generate the product-specific leachables data. The applicant will include the results in the MA dossier as a post approval submission. Any unexpected findings of concern would also be communicated to the Agency whilst the study is on-going.

2.5. Non-clinical aspects

2.5.1. Introduction

The non-clinical program is based on the ICH S9 guideline for evaluation of anticancer pharmaceuticals but has been supplemented with 6/9-month long repeat-dose toxicity studies, genotoxicity studies, and fertility evaluations to support chronic administration as the claimed indication of treatment of transfusion dependent anaemia in low and intermediate risk MDS does not fall under ICH S9. Pre- and Postnatal Development (PPND) and carcinogenicity studies are lacking from the program.

Concentrations of imetelstat referred throughout the non-clinical and clinical sections of this report are for the imetelstat salt as derived from the study reports. For data that are reflected in the SmPC, these concentrations have been converted to the corresponding concentration of the active moiety, i.e. of the imetelstat acid form as follows:

- 5 mg/kg salt = 4.7 mg/kg active moiety
- 7.5 mg/kg salt= 7.1 mg/kg active moiety
- 15 mg/kg salt = 14.1 mg/kg active moiety
- 30 mg/kg salt = 28.2 mg/kg active moiety

2.5.2. Pharmacology

The sequence of imetelstat (5'-TAGGGTTAGACAA-3', also referred to as GRN163L) is complementary to the template region of the RNA component of human telomerase. This region lies in the active site of the telomerase reverse transcriptase and the proposed mechanism of imetelstat is that it acts as a classical active site enzyme inhibitor. A series of *in vitro*/*ex vivo* and in vivo studies were conducted to characterize the pharmacology of imetelstat. Safety pharmacology studies were conducted *in vitro* and *in vivo* (in monkeys) to assess imetelstat effects on the central nervous system (CNS), cardiovascular and respiratory systems.

2.5.2.1. Primary pharmacodynamic studies

The primary pharmacodynamics data package consists of studies and published data, including studies conducted in a wide array of tumour/cancer cell types in vitro and in xenograft mouse models.

Imetelstat was shown to inhibit telomerase activity (TA), as measured by a cell-free telomerase repeated amplification protocol (TRAP) assay (Study GR12-023) in human cervical carcinoma cells (HT-3)., and to reduce alone or in combination with venetoclax (ABT-199), a specific BCL-2 inhibitor, the expression of human telomerase reverse transcriptase (hTERT), as measured by qPCR, in several AML cancer cell lines cancer cell lines *in vitro* (study TR2017T-009) (data not shown).

In a study performed by the applicant (PRE-14-003) it is claimed that a differential activity of imetelstat between samples from paediatric AML patients and healthy children is seen, with the potential for imetelstat to eradicate LSCs while sparing normal haematopoietic stem cells. Only the two lowest doses (2.5 µM and 5 µM) were tested on the healthy cells (yet, in cells from 1 of 4 healthy children, imetelstat reduced viability to a similar extent as in AML cells). The 2.5 and 5 µM concentrations were chosen based on that the cell death in leukaemia samples was observed at these concentrations.

In vivo, hepatic TA was measured as a surrogate in NOD.SCID mice (Study GS03-047, **Figure 5**). The Maximum tolerated dose (MTD) was not reached at any of the imetelstat doses tested (range 6.15-55.35 mg/kg, intraperitoneally (IP), three times a week (TIW)).

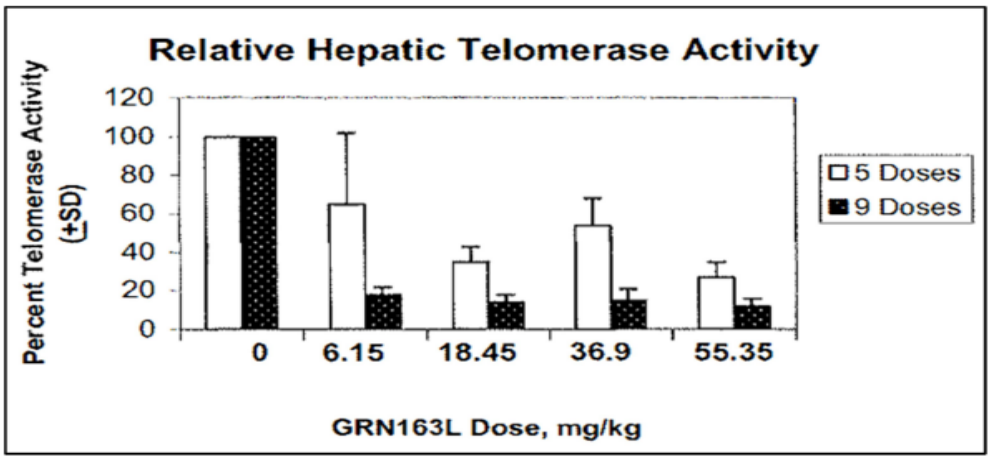


Figure 2. Effect of imetelstat on liver-associated TA. Greater inhibition of TA in liver tissue after 9 doses of imetelstat than 5 doses**.**

Single i.v. administration of imetelstat at 36.9 mg/kg in female BALB/c mice (Study GS03-034) resulted in a statistically significant inhibition of TA in the liver (**Figure 6**).

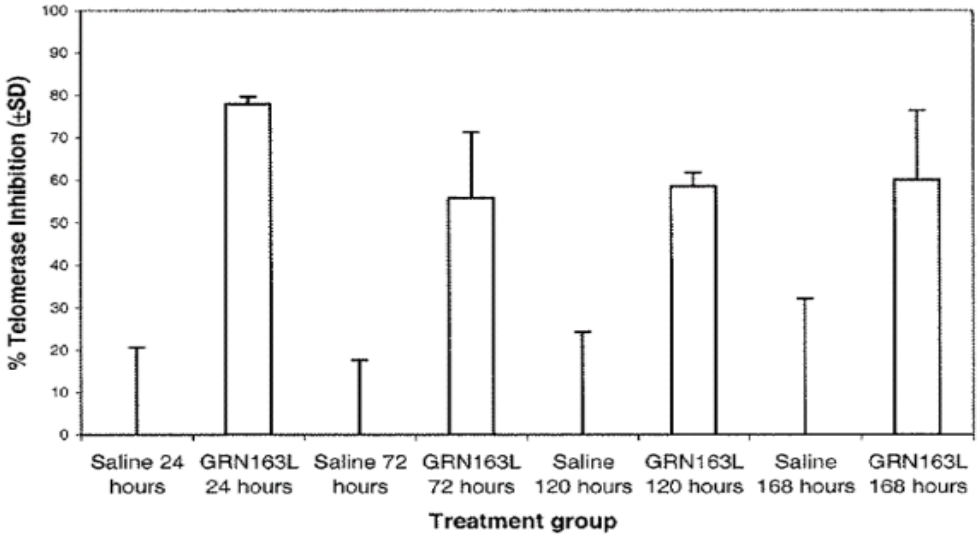


Figure 3. Effect of imetelstat on liver-associated TA. Inhibition of TA in liver tissue lasted for up to 168 hours after single dose of imetelstat (*GRN163L: imetelstat)*

Similarly, a single i.v. treatment of imetelstat at 33.7 mg/kg was well tolerated in nu/nu mice and resulted in a significant tumour (human DU145 prostate cancer cells)-associated telomerase inhibition (~50%) for up to 72 hours after treatment compared to vehicle control (Study GS03-015, data not shown).

Imetelstat administered IP at both 15 and 30 mg/kg TIW, reduced the tumour volume in nude (nu/nu) mice bearing human OVCAR-5 ovarian cancer cells (Study 0017-2009, **Figure 7**).

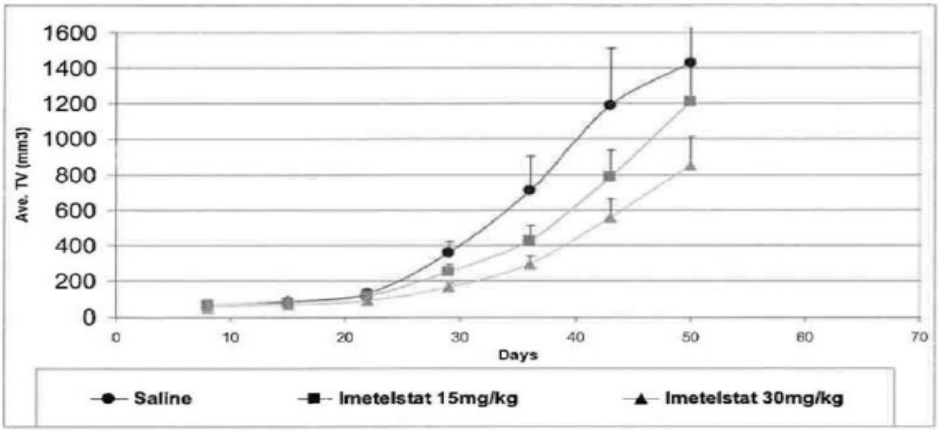


Figure 4. Effect of imetelstat on OVCAR-5 xenograft tumour volumes over time.

The effects of imetelstat alone or in combination with venetoclax (ABT-199), a specific BCL-2 inhibitor, were evaluated in SCID-beige mice bearing MOLM-13 AML xenografts (Study TR2017-009, **Figure 8**).

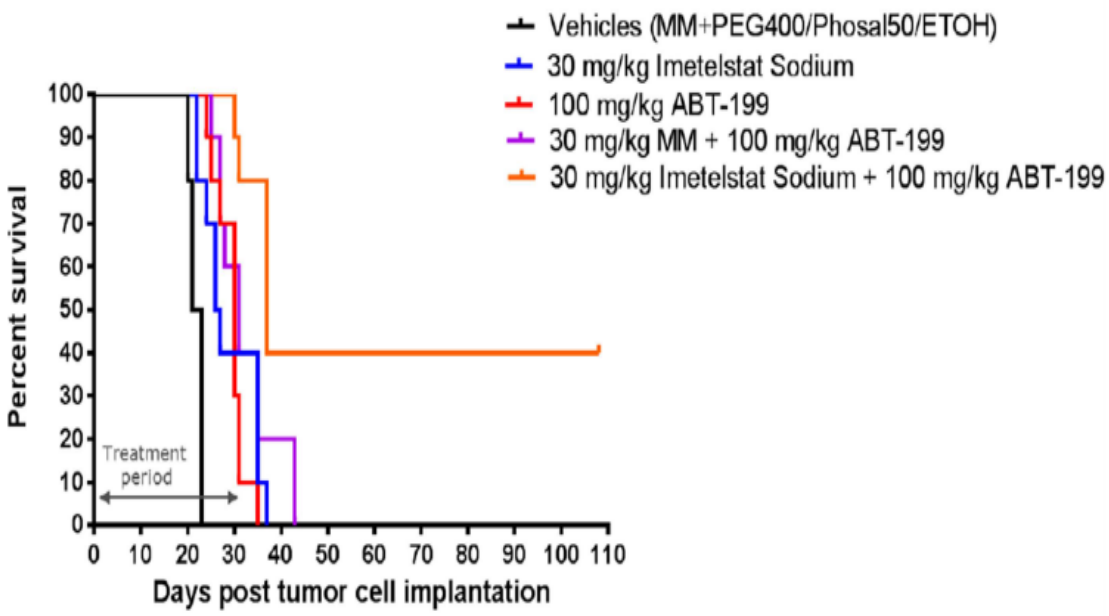
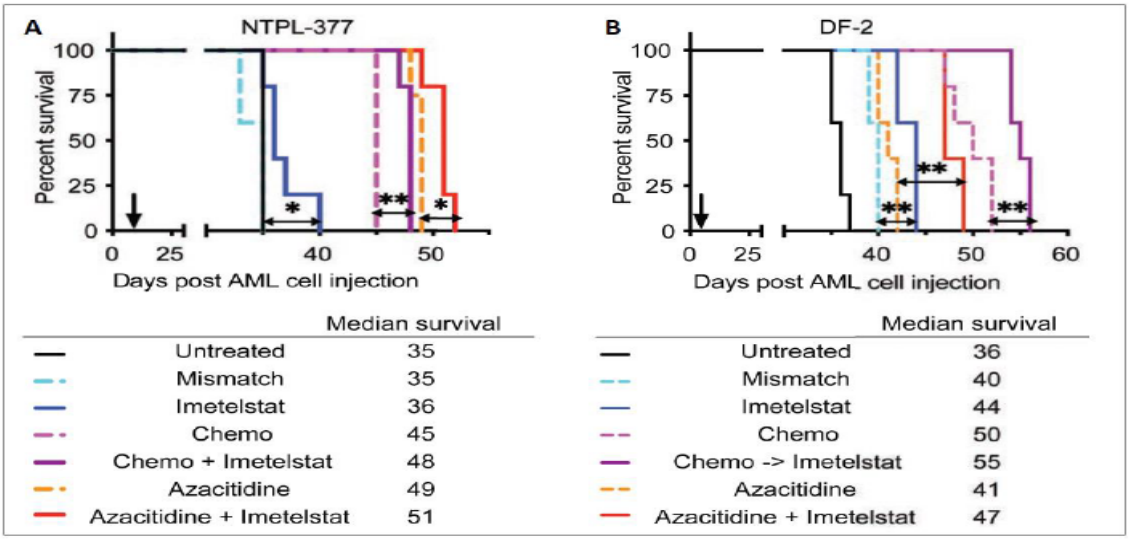


Figure 5. Effect of Imetelstat in combination with Venetoclax (ABT-199) on survival of MOLM-13 acute myeloid leukaemia xenograft.

The effect of imetelstat on the expansion and engraftment of primary paediatric AML cells in vivo in NSG-SGM3 mice, the survival of primary paediatric PDX models, and the capacity for self-renewal of imetelstat-treated engraftment in secondary recipient mice was evaluated (Study PRE-14-004, **Figure 9** and **Figure 10**).



	Median survival
Untreated	35
Mismatch	35
Imetelstat	36
Chemo	45
Chemo + Imetelstat	48
Azacitidine	49
Azacitidine + Imetelstat	51

	Median survival
Untreated	36
Mismatch	40
Imetelstat	44
Chemo	50
Chemo -> Imetelstat	55
Azacitidine	41
Azacitidine + Imetelstat	47

Figure 6. Survival curves of treatment groups with mice bearing paediatric AML patient-derived xenograft cells (NTPL-377 and DF-2).

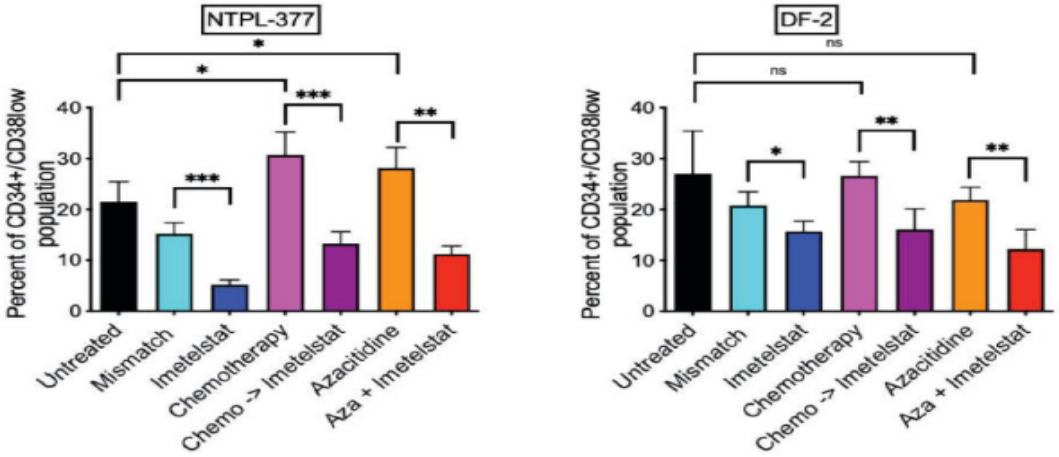


Figure 7. Effect of imetelstat on the leukaemia stem cell population *in vivo* in two patient-derived xenograft models.

The secondary transplantation of cells collected from mice treated with imetelstat showed significantly delayed engraftment in mice and improved survival ($P < .05$), confirming the effect of imetelstat to diminish the LSC population (data not shown).

In addition to the nonclinical studies to assess the pharmacodynamics of imetelstat conducted by the applicant, a wide-ranging series of studies published in the scientific literature are described and cited by the applicant to support such effects of imetelstat. Of note is the study by Steensma et al. 2021, reporting data from primary cells from patients with transfusion-dependent MDS.

These data come from the *ex vivo* study of primary cells from patients in the Phase 2 portion of the Sponsor's Phase 2/3 clinical study (MDS3001) and demonstrate that hTERT RNA expression level was reduced in peripheral blood of transfusion-dependent MDS patients who received imetelstat 7.5 mg/kg, every 4 weeks. The proportion of patients who achieved ≥50% hTERT reductions from baseline was significantly higher among patients with 8-week transfusion independence (TI) versus without 8-week TI (80% [12 of 15] vs 35% [7 of 20]) and with 24-week TI versus without 24-week TI (91% [10 of 11] vs 38% [9 of 24]), with Fisher exact test P = .016 and P = .004, respectively. The significant correlation of ≥50% reduction of hTERT from baseline with ≥ 8-week and ≥ 24-week TI may provide a link between the on-target effect of imetelstat and clinical benefit in lower risk MDS patients presenting reduction of hTERT and correlation with clinical response.

2.5.2.2. Secondary pharmacodynamic studies

In methylcellulose-based and collagen-based *in vitro* colony forming assays (Studies GRN01 and GRN05) imetelstat did not significantly inhibit erythroid or myeloid colony number (although colony morphology was compromised at 15 µM), but significantly inhibited the number of megakaryocyte colony growth at 3.75, 7.5 and 15 µM.

Imetelstat-related thrombocytopenia adverse events in clinical studies led to the hypothesis that imetelstat may promote thrombocytopenia via off-target effects on TLR signalling that has been observed with other ODN structures that contain single-stranded DNA with CpG dinucleotide motifs characteristic of bacteria and virus genomes that activate the innate immune response through TLR9 signalling. Therefore, the ability of imetelstat to interact with and stimulate TLR signalling was examined in cell-based assays (Study GRN2017T-008). Imetelstat did not stimulate signalling through any of the TLRs evaluated, except for a slight stimulation of TLR8 at higher concentrations (data not shown).

In addition to the studies submitted by the applicant on the effect of imetelstat on normal megakaryocyte progenitor cells, studies on malignant megakaryocytes described in the scientific literature are cited in the dossier. In contrast to its effects on normal megakaryopoiesis, imetelstat is claimed to have more global effects on several stages along the hierarchy of malignant megakaryopoiesis, including selectively decreasing clonogenicity, preventing MK maturation and reducing the secretion of fibrogenic factors. The potential for imetelstat to delay normal MK maturation may account for one of the potential mechanisms of imetelstat-induced, reversible thrombocytopenia in patients, in addition to the known class effect of polyanionic ODNs on haematopoiesis ascribed to immunostimulatory properties (i.e., the direct effect of cytokines on stem cell maturation) that could also lead to underproduction of platelets in the bone marrow.

Imetelstat is a thio-phosphoramidate oligonucleotide known not to activate RNase-H and likely do not degrade its RNA target. However, to assess if imetelstat has the potential for cross-hybridisation with other sequences from the human transcriptome, an *in-silico* analysis was performed. This search identified two known mRNA transcripts, ARMC9 and TAF8, with 100% and 92% sequence homology to imetelstat, respectively. ARMC9 may play role in cell cycle regulation (Huang, 2021) and TAF8 is one of the integral subunits of the general transcription factor complex TFIID, which is required for activator proteins to stimulate transcription (Papai, 2009). In addition, several predicted transcript variants possibly encoded by known genes (ZNF462, UBQLN1, PKHD1, PGGT1B, NR2C2, SEPTIN11, FILIP1L, SRSF6, RFC3, DYDC1 and SFR1) and four uncharacterised long non-coding RNA transcripts were identified to have potential cross-hybridisation sites for imetelstat.

2.5.2.3. Safety pharmacology programme

In HEK293 cells expressing hERG, imetelstat did not inhibit hERG currents up to a concentration of 50 µM (Study 007-TOX-2007 (non-GLP). Instead, there was a slight agonist effect by enhancing the hERG channel current by 6.6% at 10 µM and by 17% at 50 µM. The IC50 was not determined since the maximal effect was below 50% at the highest concentration.

The objective of the repeat study, PRE-14-002, was to examine the *in vitro* effects of imetelstat on the hERG channel current at near-physiological temperature by the CiPA assay to evaluate proarrhythmic risk under GLP conditions. Imetelstat did not inhibit hERG currents up to a concentration of 750 µg/ml (~150 µM). The hERG inhibition at 125 µg/mL (~25 µM) of imetelstat was below that produced by the negative vehicle control article, while slight increases in hERG current were observed at 250 and 750 µg/mL. The IC50 for the inhibitory effect of imetelstat on the hERG potassium current could not be calculated but was estimated to be greater than 750 µg/mL.

The effects of imetelstat on the CNS, cardiovascular and respiratory systems was evaluated in Study GS04-072. Single i.v. doses of imetelstat up to 15 mg/kg (administered by i.v. infusion over a 6- or 24-hour period) were well tolerated by Cynomolgus monkeys, with no treatment-related clinical signs or changes in mean arterial pressure, heart rate, body temperature, electrocardiographic activity, neurological condition, blood gas parameters or chemistry and haematology parameters.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies with imetelstat were submitted.

2.5.3. Pharmacokinetics

Absorption

No dedicated single-dose PK (absorption) studies have been conducted for imetelstat. Instead, one single-dose rat distribution GLP-study also included plasma concentrations and additional blood analysis was conducted in the repeat-dose toxicity mouse and cynomolgus studies and the mouse and rabbit embryo-foetal development studies. In the rat distribution study, the plasma Cmax was 17 ug/g and 72 ug/g at 1 and 5 mg/kg respectively. The plasma AUC0-∞ was 17 and 113 ug x h/mL respectively. The blood cellular fraction had an Cmax of 6.4 and 28 ug/g respectively while the AUC0-∞ was 9.4 and 50 ug x h/mL respectively. The systemic dose increase in rat was roughly dose-proportional between 1 mg/kg and 5 mg/kg in the rat plasma and blood cell fraction. The tmax, as expected for an IV-injected oligo, was reached quickly (between 0.08h and 0.25h). Additionally, in mice subcutaneously injected with OVAR 5 neoplastic cells, LC-MS/MS measurements in plasma, bone marrow and xenograft tumours found that imetelstat concentrations peaked between 2 to 4 hours.

Distribution

Imetelstat is bound to plasma proteins at >92% in all tested species (human, Sprague-Dawley rat, CD-1 mouse, and Cynomolgus with a range between 92.7% and 94.4%) in a concentration-independent manner (i.e., no difference in binding extent at 10 uM, 30 uM or 100 uM). Two male Sprague-Dawley rat distribution studies using ^{35}S-radiolabeled imetelstat provided Cmax, tmax, AUC and $t_{1/2}$ values (up to 168h post-exposure after IV bolus doses at 1 or 5 mg/kg) for the different solid organs/tissues. The distribution patterns were roughly similar between studies. The greatest distribution/uptake in the first study (using ~8 weeks old rats) was to liver, kidney, adipose tissue, bone marrow, spleen, and pituitary. In the second study (with ~7w old rats), the top organs/tissues were kidney, liver, bone marrow and spleen. Overall, the rat liver contained approximately 30% to 40%, and the kidneys contained approximately 10% of the ^{35}S-imetelstat dose.

Across studies, the Cmax and $AUC_{0\text{-}168h}$ for the liver was 8.2-9.8 and 612-824 ug x h/g respectively (1 mg/kg dose) and 26.8-44.1 ug/g and 2766-3916 ug x h/g respectively (5 mg/kg dose), for the kidneys it was 8.3-12.8 ug/g and 593-1320 ug x h/g respectively (1 mg/kg dose) and 27.1-38.0 ug/g and 2207-4087 ug x h/g respectively (5 mg/kg dose), for the bone marrow it was 6.0-6.3 ug/g and 473-627.5 ug x h/g respectively (1 mg/kg dose) and 15.47-25.1 ug/g and 1861-2705.2 ug x h/g respectively (5 mg/kg dose), and for the spleen it was 4.0-5.3 ug/g and 346-459 ug x h/g respectively (1 mg/kg dose) and 14.1-21.6 ug/g and 1459-2249 ug x h/g respectively (5 mg/kg dose). The half-lives were 50-68h (liver), 89-98h (kidney), 64-97h (bone marrow) and 58-105h (spleen).

For most tissues, concentrations of ^{35}S-imetelstat equivalents declined roughly in parallel with the terminal slope of the plasma curve, suggesting that plasma clearance is a primary determinant of exposure in most tissues. Exposure to imetelstat in the liver, kidney, bone marrow, pituitary, fat, spleen, and thyroid exceeded the plasma exposure by approximately 10-fold or more. Around, ~80% of the imetelstat in bone marrow was found within cells but in a degraded form (within 24h post-dose). Mean concentration of imetelstat equivalents was approximately 85 µg/g in bone marrow samples.

Besides the pituitary in the first study (Cmax 10.45-12.82 ug/g and AUC0-168h 480-1114 ug x h/g, but only Cmax 0.43-2.44 ug/g and $AUC_{0\text{-}168h}$ 12.8-91.5 ug x h/g in the second study), there is very little uptake in neural structures (i.e., brain with a Cmax of 0.05-0.15 ug/g and $AUC_{0\text{-}168h}$ 1-6 ug x h/g in the first study and Cmax 0.04-0.19 ug/g and $AUC_{0\text{-}168h}$ 3-10.5 ug x h/g in the second study). The distribution to the testes and epididymis was relatively low (compared to the uptake in other organs) at Cmax 0.21-2.51 ug/g and $AUC_{0\text{-}168h}$ 17-261.4 ug x h/g across studies.

Metabolism

No specific metabolite studies have been conducted (*in vitro* or *in vivo*) and the information from radiolabel-based elimination studies in rats indicate mainly that intact imetelstat degrades into shorter oligo-metabolites within 24 h (based on bone marrow, plasma, and urine samples).

Elimination/excretion

Based on excretion studies in male Sprague-Dawley rats, urine was the primary route of elimination following IV exposure to ^{35}S-imetelstat. For 168h post-dose, and across two studies, roughly 61.7-81.6% of the radioactivity was in the urine and 11.6-20.8% in the faeces. No intact imetelstat was detected in the urine by Radio/UV-HPLC-MS.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

GS04 059 (non-GLP)

The objective of the study was to evaluate the acute toxicity of GRN163L in a dose range-finding study in nude mice. Treatment groups included saline control and GRN163L administered once intravenously (IV) at doses ranging from 36.9 to 1230mg/kg. Clinical observations and body weights were determined in-life. At termination, blood was collected for haematology and coagulation analyses, a gross necropsy was performed, and tissue samples were collected for histopathology evaluations.

There were no significant changes in body weight or haematology parameters noted for any of the treatment groups. Coagulation assessment was not done. Dose-related acute mortality occurred in the 221.4, 664.2, and 1230 mg/kg treatment groups. In the 1230 mg/kg treatment group, all animals died within 4 hours of treatment. Death was due to systemic haemorrhage. Gross necropsy showed evidence of significant haemorrhage in lung (6/6F, 2/6M), intestine (6/6F, 2/6M), heart (3/6F), subdural brain (6/6F, 2/6M). Additionally, mottling/discoloration of heart, liver, spleen, and kidneys was seen sporadically in this treatment group, and may also have been related to haemorrhage.

GS04062 (GLP)

The objective of this study was to determine the maximum tolerated (or feasible) dose of imetelstat when administered as a single dose by intravenous (IV) infusion to cynomolgus monkeys.

Administration of a single-dose of GRN163L at dose levels of 80 or 130 mg/kg (administered by IV infusion over a 2-hour period) resulted in early death. Two animals (80 mg/kg female and 130 mg/kg male) were found dead approximately 8 hours after the end of infusion and two animals were euthanized in moribund condition (80 mg/kg male approximately 8 hours after the end of infusion and 130 mg/kg female approximately 20 hours after the end of infusion). The moribundity and death were due to hypovolemic shock resulting from extensive multifocal haemorrhage into skeletal and cardiac muscle.

GS04069 (GLP)

The objective of this study was to determine the maximum tolerated (or feasible) dose of imetelstat when administered as single doses by intravenous (IV) infusion to cynomolgus monkeys.

IV infusion of imetelstat was well tolerated in monkeys at 5 mg/kg when infused over 0.5 or 2 hours, and the only effect at that dose level was a moderate and transient increase in aPTT without correlating anatomic pathology findings, which returned to pre-dose levels by18 hours following the end of infusion. The complement system was not activated at the 5-mg/kg dose level. There were no clinical signs or effects on physiologic parameters (blood pressure, heart rate, respiratory rate, and body temperature) across all doses and infusion durations.

A blood-level-related effect on the intrinsic coagulation pathway (i.e., characteristic inhibition, reflected by aPTT prolongation) was observed in this study, but this inhibition did not translate into any haemorrhage in internal organs or any life-threatening sequelae.

2.5.4.2. Repeat dose toxicity

Non-pivotal studies were conducted in mice (GR05-031 and GR05-030), Rat/ Sprague Dawley (GS03-030) and Cynomolgus monkeys (GS03-044 and GS03-046).

In both the mouse and rat studies, the highest dose of imetelstat (45 mg/kg) was associated with haemorrhage and deaths in male animals. Haematological changes, including increased red blood cell consumption and regeneration, were observed in both mouse and rat studies at higher doses of imetelstat.

In monkeys increased basophilic granules in renal tubular epithelial cells and hepatic Kupffer cells at 15 mg/kg was shown. Furthermore, in the cynomolgus monkey study, a decrease in circulating red blood cell mass was observed at 15 mg/kg of imetelstat.

Pivotal studies

GS04-070 was an eight-week Intravenous Toxicity Study of GRN163L (5-30 mg/kg, twice a week) in Mice with a Four-week Recovery Period. In the 30 mg/kg, 14 male mice were found dead due to apparent unexpected toxicity between Study Dates 1-6. In the same dose group, 2 female mice were found dead on Study Day 29 and Study Day 37 respectively. One male mouse on the 15 mg/kg died on Study Day 50. The exact cause of mortality remained unclear based on clinical or anatomic pathology findings.

At the intermediate dose level of 15 mg/kg/injection, the test article-related effects were limited, including a modest reduction in lymphocyte counts, marginal fluctuations in serum chemistry parameters in males, increased extramedullary haematopoiesis in the spleen, heightened severity of procedure-related injection site haemorrhage, and minor cardiac myocyte mineralization in a single male animal. Crucially, all these effects were reversible during the recovery phase, underscoring their transient nature and potential for recovery.

There were no observable impacts on body weight, feed consumption, or other parameters at the 15 mg/kg/injection dose level, thus, the 15 mg/kg/injection dosage, characterized by benign and reversible findings, was identified as a no-adverse-effect level (NOAEL).

003-TOX-2008 was a 6-month intravenous toxicity study in mice with an 8-week recovery period. 16 early deaths or sacrifices were observed during the study period. These early deaths are evenly distributed along all exposure groups. Systemically, mild haematological alterations were observed, such as increased total white blood cell counts in males at ≥ 5 mg/kg, changes in globulin/albumin ratios in females at ≥ 15 mg/kg, and a mild increase in AST levels in females at 20 mg/kg. Concurrently, mild decreases in red blood cell parameters occurred at ≥ 15 mg/kg in both sexes, aligning with microscopic spleen haematopoiesis at 20 mg/kg and increased spleen weights across all dose levels.

Organ weight changes included elevated liver weights at ≥ 15 mg/kg in both sexes and increased kidney weights in males at 20 mg/kg. Microscopic liver findings indicated augmented mixed inflammatory foci, hyperplasia of Kupffer cells, and/or histiocytic aggregates containing brown and/or blue pigment. These systemic effects exhibited evidence of recovery after an 8-week treatment-free period.

Local tolerance assessment focused on the injection site, revealing reactions such as tail discoloration (commonly black) at 20 mg/kg, aligning with microscopic evidence of necrosis, inflammation, and vascular/perivascular fibrosis. These injection site pathologies were attributed to extravasation of imetelstat from the small tail veins, a common occurrence in rodent studies. Thrombosis and infarcts in various tissues were considered secondary to the reaction at the injection site, further emphasizing the localized impact of imetelstat administration.

The suggested NOAEL for systemic toxicity is 20 mg/kg in this study.

GS04-071 was an 8-week toxicity study of imetelstat administered weekly by intravenous infusion to Cynomolgus Monkeys, with a 4-week recovery period.

No unscheduled mortality or adverse signs were observed, except transient facial reddening.

Clinical pathology changes, including prolonged APTT and complement pathway activation, were noted, with greater effects at 15 mg/kg than in 20 mg/kg. As the infusion rate was higher in 15 mg/kg group compared to 20 mg/kg group, it can be assumed that Cmax is more relevant than AUC for effects on coagulation. No adverse effects were seen om haematological parameters.

Changes in plasma urea nitrogen and creatinine, indicating effects on renal function, were observed following 20 mg/kg. Mesangial thickening in renal glomeruli was observed in males at 10 mg/kg (minimal grade) and in both sexes at ≥15 mg/kg (mild grade). Additionally, degenerative/inflammatory changes were noted in the kidney, ureter, and/or urinary bladder of individual animals receiving 15 mg/kg over 6 hours or 20 mg/kg over 24 hours. The renal changes at≥15 mg/kg were considered adverse due to their severity and occurrence across sexes. Furthermore, one female at 20 mg/kg (infused over 24 hours) experienced marked glomerulonephritis.

Changes in serum albumin and globulin levels were noted in 15 and 20 mg/kg groups was noted. Elevated hepatic multifocal mononuclear cell infiltration across all groups was shown, without a clear dose-dependency. Furthermore, increased vacuolation of hepatic Ito cells was noted in some animals, particularly in females, and one male from in 20 mg/kg group.

Brain mononuclear cell infiltration was observed at doses ≥10 mg/kg, resolving by the end of the recovery period in the 10 mg/kg group but persisting in the group given 20 mg/kg.

Histopathology changes noted at terminal sacrifice generally persisted in brain (only at 20 mg/kg), kidney and tissues surrounding the intravenous catheter tip.

The suggested NOAEL in this study is 10mg/kg.

002-TOX-2008 was a 9-month toxicity study of GRN163L in Cynomolgus Monkeys followed by a 14-week recovery period.

In the low-dose group (5 mg/kg/week), there were moderate reductions in red blood cell mass, alterations in serum albumin and globulin concentrations, acute changes in clotting factors, and microscopic changes in the liver and brain. Additionally, an enlarged spleen was observed.

In the 10 mg/kg/week group, effects observed in the low-dose group were present; finding also revealed that there was a moderate decrease in platelet counts, signs of complement activation, histopathologic changes in the kidneys (renal tubular haemorrhage and protein casts), and inflammatory changes in the arteries.

At the high dose (15 mg/kg/week), effects seen in lower doses were generally magnified. Also, an increased incidence of unformed stools, a slight decrease in body weight, acute changes in prothrombin time, discoloration of kidneys (glomerulosclerosis) and liver, and endometrial atrophy in females.

Test article-related changes that persisted through the end of the recovery period in high-dose (15 mg/kg/week) animals included increased kidney weights, decreased indices of red cell mass, enlarged spleen, discoloration of the liver and kidney, and microscopic changes in the kidneys, liver, and brain. NB: 5 and 10 mg/kg groups were not evaluated during recovery.

The haematological data indicate a dose-dependent reduction in red blood cells, haemoglobin, and haematocrit, affecting males in all dosage groups and primarily females in the 15 mg/kg group. Platelet counts are lower across treatment groups. Male monkeys in the 15 mg/kg group exhibit lower myeloid:erythroid ratios, and females in all imetelstat groups show moderately lower ratios, with incomplete recovery noted in females. The observed changes in myeloid:erythroid ratios and red cell mass parameters may be indicative of a compensatory response to anaemia.

Female monkeys receiving 15 mg/kg imetelstat weekly showed uterine endometrial atrophy. However, after a 14-week recovery, this finding was absent, suggesting complete reversibility.

No NOAEL could be determined. Instead, a highest non-severely toxic dose (HNSTD) of 15 mg/kg was established, as no mortalities or life-threatening were observed at this dose.

The recommended clinical dose of imetelstat is 7.5 mg/kg resulting in a Cmax value of 89,5 ug/ml and an AUC0-24 mean value of 403 h*ug/ml. A comparison of exposure in non-clinical studies with imetelstat administration at the NOAEL (or HNSTD) versus the clinical exposure is presented in **Table 5**.

Table 1. Exposure margins at NOAEL/HNSTD in non-clinical studies to human exposures.

Study ID	**NOAEL/ HNSTD**	**Dose (mg/kg)**	**Cmaxc (µg/mL)**		**Exposure Ratios (Cmax in Animals/Cmax in Humans)**		**AUC0-∞ / AUC0-last b (µg.h/mL)**		**Exposure Ratios (AUC in Animals/AUC in Humans)**	
			♂	♀	♂	♀	♂	♀	♂	♀
Repeat-dose toxicity										
Mouse										
6-month Chronic Toxicity	NOAEL	20	250.3	311.1	2.8x	3.5x	960.9	925.5	2.4x	2.3x
Monkey										
9-month Chronic Toxicity	HNSTD	15	611.9	528.3	6.8x	5.9x	11339.4	8056.2	28.1x	20.0x
Embryo-Fetal Toxicity										
Mouse										
Maternal Toxicity	NOAEL	30		707.7		7.9x		1374		3.4x
EFD Toxicity	NOAEL	15		524.8		5.9x		622.27		1.5x
Rabbit										
Maternal Toxicity	NOAEL	5		124.2		1.4x		412.4		1.0x
EFD Toxicity	NOAEL	5		124.2		1.4x		412.4		1.0x

2.5.4.3. Genotoxicity

The genotoxicity potential was evaluated in a standard battery of *in vitro* and *in vivo* tests (**Table 6**).

Table 2. Summary of genotoxicity studies performed with imetelstat.

Type of test/study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results Positive/negative/equivocal**
Gene mutations in bacteria Study **GS04-068** GLP	Strains: -*Salmonella typhimurium* TA98, TA100, TA1535, and TA1537. -*Escherichia coli* WP2uvrA	*Mutagenicity*: 100, 333, 1000, 3330, and 5000 µg / plate *Dose range finding*: 6.67 to 5000 µg / plate +/- S9	Dose range-finding study conducted with doses ranging from 6.67 to 5000 µg per plate - No cytotoxicity observed in the range finding assay Mutagenicity assay conducted with doses of 100, 333, 1000, 3330, and 5000 µg per plate - No positive increases in revertants per plate observed in both mutagenicity trials (B1 and C1). **Negative**
Chromosomal aberrations in vitro Study **GS04-066** GLP	Human peripheral blood lymphocytes	Incubation imetelstat up to 5000 µg/ml +/- S9	A reduction in mitotic indices at various concentrations in both activation conditions. Chromosomal aberrations analysed, with no significant increase observed. Cytotoxic Effects: None Genotoxic Effects: None **Negative**
Chromosomal aberrations in vivo Study **GS04-067** GLP	Mouse, micronuclei in bone marrow	27.5, 55 and 110 mg/kg.	<u>Toxic effect at 110 mg/kg:</u> Caused mortality and clinical signs of toxicity including rough haircoat, hypoactivity, squinted eyes and irregular respiration. <u>Micronucleus frequencies:</u> Significant increase in microneucleus frequencies were observed in male mice treated with 110 mg/kg. <u>Cytotoxicity:</u> Significant decrease in PCE/NCE ratio was observed. Cytotoxic Effects: [Bone marrow] Yes (at 110 mg/kg) Genotoxic Effects: None **Negative**

2.5.4.4. Carcinogenicity

No carcinogenicity studies were conducted with imetelstat.

According to the applicant, carcinogenicity studies are not required to support marketing for therapeutics intended to treat patients with advanced cancer, as stated in the ICH S9 (ICH S9 2009) and ICH S1A (ICH S1A 1995) guidelines.

2.5.4.5. Reproductive and developmental toxicity

Non-pivotal, dose range finding studies were conducted in Crl:CD1 mice (Study 004-TOX-2008) and New Zealand White Hra rabbits (Study 005-TOX-2008).

In the mouse DRF study, imetelstat administration at various doses did not result in adverse clinical effects or changes in gestation parameters, except for increased post implantation loss at 30 mg/kg/dose, mainly due to early resorptions. No foetal external malformations were observed. Consequently, doses of 0, 5, 15, and 30 mg/kg/dose were chosen for the definitive mouse developmental toxicity study.

Similarly, in the rabbit study, imetelstat did not cause test article-related clinical effects, but there was a slight decrease in body weight change and food consumption initially. An increase in post implantation loss at 30 mg/kg/dose, primarily due to early resorptions, was noted. No foetal malformations were observed, leading to the selection of doses 0, 5, 15, and 30 mg/kg/dose for the definitive developmental toxicity study in rabbits.

Pivotal studies

Embryo-fetal Developmental Toxicity Study in Mice (Study 006-TOX-2008)

Pregnant mice were administered imetelstat at doses of 0, 5, 15, and 30 mg/kg/dose on gestational days 6, 9, and 12 through intravenous bolus injection. The study found no evidence of maternal toxicity, as indicated by the absence of adverse clinical findings, and no detrimental effects on maternal body weight or food consumption.

During the study, three animals in the main study phase and one control animal in the toxicokinetic (TK) group died during dosing. The cause of death was inconclusive as necroscopy did not reveal any treatment related cause of death. Maternal necropsy evaluations in general did not reveal any test article-related findings. No adverse effects on body weight or food consumption were discerned in the treatment groups.

Notably, there was a statistically significant decrease in post implantation loss (i.e., post-implantation increase compared to controls) and decrease in early resorptions in treated females compared to controls during uterine examination which was considered to be non-adverse. The diminished post-implantation loss, likely influenced by reduced early resorptions, thus suggests improved reproductive outcomes in the exposed group compared to the control group. Contrastingly, in the mouse DRF study (004-TOX-2008), an opposite trend was noted; there was an increased incidence of post-implantation losses in exposure groups, possibly driven by increased early resorption. The fact that the relationship is reversed for both parameters (i.e., early resorption and post-implantation loss) underscores a notable difference between these two studies. Furthermore, results from rabbits (see 007-TOX-2008 below) align with the DRF in mice, adding to the perplexity in the pivotal mouse EFD study.

Other parameters, including fetal evaluations, revealed no statistically significant effects on fetal sex ratio, fetal weight, or malformations in the treatment groups compared to controls.

An intravenous developmental toxicity study in rabbits (Study 007-TOX-2008)

Administration of imetelstat by intravenous infusion (over 2 hours) to pregnant rabbits at dose levels of 0, 5, 15 and 30 mg/kg/dose on GD 6 and 13, produced maternal toxicity particularly at 30

mg/kg/dose. At this dose level, this was evidenced by significant body weight and food consumption effects, and one female that was found dead on GD 14. At 15 mg/kg/dose there were slight body weight changes observed during the dosing period and included one female that aborted on GD 22.

A clinical observation of red material in the pan/bedding was noted at 30 mg/kg/dose in six does, and in one doe, each, at 5 and 15 mg/kg/dose. The observation of red material was considered adverse given that it was correlated with an increase in the incidence of rabbits with early resorptions, which likely caused this finding. As mentioned, females at 30 mg/kg/dose had statistically significant increase in the incidence of early resorptions, which correlated with the increased rate of post implantation loss and a decreased mean uterine weight at this dose level. There were no other statistically significant changes in the uterine parameters at the other treatment levels, as compared to the control animals. Mean foetal body weights and foetal sex ratios were comparable among the groups.

In this study, a dose-related increase in mean % post-implantation loss was observed; 8.91%, 9.70% and 28.21% at 5, 15 and 30 mg/kg, respectively, to be compared with 2.79% in the control group.

The examination of foetal development did not show significant changes in malformations at the tested treatment levels. However, there was a noticeable increase in malformations in litters at certain doses related to skeletal alterations. Number of foetuses with fused sternebrae, categorized as malformations, are noted at the following incidence: control: 1.6%; 5 mg/kg: 1.1%; 15 mg/kg: 1.7% and 30 mg/kg: 8%.

2.5.4.6. Toxicokinetic data

Toxicokinetic data are described in the pivotal repeat toxicity and reproductive and developmental toxicity studies.

2.5.4.7. Local tolerance

No dedicated local tolerance studies with imetelstat have been submitted. Local tolerance of intravenously administered imetelstat was evaluated in the mouse, rat, and monkey repeat-dose toxicity studies.

2.5.4.8. Other toxicity studies

Immunotoxicity

A systematic assessment of the immunotoxicity potential of imetelstat in the 6-month mouse and 9-month monkey chronic toxicity studies was conducted. No adverse effects on lymphatic organs (spleen, lymph nodes, thymus) suggestive of an immunotoxic response to imetelstat treatment were observed. Additionally, there was no evidence of an immune suppression response, including no increased incidence of opportunistic infections due to effects on host resistance.

In an exploratory in vitro screening study to evaluate the potential of imetelstat to activate complement in normal human serum (004-TOX-2007) no clear effects based on haemolytic activity, chemotaxis and Bb split product formation were shown for imetelstat. A small reduction of haemolysis was shown both in water and in Hank's balanced salt solution (HBSS) for the highest tested concentration 150ug/ml (15-19% reduction).

Effects on Bb showed an inverse dose dependency for 163, 833, and 878 on Bb levels. 163L exhibited consistently higher Bb levels. C5a-dependent chemotactic activity was similar to buffer-treated NHS, less than ZAS control.

Phototoxicity

The cytotoxicity and phototoxicity of the test compound to 3T3 cells (in the presence or absence of UVA light) is assessed by Neutral Red Uptake (Study MB 10-19402.30). The method involved preincubating cells with different concentrations of the test article, exposing one set to solar-simulated light and keeping the other in the dark, followed by assessing cell viability. The results, including EC50 values and Photo-Irritant Factor (PIF), were calculated in both the range-finding screen and the definitive test.

Imetelstat demonstrated little potential for phototoxicity as it does not show appreciable absorption of ultraviolet light at wavelengths between 290–400 nm (within the range of natural sunlight).

Imetelstat Product Related Impurities/Qualification

The qualified levels of imetelstat specified impurities and related safety margins in relation to the proposed specification limits, were determined based on evaluation of the imetelstat lots used in the chronic toxicology studies.

2.5.5. Ecotoxicity/environmental risk assessment

Table 3. ***Summary of main study results***

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	>-2.30 at pH 5.0, 7.0, and 9.0	Potential PBT N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0005	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N

2.5.6. Discussion on non-clinical aspects

Pharmacology

According to published data, imetelstat inhibits telomerase in cell-free assays with IC50=7.8 nM, and in various tumour cell lines with IC50 values ranging from 0.15 to 1.4 µM. Imetelstat is a direct competitive inhibitor of human telomerase by binding to the template region of its RNA component (melting temperature 66°C).

The template region of the hTR RNA is well conserved across a broad range of animal species including those used in the toxicity studies. The 13 nucleotides of imetelstat are 100% complimentary to the RNA component of human and monkey telomerase whereas only 9/13 imetelstat nucleotides are complementary to mouse telomerase and 11/13 imetelstat nucleotides are complimentary to the telomerase of rat and rabbit. Despite the mismatches, IC50 values are similar in tumour cell lines from all tested species, supporting their relevance for toxicology studies.

No specific proof-of concept for the proposed indication (MDS) is presented due to lack of MDS-specific cell lines and xenograft models, but non-clinical data from models of other myeloid malignancies

originating from malignant HSCs and HPCs indicate that inhibition of telomerase by imetelstat leads to reduction of telomere length, inhibition of malignant stem and progenitor cell proliferation and induction of apoptotic cell death.

Effects of imetelstat on non-canonical functions of telomerase, such as regulation of non-telomeric DNA damage responses, promotion of cell growth and proliferation, acceleration of cell cycle kinetics, and control of mitochondrial integrity following oxidative stress, may also contribute to its anti-tumour activity. The relative contribution of these mechanisms in the current indication is unknown.

In the submitted studies, effect of imetelstat is demonstrated in various cancer cell lines alone or in combination with a number of standard-of-care agents for haematologic malignancies. Imetelstat showed limited, effect on cancer cell viability in many of the submitted *in vitro*/*ex vivo* studies likely because these studies were not designed to detect an effect of inhibition of telomere-maintenance (i.e., full telomerase inhibition would still require multiple cell divisions before tumour cells would approach telomere crisis. *In vivo*, tumour growth inhibition and prolonged survival were demonstrated in xenograft mice models using cancer cell lines (ovarian cancer or AML cell lines) and patient-derived cancer cells (paediatric AML). Imetelstat treatment for 4-6 weeks at doses 15 to 30 mg/kg IP TIW resulted in reduction in tumour volumes and increase of survival in multiple xenograft cancer models.

In addition to haematopoietic progenitor cells, telomerase is known to be expressed also in other normal (non-cancer) cells, e.g. dynamically in the endometrium during the menstrual cycle, in a subset of hepatocytes, in gastrointestinal epithelia, and in somatic stem- and progenitor cells. It is argued that the generally high expression of telomerase in malignant cells, compared with the expression in somatic cells with proliferative capacity, makes these more sensitive to imetelstat. No findings in the toxicology studies (except for thinning of the endometrial wall in monkeys) obviously related to inhibition of telomerase in normal cells were made, and clinical data showed no concern for GI AEs. Liver findings observed in the non-clinical chronic toxicity studies, and concerns for hepatotoxicity in the clinical studies, may be reflective of known oligonucleotide class effects.

The applicant has performed an in-silico analysis comparing the imetelstat sequence with the human transcriptome and found complementarity with two known human transcripts (ARMC9 and TAF8, with 100% and 92% homology, respectively) four uncharacterized long non-coding RNA transcripts, and several predicted transcript variants possibly encoded by known genes. Hybridization of imetelstat with these targets may occur, and an RNase-H-independent effect of such off-target interaction cannot be ruled out with the information provided (i.e. interference with RNA processing, transport, or steric blockage of the translational machinery). However, none of the findings in the nonclinical toxicity or clinical safety studies of imetelstat are obviously related to functional consequences that would be expected from off-target effects, based on a literature-based risk analysis of the identified transcripts. Importantly though, many of the identified transcripts were not covered in the nonclinical toxicology studies due to lack of sequence homology in the toxicology species.

Pharmacokinetics

No dedicated metabolism studies were conducted with imetelstat. The rat data indicates that imetelstat is rapidly degraded (including in the bone marrow) but the resulting degradation metabolites have not been identified (e.g., no identification of N-1, N-2 etc. metabolites has been provided by the applicant). As such, no information is available about the functional properties (pharmacological or toxicological) about these metabolites. While one can suspect that imetelstat is similar to other oligos in its degradation profile and that there are no particular species-specific differences in this regard, it has its own unique chemical composition, and direct comparisons are not possible. As a consequence, the non-clinical data cannot inform the clinical situation beyond indicating that imetelstat is quickly distributed to the different solid organs/tissues and also relatively rapidly degraded into unknown metabolites (within 4-12h).

The rat distribution data seems to correlate with the target organs identified in the toxicity studies (e.g., liver, kidney, spleen, bone marrow). Among the high imetelstat uptake organs, liver and spleen demonstrate some weight changes (increased organ weight) and signs of extracellular extramedullary haematopoiesis and some other histological alterations in a different rodent species (mice). Only male rats were used for the distribution assessments, resulting in a lack of female organ data. It can be noted that cynomolgus manifested uterine toxicity (atrophy) but there is no guarantee that female rodent distribution studies would provide any insight for those observations.

No immunogenicity (e.g., anti-drug antibody) assessment has been conducted. As the extrapolation value of such immunological responses across species (i.e., to humans) is uncertain, the absence is acceptable.

Toxicology

In 6-month mouse and 9-month monkey studies, dose related increases in liver and kidney weights were observed. Microscopic analysis showed mild to moderate liver changes (inflammatory cell foci, increases in Kupffer cells, pigment deposition, telangiectasis) and kidney changes (mesangial thickening, glomerulonephritis/sclerosis, interstitial deposition, renal tubular haemorrhage, protein casts). These changes were fully recovered or reduced in severity after the 8 to 14-week treatment free period. There were no significant alterations in hepatic or kidney function parameters. In these studies, the no observed adverse effect level (NOAEL) in mice and highest non severely toxic dose (HNSTD) in monkeys were identified as the highest doses administered, which produced exposures that were up to 2.4 and 28.1 times, respectively, the human exposure at the recommended clinical dose. With regard to the clinical relevance of the renal findings, the clinical dosing regimen is less frequent than in the animal studies (once per 4w compared to once per week) and in the safety data from the Phase 3 Study (MDS3001), no increased risk for kidney injury was seen in subjects treated with imetelstat as compared to placebo.

The observed toxicity of imetelstat generally aligns with known class-effects associated with the drug's backbone, as documented in previous studies (Frazier 2015, Henry 2008, Henry 1997a, Henry 1997b). This toxicity encompasses impacts on hemopoiesis (anaemia and thrombocytopenia), as well as liver and kidney-related issues indicative of inflammatory responses. Furthermore, erythroid hyperplasia in the bone marrow at and lower myeloid:erythroid ratios is indicative of ineffective erythropoiesis.

Imetelstat was not mutagenic in a bacterial mutagenicity assay (Ames test) or clastogenic in an in vitro chromosomal aberration assay (using cultured human peripheral blood lymphocytes) or in a standard mouse in vivo micronucleus assay.

Imetelstat has not been evaluated in dedicated rodent carcinogenicity studies. The applicant justified the lack of such studies by referring to ICH S9, ICH S1A. In addition, no signs indicating carcinogenesis in the general toxicity studies or clinical studies were observed. Literature reports, with knock-out models of telomerase also do not indicate a carcinogenic potential. The long-terms risk for carcinogenesis however remains unknown. Carcinogenicity studies will be generated for imetelstat in the future (i a life-time rat study planned to be submitted in 2031) and the CHMP recommended that these studies should be submitted post-approval as they can provide extra insights into the toxicological profile of this novel drug class.

Uterine endometrial atrophy was observed in monkeys administered 14.1 mg/kg once weekly for 9 months, at a mean exposure (based on AUC) that is approximately 20.0 times the human exposure at the recommended clinical dose. This effect was reversible following a 14-week recovery period. No gross or histological changes for the male reproductive tissues were observed at any dose tested in chronic repeat dose toxicity studies (up to 18.8 mg/kg in mice and 14.1 mg/kg in monkeys), with mean exposures (based on AUC) that are 2.4 times (mice) and 28.1 times (monkeys) the human

exposure at the recommended clinical dose. No information on imetelstat distribution to the uterus have been presented, as female rats were excluded from the distribution study. Prescribers are informed in the SmPC that imetelstat may impair fertility in females of reproductive potential.

The EFD toxicity studies were conducted in mice and rabbits. Imetelstat was not teratogenic, and there was no evidence of any foetal malformations in mice. Non-significant increases in fused sternebrae were noted at 28.2 mg/kg in rabbits. In mice and rabbits, embryo-lethality was noted as increased post-implantation loss at 28.2 mg/kg (a maternally toxic dose in rabbits) due to an increase in early resorptions, resulting in higher incidence of litter loss at this dose level that correlated to a decrease in litter size and viable foetuses. No significant increase in post-implantation loss was observed at exposures (based on AUC) up to 1.5-times (mice) or 13.0-times (rabbits) the human exposure at the recommended clinical dose. The significance of these effects in humans is unknown.

For mice the NOAEL was F0 28.2 mg/kg and F1 28,2 mg/kg, and for rabbit the suggested NOAELs are F0 4.7 mg/kg and F1 4.7 mg/kg. The pregnancy status of females of reproductive potential should be verified before starting treatment with imetelstat as its use is not recommended during pregnancy. Women of childbearing potential should be advised to use effective contraception during treatment with imetelstat and for at least 1 week after the last dose.

No PPND study has been submitted. This was considered acceptable based on the proposed indication which is primarily relevant for older people and that imetelstat has little or no oral bioavailability thereby removing the likelihood of postnatal exposure via lactation.

Imetelstat at high concentrations activated the alternate complement pathway. There was no other indication of adverse effects, on lymphatic organs such as the spleen, lymph nodes, and thymus relevant for immunotoxicity. There was no imetelstat-related haemolytic activity *in vitro*.

The use of NOAELs from toxicity studies are generally accepted, and based on extrapolation to humans, it is agreed that impurities are qualified in general toxicity studies.

The Balb/c 3T3 Neutral Red Uptake Phototoxicity Assay in mouse fibroblast cells suggested no phototoxic potential for imetelstat.

The finished product may contain residual solvents as impurities. Appropriate specification limits have been set in line with relevant guidelines and considering results of repeat-dose toxicity studies.

ERA

Experimental data on the Log Dow of imetelstat indicates (as imetelstat is not soluble in n-octanol) that the log Dow is <-2.3. As such, an PBT assessment is not necessary.

Using the adjusted Fpen and the equation provided in EMEA/CHMP/SWP/4447/00 corr 2 the PEC in surface water (PEC_{SW}) was calculated to be 0.0005 µg/L. This value is below the action limit of 0.01 µg/L and therefore Phase II analyses are not triggered.

Therefore, imetelstat is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

From a non-clinical point of view imetelstat has been adequately characterised and is recommended for marketing authorisation.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
CP14A 004	**Primary**: To determine the safety and the maximum tolerated dose of imetelstat when administered to patients with relapsed or refractory multiple myeloma. **Secondary**: To characterize the PK profile of imetelstat when administered at the indicated dose levels in this patient population.	Phase I open-label, multicentre, sequential dose cohort, dose-escalation study.	Imetelstat: **Enrolled**: N = 20 **Treated**: 3.2 mg/kg n=3, 4.8 mg/kg n=4, 6.0 mg/kg n=7, 7.2 mg/kg n=5 6.0 mg/kg n=1	Relapsed or refractory multiple myeloma	6 weeks for the first 2 cycles, then 3 weeks for each additional cycle, and 4 weeks for follow-up. Additional cycles were administered until disease progression or toxicity necessitated discontinuation.
CP04-151	**Primary**: To determine the safety, tolerability, DLTs, and MTD or R2PD of imetelstat in patients with R/R CLL (B-cell phenotype). **Secondary**: To characterize the PK profile of imetelstat; to evaluate the utility of potential PD markers of imetelstat action and to estimate, if feasible, the magnitude and duration of telomerase inhibition and to obtain preliminary information on the antineoplastic activity of imetelstat.	Phase 1, sequential dose cohort, dose-escalation study to determine the safety, tolerability, and MTD of imetelstat.	Imetelstat: **Enrolled**: N = 28 **Treated**: 6-hour infusions: 20 mg/m^2: n=3, 40 mg/m^2: n=3, 80 mg/m^2: n=3, 160 mg/m^2: n=6, 240 mg/m^2: n=1 2-hour infusions: 160 mg/m^2: n=3, 200 mg/m^2 4 wk cycle: n=8 and 200 mg/m^2 3 wk cycle: n=1.	Relapsed or refractory chronic lymphoproliferative disease (with related biology or similar clinical pattern to B cell chronic lymphocytic leukaemia [B- CLL])	Until disease progression or unacceptable toxicity.

CP05-101	**Primary**: To determine the safety, tolerability, DLTs, and MTD of imetelstat. **Secondary**: To characterize the PK profile of imetelstat and to obtain preliminary information on the antineoplastic activity of imetelstat.	Phase 1 open-label, multicentre, sequential dose cohort, dose-escalation study	Imetelstat **Enrolled**: N = 75 **Treated**: 0.4 mg/kg: n=2, 0.8 mg/kg: n=2, 1.6 mg/kg: n=2, 3.2 mg/kg: n=8, 4.8 mg/kg: n=14 4.8 mg/kg: n=6, 6 mg/kg: n=4, 7.5 mg/kg: n=3, 9.4 mg/kg: n=12, 11.7 mg/kg: n=6 9.4 mg/kg: n=3, 11.7 mg/kg: n=13	Relapsed or refractory solid tumour malignancies that are locally advanced or metastatic, as well as non- amenable to standard therapy or surgical resection.	6 or 8 weeks for the first 2 treatment cycles, then 3 or 4 weeks for each additional cycle, and at least 4 weeks for follow-up. Additional cycles were administered until disease progression or toxicity necessitated discontinuation.
63935397MDS 3001-Phase 3[d]	**Primary**: To compare the efficacy, in terms of RBC TI, of imetelstat to placebo in transfusion dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment. **Secondary**: Safety; time to and duration of RBC-TI; HI rate; response rate (CR, PR, mCR); OS; PFS; progression to AML; utilization of supportive care and myeloid growth factors; PK and immunogenicity; HCRU	Phase 3, double-blind, randomized (2:1), placebo controlled.	N = 177 Imetelstat : n = 118 placebo: n = 59	Low or intermediate-1 risk MDS that is relapsed/ refractory to ESA treatment.	As long as subjects were experiencing clinical benefit in the study without significant toxicity
63935397MDS 3001-Phase 2[c]	**Primary**: To evaluate the efficacy and safety of imetelstat in transfusion dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment. **Secondary**: Safety; time to and duration of RBC-TI; HI rate; response rate (CR, PR, mCR); OS; PFS; progression to AML; PK and immunogenicity.	Phase 2 open label, multicentre single-arm.	Imetelstat: N = 57	Low or intermediate-1 risk MDS that is relapsed/ refractory to ESA treatment.	As long as subjects were experiencing clinical benefit in the study without significant toxicity

63935937MYF 2001	**Primary**: To evaluate spleen response rate and symptom response rate in patients with Intermediate-2 or high-risk MF who are relapsed after or refractory to JAK inhibitor treatment. **Secondary**: Safety, CR or PR rate, spleen response, symptoms response, and anemia response per modified 2013 IWG-MRT criteria, duration of responses, OS, PK PK/PD relationships with factors that include Hgb concentration, spleen size, and platelet count immunogenicity, PRO.	Randomized (1:1), single-blind, multicentre, Phase 2 study 2 dosing regimens of single-agent imetelstat	Imetelstat : **Enrolled**: N = 107 **Treated**: 9.4 mg/kg: n = 59 4.7 mg/kg: n = 48	Intermediate-2 or high-risk MF who are relapsed after or refractory to JAK inhibitor treatment.	Until discontinuation of study treatment due to disease progression, unacceptable toxicity, or withdrawal of consent for treatment.
CP14B019	**Primary**: To evaluate overall response rate in each arm using appropriate response criteria. **Secondary**: Safety and tolerability of imetelstat in each arm Efficacy: reduction of spleen size; improving anaemia or inducing RBC TI in previously transfusion- dependent patients (per IWG-MRT criteria) in each arm; onset and durability of response	Phase 2, open-label, single-centre, pilot study	Imetelstat **Enrolled**: N = 80 **Treated** Arm A: n=19 Arm B: n=16 Arm C: not initiated Arm D: n=9 Arm E: n=9 Arm F: n=18 Arm G: n=9	PMF per WHO criteria or post- ET/PV MF according to IWG-MRT criteria (Arms A, B, E, and F); blast-phase MF/AML (Arm D), defined as the presence of 20% or more blasts in the peripheral blood or bone marrow; MDS/MPN or MDS with spliceosome mutations or ring sideroblasts per WHO criteria (Arm G).	Up to nine 21-day (Arms A and B) or 28-day (Arms D, E, F, G) cycles of treatment during the Core Phase of the study.
CP14B013	**Primary**: To determine the rate of improvement in response in patients with previously treated multiple myeloma following treatment with imetelstat alone or in combination with lenalidomide maintenance therapy. **Secondary**: PFS, changes in the number of peripheral circulating myeloma progenitor cells, safety and tolerability.	Open label Phase 2 study	**Enrolled**: N = 13 **Treated**: Imetelstat 7.5 mg/kg: n = 4 9.4 mg/kg: n = 5 Imetelstat + lenalidomide: 7.5 mg/kg + 10 mg: n = 2 9.4 mg/kg + 10 mg : n = 2	Patients with previously treated multiple myeloma	Until disease progression or unmanageable toxicity.

CP14A011	**Primary**: To determine the MTD of imetelstat in combination with bortezomib with and without dexamethasone in patients with relapsed or refractory MM. **Secondary**: Safety and PK, ORR, DOR, and PFS	Phase I, open label, dose escalation study	Imetelstat **Enrolled**: N = 9 **Treated**: 160 mg/m^2: n = 3 200 mg/m^2: n = 6	Relapsed or refractory MM	Until disease progression or toxicity necessitated discontinuation. The study was to end 12 months after the last patient had been enrolled.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The pharmacokinetic properties of imetelstat were analysed in a number of clinical studies with various haematological disorders and solid tumours, including one in patients with MDS.

Methods

Quantification of imetelstat in plasma and bone marrow

A competitive ELISA method was validated and used for the quantification of imetelstat in human plasma. No data has been presented on whether the applied bioanalytical method can discriminate between parent compound and potential metabolites.

A validated ELISA method was used for the quantification of imetelstat in bone marrow in study MYF2001 and a qualified LCMSMS method was used for the quantification of imetelstat in bone marrow in studies CP14A004 and CP14B013. No stability data for 533 days at -80°C that cover the period between sample receipt and analysis of bone marrow samples is available.

Immunogenicity

A sufficiently validated standard three-tier electrochemiluminescence (ECL) immunoassay has been used to detect ADAs in studies MYF2001 and MDS3001. A neutralization assay has not been developed for imetelstat ADAs due to imetelstat's intranuclear target. The effect of ADAs on the PK, efficacy and safety has been evaluated.

Pharmacokinetic data analysis

The pharmacokinetics were analysed by standard noncompartmental methods and by population pharmacokinetic analysis.

Absorption

Imetelstat is administered as a 2-hour intravenous infusion with peak concentrations generally observed at the end of the infusion. There have been no studies performed with other routes of administration.

No biopharmaceutic studies with imetelstat were performed. The formulation of imetelstat drug product has not changed throughout clinical development or to the proposed commercial formulation.

Imetelstat has not been evaluated as a substrate of transporter proteins.

Distribution

The NCA estimate for Vss is 8.95 L (35.0%) (geometric mean (CV%)) for observed serial PK data for MDS (N=10).

Imetelstat plasma protein binding was 94% in human plasma without any concentration dependence. No data are available on the blood to plasma ratio in humans. After IV administration imetelstat is distributed to the target tissue bone marrow. In limited data from patients with myelofibrosis or multiple myeloma imetelstat could not be detected in bone marrow after 7 days post dose. In samples collected up to 48 h after the last imetelstat administration (of doses between 4.7 mg/kg-9.4 mg/kg) the concentrations ranged from approximately 15 to 28000 ng/g.

Elimination

The excretion pathways of imetelstat have not been evaluated in humans. The size of imetelstat is approximately 4.6 kDa and renal excretion is expected. High protein binding likely reduces glomerular filtration and enhances tissue uptake. Imetelstat concentrations in urine have not been measured in humans and it is thus unknown what fraction of the dose that is renally excreted as unchanged substance. Considering literature data for other modified highly protein bound oligonucleotides renal excretion of unchanged oligonucleotide is unlikely to be a substantial elimination pathway in humans. This is supported by mass balance studies in rats.

The NCA estimate of plasma t½ for subjects with MDS with serial sampling (N=10) has a geometric mean (CV%) of 4.8 h (15.8%).

Dose proportionality and time dependencies

Imetelstat C_{max} and AUC increases more than dose proportionally across the dose range of 0.4 to 11.7 mg/kg in subjects with solid tumors and ET/PV. This may be partially explained by saturation of uptake receptors that facilitate distribution from plasma and sequestration within tissue. No accumulation of Cmax was observed over multiple treatment cycles with the intended dose. Pre-dose samples were below limit of quantification (BLQ).

In study MDS3001 17% of the treated subjects developed ADAs with a median onset of 38 weeks following the first dose of imetelstat. The median peak titer was 30 (range 10 to 160). Based on graphical evaluation, there was no clear difference in the observed concentration-time data between ADA-positive and ADA-negative samples.

Target population

Following administration of 7.5 mg/kg imetelstat on Cycle 1 Day 1, imetelstat plasma concentrations peaked at the end of the nominal 2-hour infusion (EOI) with median Tmax values of 2 h (range 1.92 to 2.13 h). Based on NCA-analysis of 11 subjects the mean (CV%) Cmax 78.6 µg/mL (34.8%), AUC0-24h 373 hx µg/mL (46.8%). The mean (CV%) EOI-concentration observed for additional 129 subjects with sparse sampling in Cycle 1 was 101 µg/mL (43.9%) and remained similar throughout 27 treatment cycles.

Imetelstat plasma concentrations rapidly declined but remained quantifiable for all subjects through the entire 24-hour sampling period. The mean (CV%) t½ was estimated to be 4.76 (15.8%) due to limited sampling in the terminal elimination phase, the t½ estimated is thought to mainly reflect the distribution t½ and not the terminal elimination t½.

Of the 150 PK pre-dose samples collected in different treatment cycles, 146 (97%) were BLQ.

Special populations

No dedicated clinical studies have been conducted in special populations. As imetelstat is not primarily renally cleared (i.e., <30% eliminated unchanged in the urine based on non-clinical studies) and not metabolised by hepatic enzymes nor targeted for hepatic uptake, subjects with hepatic impairment and renal impairment were included in the clinical studies.

Among the 118 subjects with MDS, who received Rytelo during Study MDS3001: 42 had mild renal impairment, 39 had moderate renal impairment, and 1 had severe renal impairment. Based on NCI-ODWG criteria, 31 had mild hepatic impairment, 17 had moderate hepatic impairment, and 2 had severe hepatic impairment.; 71 (60.2%) were males; 95 (80.5%) were white/Caucasian; the body weight range was 47.7 to 116 kg (median body weight: 73.8 kg); and the age range was 44 to 87 years (median age: 71.5 years).

The developed population PK model is flawed and no conclusions regarding potential covariate effects should be based on the model. There is hence no relevant PK data available for evaluation of PK in special populations.

Pharmacokinetic interaction studies

Imetelstat has not been evaluated as a substrate for either CYP enzymes or transporter proteins. Based on the current literature data oligonucleotides are not substrates for CYP enzymes or transporters. Interaction potential of imetelstat as a perpetrator has been investigated in vitro. No clinical DDI studies have been conducted. As imetelstat is an IV-formulation only the systemic cut-off (50X $Cmax_u$) of 54 μM is of relevance.

In cultured hepatocytes imetelstat did not inhibit CYP enzymes at clinically relevant concentrations (data not shown). At high concentrations inhibition of CYP2C8 was detected. Time dependent inhibition of enzymes has not been evaluated. Evaluation of imetelstat induction potential was only conducted measuring enzyme activity and not at the mRNA level. No induction signal was seen in this experiment, but the high concentration was cytotoxic.

In vitro imetelstat is an inhibitor of BCRP (IC_{50} 27.5 μM), OATP1B1 (IC_{50} 5.9 μM), OATP1B3 (IC_{50} 1.2 μM) and OAT1 (IC_{50} 8.8 μM) at clinically relevant concentrations when applying the systemic cut-off based on $Cmax_u$. However, this high concentration is only achieved once per month at the end of infusion after which the plasma concentration rapidly declines. In the context of the infrequent q4w dosing schedule, the risk of clinically meaningful DDIs is unlikely on subsequent days. An integrated assessment was performed on clinical PK characteristics, data for an endogenous probe substrate, and safety profiles when administered with concomitant medications in the Phase 3 Study MDS3001. Though hampered by methodological issues these analyses further support limited clinical relevance of the in vitro signals.

2.6.2.2. Pharmacodynamics

Mechanism of action

Imetelstat is a 13-nucleotide (13-mer) oligonucleotide with a covalently bound lipid tail. Imetelstat is a first in class telomerase inhibitor that targets malignant cells characterized by the abnormal elevation of telomerase activity (TA).

Primary and Secondary pharmacology

Imetelstat has a nucleotide sequence that is complementary to, and specifically binds with high affinity to the template region of the RNA component of human telomerase, which lies in the active or catalytic

site of the telomerase reverse transcriptase (hTERT), resulting in competitive inhibition of hTERT enzymatic activity, which prevents telomere binding. While there may be some structural similarities between imetelstat and other oligonucleotide classes, the mechanism of action for imetelstat is not antisense based, as it does not target mRNA of any gene, and does not activate RNase-H-based degradation of its target sequence; instead, it behaves like a classical active site enzyme inhibitor. The structure of imetelstat allows for high sequence-specific binding and enhanced entry into cells to increase the inhibition of TA (Asai, 2003; Herbert, 2005).

Nonclinical studies have indicated that inhibition of TA by imetelstat results in inhibition of cell proliferation of several cancer cell lines and human tumours in mouse xenograft models (Hochreiter, 2006; Shammas, 2008; Marian, 2010a; Marian 2010b; Ouellette, 2011). Moreover, imetelstat also inhibits proliferation and induces apoptosis of cancer stem cells (Joseph, 2010; Bruedigam, 2014). Telomerase inhibition by imetelstat leads to the loss of a cancer cell's ability to maintain telomere length (TL), which results in broad antitumor activity as demonstrated by inhibition of proliferation, reduction in colony formation and induction of apoptosis/senescence in different cancer cell lines, and patient derived samples (Wang, 2004; Herbert, 2005; Shammas, 2008; Hochreiter, 2006; Brennan, 2010; Joseph, 2010; Marian, 2010a; Marian 2010b; Frink, 2016).

Achievement of ≥ 50% telomerase inhibition is correlated with significant tumour growth inhibition (TGI), suggesting that this level of inhibition of TA is the mechanism of the pharmacodynamic effect of imetelstat needed for anti-tumour efficacy. These findings are in concordance with results from clinical studies where pharmacodynamic effects of imetelstat, as demonstrated by ≥ 50% reductions in TA and/or hTERT expression level, correlated with clinical responses to imetelstat (Steensma, 2021; Mascarenhas, 2021).

Study CP05-101

This was a Phase 1, open-label, sequential dose cohort, dose-escalation study in subjects with relapsed or refractory solid tumour malignancies. A total of 75 subjects were enrolled. Inhibition of TA was evaluated 24 h after a single dose of imetelstat in 23 subjects (**Figure 11**).

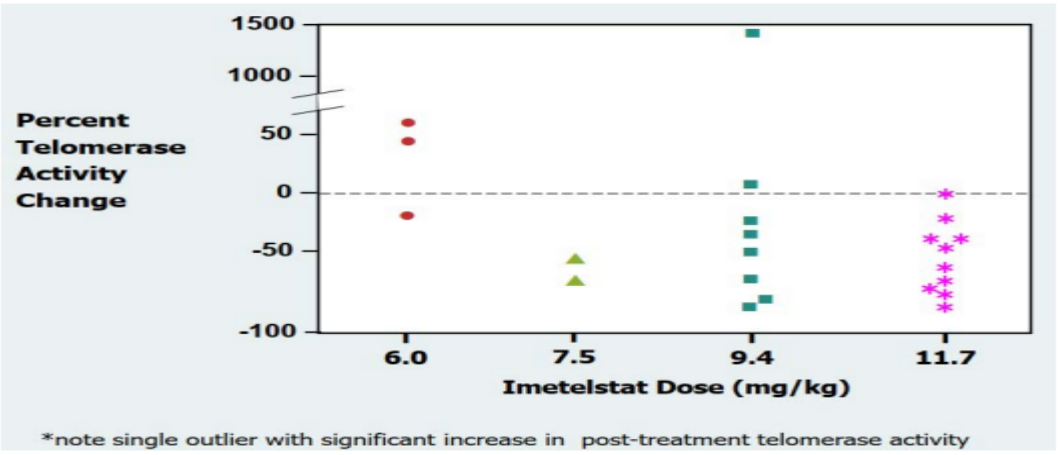


Figure 8. Inhibition of Telomerase Activity in PBMCs 24 Hours After a Single Dose of Imetelstat (Study CP05-101)

PBMCs = peripheral blood mononuclear cells; TA = telomerase activity. Points are individual change from baseline in telomerase activity at 24 h after a single dose of imetelstat

Study CP14B019

Preliminary evidence for efficacy of imetelstat in patients with MDS comes from a completed Phase 2, open-label, single-institution, pilot study of imetelstat monotherapy in subjects with myelofibrosis and other myeloid malignancies. 9 subjects with MDS/MPN or MDS per World Health Organization (WHO) criteria were enrolled. These subjects were required to have spliceosome mutations or MDS RS+ and received imetelstat at a starting dose of 7.5 mg/kg every 4 weeks.

The objective response rate (best response of CR, partial remission [PR], or HI) was 33% in the first 9 cycles.

Study MDS3001

The reduction from baseline in the key PD marker, TA, and in the supportive PD marker, hTERT RNA levels, was assessed in the Phase 2 and Phase 3 portion of MDS3001. In the Phase 2 portion of MDS3001, 23.1% (3/13) and 54.3% (19/35) (subjects in the target population with available data) had ≥50% reduction in TA and hTERT, respectively. In the Phase 3 placebo-controlled portion, the proportion of subjects with ≥50% reduction from baseline in TA was higher in the imetelstat group at 60.0% (21/35) than the placebo group at 37.5% (9/24). The proportion of subjects with ≥50% reduction from baseline in hTERT was similar in the imetelstat group [43.2% (41/95)] and the placebo group [54.0%, (27/50)].

Relationship between plasma concentration and effect

The relationships between imetelstat exposure and key efficacy- and safety-related endpoints were examined with univariate and multivariate exposure-response (E-R) analyses. Individual exposures were derived using the developed popPK model and the actual dosing records for each subject. Efficacy E-R analyses were conducted for the pivotal study MDS3001 only, while safety analyses were conducted for all 7 studies in the popPK analysis as well as for MDS3001 alone. In study MDS3001, most subjects received the 7.1 mg/kg Q4W dosing regimen, resulting in a relatively narrow exposure range. Across studies, dose escalations, dose reductions, and dose interruptions did occur, which hampers the interpretability due to confounding factors. Given these limitations, these analyses are not further described.

2.6.3. Discussion on clinical pharmacology

The clinical pharmacology program for imetelstat consists of 9 completed clinical studies using a wide range of doses and dose schedules in adult subjects with hematologic malignancies and solid tumours. No studies have been conducted in healthy volunteers. Serial PK samples were collected in 5 monotherapy studies for characterization of imetelstat PK with NCA. Sparse PK samples were collected in 4 additional studies. One study, the Phase 2/3 study MDS3001, evaluated the intended dose in the target population with PK-sampling. It is highlighted that doses discussed herein are for the imetelstat salt as derived from the several study reports. Concerning the proposed dosing, 7.5mg/kg correspond to 7.1mg/kg imetelstat free acid (active moiety).

The pharmacokinetic properties and biodistribution of oligonucleotides are mainly governed by the chemistry of the backbone. Imetelstat contains modifications to increase protein binding and resistance to nucleases. A lipid tail of palmitoyl is conjugated via an aminoglycerol linker to the 5’ terminus increase cellular uptake which, like other oligonucleotides, is likely mediated mainly by endocytosis (though not studied).

It is not clarified whether the bioanalytical ELISA-methods that was used for the detection of imetelstat in human plasma or bone marrow can discriminate between parent compound and potential metabolites. Although the method for plasma was found to be specific for imetelstat in the presence of sense or mismatched oligonucleotides, the specificity of the method has not been demonstrated in the presence of potential (short chained) metabolites. Therefore, it cannot be excluded that in the absence of parent imetelstat, signal could be obtained due to the presence of alternative/truncated metabolites. In addition, the LoQ of the method is rather high, leading to a high number of "missing values" in the PK study and overall from a clinical PK point of view, the method to detect imetelstat was insufficiently planned and utilised with a too high analytical range.

The ELISA method that was used for the analysis of imetelstat in bone marrow samples was appropriately validated and can be considered adequate for the analysis of imetelstat in bone marrow. No long-term stability data for 533 days at -80°C that cover the period between sample receipt and analysis of bone marrow samples were presented, however, given that the analysis of bone marrow samples was part of an exploratory assessment, the absence of long-term stability data could be acceptable.

The immunogenicity assay is sufficiently validated and the lack of NAB-assay acceptable. In the target population the ADA incidence was 17% and ADAs did not appear to affect imetelstat exposure, though data is limited.

Despite the knowledge that oligonucleotide therapeutics generally are initially cleared rapidly from systemic circulation but have longer terminal elimination phases and tissue and pharmacodynamic half-lives, the clinical PK samples were only collected the first 24 hours following dosing. The insufficient data collection results in the elimination phase likely not being fully characterized, available data from 24 hours post dose are close to the limit of quantification. Contrary to what is expected from the modifications of the backbones of imetelstat, non-clinical data implicate a rapid degradation of intact imetelstat. In conclusion, clinical plasma-PK cannot support the proposed dose regimen with infrequent dosing every 4th week. Given the limitations of the data, the population PK model developed by the Applicant is not considered adequate for its purpose and it cannot support any claims in the SmPC.

An initial dose escalation study in CLD patients (CP04-151) utilised a BSA-based dosing, ranging from 20-240mg/m² with either 2-hour or 6-hour infusion time weekly or 3-weekly. As expectable, decreasing infusion time from 6 to 2 hours increased Cmax for the 160mg/m² dose by 2.3-fold, while clearance at 2 hours was only ~40% of the same dose given over 6h. As Cmax was higher with the 2h infusion, 200mg/m² was declared as MTD here. Notably, 28.4% of samples were below LOQ. For reasons of clinical practicability and in view of suitable safety the 2-hour infusion time was further developed. Dosing was also revisited for a weight-based calculation considering upcoming published evidence for other oligonucleotides.

An early study in solid tumour patients (CP05-101, only abbreviated CSR) investigated a weight-based dosing at different weekly, 3-weekly, or 4-weekly schedules between 0.4-11.7mg/kg and 2h-infusion time. In this study it was observed that clearance decreased to below 1L/h at doses ≥6.0mg/kg with over-proportional increases in Cmax and AUC at ≥3.2mg/kg, with CL being highest at 3.2mg/kg with 3.3L/h. The study defined the Phase II dose with 9.4 mg/kg on D 1 and 8 of a 21-day cycle or on D 1 of a 28-day cycle.

Protein binding was 94% which will reduce the renal filtration which is expected for imetelstat with a size of 4.6 kDa. The main elimination pathways for oligonucleotides are known and the lack of mass balance study with imetelstat is acceptable. Oligonucleotides are metabolised by nucleases and the formed metabolites are readily excreted by the kidneys. Oligonucleotides with lesser protein binding are excreted unchanged in the urine to a higher degree. The NCA-derived CL of 1.52L/h in MDS

patients needs to be regarded as the "sum" of clearances from the central compartment by (renal/metabolic) elimination/excretion and by distribution (into tissue, tumour etc.).

There has been no attempt to try to identify metabolites to imetelstat, but likely several different chain-shortened oligonucleotides are formed by nucleases in plasma and tissues. Consequently, potential on- or off-target effects of metabolites are not known. For oligonucleotides in general it is believed that the metabolite pattern will be the same over species and that non-clinical safety studies cover potential issues. Still, this may be an issue in e.g. patients with renal impairment where metabolites may accumulate. Subjects with RI were included in the clinical studies, however few with severe RI.

Yet another deficiency with the clinical pharmacokinetic dossier is the lack of PK-samples from urine. The Applicant refers to a mass balance study in rats to claim that imetelstat is not excreted unchanged in urine and that renal impairment will not affect exposure. Generally, the extrapolation of rat mass balance studies to humans is not acceptable. This is further hampered by the Applicant mentioning metabolic rate as an explanation for the differences in clearance between non-clinical species. Oligonucleotides that are highly protein bound have in the literature been shown not to be excreted intact to any substantial degree and, to some degree supported by the rat data, this is likely the case also for imetelstat.

In the target population plasma concentrations of imetelstat appears to decline in a biphasic fashion with time, with an initial fast distribution phase followed by a slower elimination phase; however, as no data is available beyond 24 hours post-dose the elimination phase is not fully characterized. The half-life is approximately 5 hours, but if there is a longer terminal elimination half-life, which has been seen for other phosphorthioate oligonucleotides, is unknown. This information is based on NCA-analysis of a small subset of 11 individuals in study MDS3001. Moderate variability in AUC (47.6%) and Cmax (34.8%) was observed.

Imetelstat exposure increases greater than dose-proportionally after single doses in the range of 0.4 to 11.7 mg/kg possibly due to saturation of the cellular uptake mechanism which has been described for other oligonucleotides. Little or no accumulation of Cmax is seen following multiple administrations of 7.5 mg/kg imetelstat in patients with MSD. Ctrough has previously been used for oligonucleotides as a surrogate to measure tissue accumulation; however, all pre-dose samples were BLQ in study MDS3001, which may be expected due to Q4W dosing but may also depend on a rather insensitive bioanalytical method.

No dedicated clinical studies have been conducted in special populations and the developed population PK model is flawed and no conclusions regarding potential covariate effects should be based on the model. The potential use of imetelstat in any special population relies on efficacy and safety data. Patients with all grades of both RI and HI (i.e. abnormal liver function tests based on NCI-ODWG-criteria and not the common definition of HI in the EU which is based on Child-Pugh criteria) were included in the clinical studies though few with the severe forms.

Since the proposed dose of imetelstat is body weight-adjusted, only minor differences in exposure are expected for most subjects. However, allometric scaling of the elimination is in general not appropriate for obese subjects, and it is not uncommon that a body weight-adjusted dose has an upper body weight-limit, above which a flat dose is recommended. The Applicant has provided available PK and safety data for different weight categories and in conjunction with the proposed dose reductions based on toxicity in the SmPC the proposed dose without a weight cut-off could be acceptable.

Imetelstat has not been evaluated as a substrate for either CYP enzymes or transporter proteins. Based on the current literature data oligonucleotides are not believed to be substrates for CYP enzymes or transporters and the lack of studies acceptable.

In vitro imetelstat did not inhibit CYP enzymes. The study evaluating imetelstat induction potential was inconclusive mainly since it did not use mRNA as endpoint and that high imetelstat concentrations were cytotoxic. However, induction in the clinical setting is considered unlikely given the infrequent dosing and rapidly declining plasma concentrations of imetelstat and no further studies are requested.

Imetelstat directly inhibited UGT1A1 enzyme activity in human liver microsomes, with an IC50 value of 1.3 µM. However, the results for imetelstat inhibition of UGT1A1 in human liver microsomes may be artefactual due to non-specific, test-system dependent effects for the class of ODNs (Kazmi 2018). No further study was performed for UGT in CHH for confirmation of no DDI potential. UGTs are not mandatory enzymes to study and lack of data is thus acceptable. In general, UGT1A enzymes have considerable overlap in substrate specificities and the risk of a relevant interaction risk due to inhibition of UGT1A1 only is not large. Importantly the concentrations of imetelstat are only high enough to cause inhibition on the day of its administration limiting the possibility of increasing the substrate concentration to toxic levels to a brief period. To further support the low risk the Applicant has provided data on bilirubin, an endogenous substrate of UGT1A1. While not a validated substrate to be used to waive clinical DDI studies, the lab data from the pivotal phase III study MDS3001 in comparison to placebo revealed no decrease in direct, i.e. glucuronide-conjugated bilirubin or an increase in indirect, i.e. unconjugated bilirubin over placebo levels, supporting that no worrisome hyperbilirubinaemia would be expected under imetelstat treatment.

In vitro imetelstat is an inhibitor of BCRP, OATP1B1, OATP1B3 and OAT1 at clinically relevant concentrations when applying the systemic cut-off based on Cmaxu. However, this high concentration is only achieved once per month at the end of infusion after which the plasma concentration rapidly declines with an apparent half-life of 5 hours. Based on plasma concentrations the risk for interactions on the day of administration cannot be completely ignored. Statins (substrate for OATP1) were quite commonly co-administrated in the phase 3 study and while the safety data for these patients do not raise any concerns these cannot be used to exclude a risk at the day of administration. In section 4.5 the in vitro results should be described and the limited risk communicated.

Pharmacodynamics

Imetelstat inhibits the enzymatic activity of telomerase and selectively impairs proliferation of malignant HPCs and LSCs from myeloproliferative neoplasms (MPN) (including ET, MF and chronic myeloid leukaemia) and AML patient samples ex vivo and in PDX models in vivo, while sparing normal counterparts.

Nonclinical proof-of-concept studies for imetelstat correlated PK exposure, PD effect (target engagement by inhibition of TA) and tumour growth inhibition *in vivo* in xenograft mouse models and indicated that higher imetelstat doses were associated with greater plasma exposure and target engagement. Achievement of ≥ 50% telomerase inhibition was correlated with significant TGI, suggesting that this level of inhibition of TA is the mechanism of action-based optimal pharmacodynamic effect of imetelstat needed for anti-tumour efficacy.

However, there are no results from specific non-clinical studies in MDS models available to directly support the assumption of beneficial effect of achieving ≥ 50% TA inhibition in patients with the target indication, low- to intermediate-1 risk MDS.

In study CP05-101 in patients with relapsed or refractory solid tumour malignancies the median telomerase inhibition for the 9.4 mg/kg group was 34.0% and for the 11.7 mg/kg group was 48.0%.

In study CP14B019 (MDS/MPN or MDS and splicesome mutations or ring sideroblasts present), the overall response rate (best response of CR, PR, or HI) was 33.3% (95% CI: 2.5%; 64.1%). Of note, telomerase activity was not amongst the objectives / endpoints in this study. Thus, no PD correlation observed in the clinical outcome is available from this study.

In the phase 2 portion of study MDS3001, the reduction from baseline in TA and hTERT RNA levels was assessed. Among subjects with available samples, ≥ 50% reduction in TA and hTERT were observed in 3/13 (23.1%) subjects and 19/35 (54.3%) subjects, respectively, in the target population. It seems that the applicant has chosen to use only hTERT to characterize optimal pharmacodynamic effect to show the association between hTERT reduction and clinical response (8-week, 24-week, or 1-year RBC TI). Due to low number of patients, even taking into account that higher response rate was observed in subjects who achieved the optimal pharmacodynamic effect compared with those who did not, the value of this observation is questionable.

The Applicant had clarified several aspects related to assumed benefit with the chosen PD targets of imetelstat. From the data observed in both the phase 2 and phase 3 study with the target MDS population, the "link" between the ≥ 50% TA reduction and ≥ 50% hTERT reduction with the assumed beneficial effect on transfusion independence seems to be somewhat plausible, taking into consideration the observed efficacy results of imetelstat compared to placebo with longer term TI.

2.6.4. Conclusions on clinical pharmacology

Overall, pharmacokinetic development of this first-in-class oligonucleotide is unsatisfactory as PK properties such as metabolite pattern and excretion in urine have not been investigated clinically. Available data indicate low plasma concentrations, close to limit of quantification, 24 hours post dose rendering plasma-PK of limited use to predict efficacy with the proposed every 4-week administration. Clinical pharmacokinetics can thus not support final dose and administration scheme or the potential use of imetelstat in any unstudied special populations. Dosing recommendations for imetelstat are based on the dosing regimen used in the pivotal phase 2/3 study MDS3001.

While the pharmacokinetic properties of imetelstat are largely unstudied, oligonucleotides as a class have some conserved PK-properties which may fill in certain knowledge gaps for imetelstat. In the applied for orphan indication the proposed restrictions and dose reductions in the SmPC are sufficient to ensure adequate use despite lack of relevant PK-information in e.g. special populations.

To ensure adequate use of imetelstat in broader patient groups, for a possible future indication, the pharmacokinetics of imetelstat will need to be appropriately characterised, providing data on metabolite pattern and excretion in urine to exclude risks for e.g. patients with renal impairment. It is requested that future clinical studies include adequate PK-sampling and that the bioanalytical method is validated to ensure that metabolites are not contributing to the signal.

The PD of imetelstat is poorly characterized in the target population. Nevertheless, as telomerase activity and human telomerase reverse transcriptase (hTERT) RNA expression are known to be significantly increased in MDS and malignant stem and progenitor cells the mechanism of action of imetelstat support its use in the claimed indication.

2.6.5. Clinical efficacy

2.6.5.1. Dose response studies

See Clinical Pharmacology section of this report.

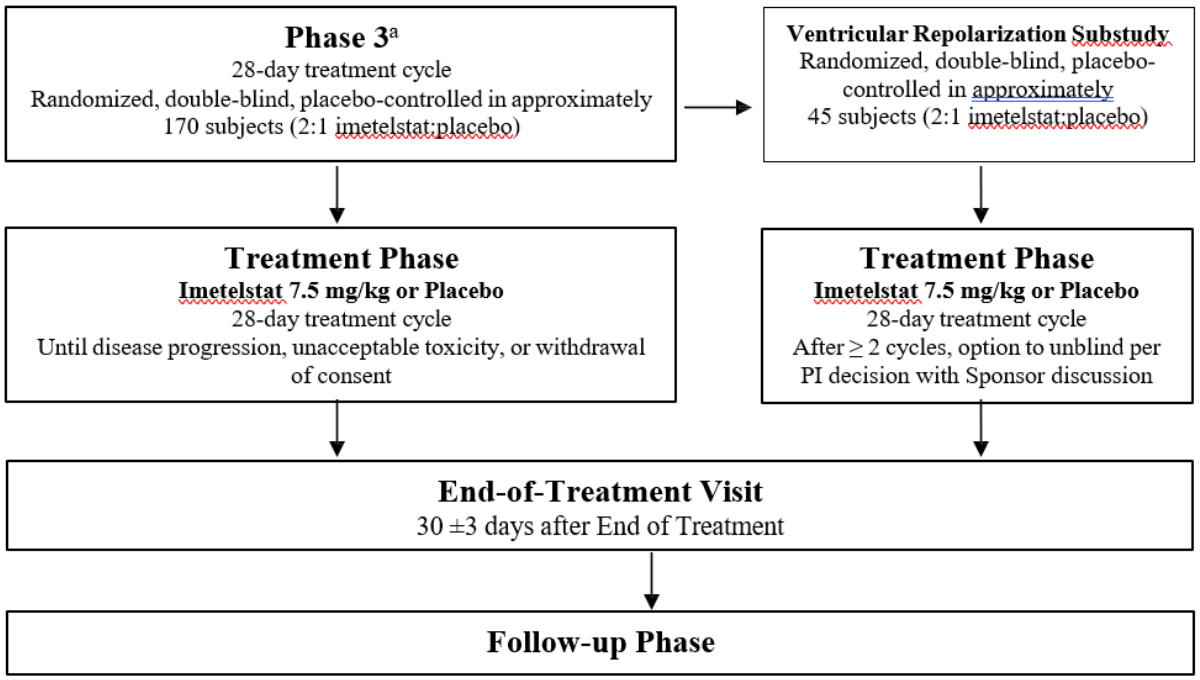
2.6.5.2. Main study

MDS3001: A study to evaluate imetelstat (GRN163l) in transfusion dependent subjects with IPSS low

or intermediate-1 risk myelodysplastic syndrome (MDS) that is relapsed/refractory to erythropoiesis-stimulating agent (ESA) treatment.

Methods

A diagrammatic representation of the phase 3 part of the study is presented in **Figure 9.**



[a] Supportive care, including transfusions or myeloid growth factors, is to be administered as needed per investigator discretion and according to local standard practices.

Figure 9. Schematic Overview of Phase 3 part of Study MDS3001

- **Study participants**

Main inclusion criteria

1. Man or woman ≥ 18 years of age.
2. In the Phase 3 study, diagnosis of MDS according to World Health Organization (WHO) criteria confirmed by bone marrow aspirate and biopsy within 12 weeks prior to randomization. A sample of the baseline bone marrow aspirate and biopsy must be submitted to the Independent Central Pathology Reviewer for diagnostic confirmation. Central laboratory review is required to confirm diagnosis prior to randomization.
3. IPSS low or intermediate-1 risk MDS.
4. RBC transfusion dependent, defined as requiring at least 4 RBC units transfused over an 8-week period during the 16 weeks prior to randomization; pre-transfusion Hb should be ≤ 9.0 g/dL to count towards the 4 units total.
5. Had MDS that was relapsed/refractory to ESA treatment as defined by meeting any one of the criteria below:

5.1. Received at least 8 weeks of treatment with a minimum weekly dose of epoetin alfa 40,000 U, epoetin beta 30,000 U or darbepoetin alfa 150 mcg (or equivalent agent/dose), without having achieved a Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement by at least 4 units over 8 weeks

5.2. Transfusion dependence or reduction in Hb by ≥ 1.5 g/dL after haematologic improvement from at least 8 weeks of treatment with therapies outlined in inclusion criterion 5.1, in the absence of another explanation.

5.3. Endogenous serum EPO level > 500 mU/mL

6. Adequate iron stores, defined as transferrin saturation greater than 20% and serum ferritin greater than 400 ng/mL, measured within the screening period, or adequate iron stores as demonstrated by recent (within 12 weeks prior to randomization) bone marrow examination with iron stain

7. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2

8. Haematology lab test values within the following limits:

8.1. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L independent of growth factor support

8.2. Platelets ≥ 75 x 10^9/L independent of platelet transfusion

9. Biochemical laboratory test values must be within the following limits:

9.1. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) ≤ 2.5 times the upper limit of normal (x ULN)

9.2. Serum creatinine ≤ 2.0 x ULN

9.3. Total bilirubin ≤ 3 x ULN and direct bilirubin ≤ 2 x ULN (unless due to Gilbert's syndrome, ineffective erythropoiesis due to MDS, or haemolysis due to RBC transfusion)

Main exclusion criteria

1. Had received corticosteroids > 30 mg/day prednisone or equivalent, or growth factor treatment within 4 weeks prior to randomization

2. Prior treatment with a hypomethylating agent (e.g., azacitidine, decitabine)

3. Prior treatment with lenalidomide, thalidomide, or other thalidomide analogues

4. Had received an ESA or any anti-MDS therapy, chemotherapy, immunomodulatory, or immunosuppressive therapy within 4 weeks prior to randomization (8 weeks for long-acting ESAs)

5. Prior history of HSCT

6. Anaemia attributed to factors other than MDS (including haemolysis, chronic renal failure, hepatitis, gastrointestinal bleeding)

7. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of randomization, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification

8. Active systemic hepatitis infection requiring treatment (carriers of hepatitis virus are permitted to enter the study), or known acute or chronic liver disease including cirrhosis

9. Subject with del(5q) karyotype

- **Treatments**

Imetelstat sodium for injection (imetelstat) is the investigational product in this study and was provided along with placebo, by the Sponsor.

Study drug (imetelstat or placebo) was to be administered as a 2-hour IV infusion (± 10 minutes) at a constant rate using an infusion pump.

The first dose of study drug was to be administered within 72 hours of randomization. All subjects received a starting dose of 7.5 mg/kg of study drug given IV every 4 weeks.

Study drug dose delay or reduction for Grade 3 or Grade 4 toxicities observed at the time of the planned dose of the next cycle was to be instituted as needed (**Table 4**). Imetelstat could have been held for up to 28 days from the expected start date of the scheduled cycle; a hold > 28 days had to be reviewed and approved by the Sponsor.

Table 4. Dose Titration in Study MDS3001

Titration		**Dose Regimen of Imetelstat**
0	Starting dose	7.5 mg/kg IV every 4 weeks
-1	Dose reduction #1	6.0 mg/kg IV every 4 weeks
-2	Dose reduction #2 (Minimum dose)	4.7 mg/kg IV every 4 weeks

- **Objectives**

Primary objective

The primary objective of the Phase 3 study was to compare the efficacy, in terms of RBC TI, of imetelstat to placebo in transfusion-dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment.

Secondary objectives

The secondary objectives of the Phase 3 study were:

- To assess the safety of imetelstat in subjects with MDS
- To assess the time to RBC TI and duration of RBC TI
- To assess the rate of haematologic improvement
- To assess the rates of CR, partial remission (PR) or marrow complete remission (mCR**)**
- To assess OS
- To assess PFS
- To assess time to progression to AML
- To assess the rate and amount of supportive care, including transfusions and myeloid growth factors
- To evaluate the pharmacokinetics (PK) and immunogenicity of imetelstat in subjects with MDS
- To assess the effect of treatment on medical resource utilization

- **Outcomes/endpoints**

Primary efficacy endpoint

The primary efficacy endpoint of this study is the rate of RBC TI lasting at least 8 weeks. The 8-week RBC TI rate is defined as the proportion of subjects without any RBC transfusion during any consecutive 8 weeks (56 days) starting from Study Day 1 until the start of subsequent anti-cancer therapy (if any). Study Day 1 for was defined as the day of randomization.

The starting date of 8-week RBC TI duration was between Study Day 1 and the date of last dose of study drug + 30 days or End of Treatment Visit whichever occurred first, or Study Day 31 if randomized but not treated.

Secondary endpoints (selection)

- Safety of imetelstat in subjects with MDS (e.g., incidence, intensity, and type of adverse events, vital signs measurements, clinical laboratory values, electrocardiogram (ECG) changes, and deaths)
- 24-week RBC TI rate, defined as the proportion of subjects without any RBC transfusion during any consecutive 24 weeks (168 days) starting from Study Day 1 until the start of subsequent therapy (if any)
- Time to the 8-week (24-week) RBC TI, defined as the interval from Study Day 1 to the first day of the first 8-week (24-week) RBC TI period
- Duration of RBC TI, defined as the first day of the longest RBC TI period to the date of the first RBC transfusion after the TI period starts
- Rate of haematologic improvement, including HI-E, per modified IWG 2006
- Rates of CR, PR, or mCR per modified IWG 2006
- OS, defined as the interval from Study Day 1 to death from any cause. Survival time of living subjects will be censored on the last date a subject is known to be alive or lost to follow-up
- Progression free survival, defined as the time interval from Study Day 1 to the first date of disease progression or death from any cause, whichever occurs first
- Time to progression to AML, defined as the interval from Study Day 1 to the date of AML diagnosis
- Amount and relative change in RBC transfusions
- Rate of myeloid growth factors usage, defined as the proportion of subjects receive any myeloid growth factors starting from Study Day 1; duration of myeloid growth factor administered starting from Study Day 1

Exploratory endpoints

- TA and hTERT at baseline and the change from baseline, TL at baseline only
- Cytogenetic status at baseline and change over time for cytogenetic response
- Mutation status at baseline and change over time including at the time of suspected response (CR, PR, HI-E [haemoglobin (Hb)]) or progressive disease (PD)

- Assessment of Quality of Life in Myelodysplasia Scale (QUALMS), Functional Assessment of Cancer Therapy - Anaemia-Related Effects (FACT-An), and EuroQol- EQ-5D-5L (EQ-5D-5L)

- **Sample size**

On the basis of historical data, 8-week RBC TI rate was expected to be approximately 7.5% in patients with low or intermediate-1 risk MDS without any active treatment (Raza, 2008; Santini, 2014). The 8-week RBC TI rate with imetelstat treatment was expected to be approximately 30% based on preliminary data from a cohort of 9 subjects in Study CP14B019 (Tefferi, 2016).

Approximately 170 subjects were initially planned to be randomized in a 2:1 ratio to receive either imetelstat or placebo. Using a 2:1 ratio randomization and a 2-group continuity corrected Chi-square test with 0.05 (2-sided) significance level, 150 subjects were needed to achieve a power of approximately 88% to detect the difference between a RBC TI rate of 30% in the imetelstat group and a RBC TI rate of 7.5% in the placebo group. After correction for a 10% drop-out rate, a total of approximately 170 subjects (115 in imetelstat group and 55 in placebo group) were planned.

- **Randomisation and blinding (masking)**

Subjects were randomly assigned 2:1 to receive either imetelstat or placebo. Randomization was based on a computer-generated randomization schedule prepared before the study by or under the supervision of the Sponsor. Randomization was stratified by prior RBC transfusion burden (≤ 6 or > 6 units RBC) and by IPSS risk group (low versus intermediate-1). Prior RBC transfusion burden is defined as the maximum number of RBC units transfused over an 8-week period during the 16 weeks prior to randomization. Pre-transfusion Hb should have been ≤ 9.0 g/dL to count toward the 4 units total unless there was a clinical rationale for transfusing at a higher Hb level.

This was a double-blind study.

- **Statistical methods**

Analysis of Efficacy Endpoints

Unless otherwise specified, all statistical tests were interpreted at a 2-sided nominal significance level of 0.05 and all confidence intervals (CIs) at a 2-sided level of 95%. The overall type I error rate is 0.05 (2-sided) for the primary and secondary efficacy hypotheses.

The primary efficacy analysis was planned at 12 months after the last subject was randomized in the main part of Phase 3 study. The study is still ongoing at the time of writing, and the final analysis will be performed at the End of the Study, defined as 24 months after randomization of the last subject in the main part of Phase 3 study or anytime the sponsor terminates the study, whichever comes first.

Statistical Hypotheses for Trial Objectives

The primary hypothesis of this study was that imetelstat will significantly improve the rate of RBC TI as compared to placebo in transfusion-dependent subjects with low or intermediate-1 risk MDS that is relapsed or refractory to ESA treatment. The hypothesis was tested using a stratified Cochran-Mantel-Haenszel test adjusting for the stratification factors at a 2-sided significant level of 0.05.

Analysis method

The 8-week RBC TI rates were summarized with frequencies and percentages along with 2-sided 95% exact Clopper-Pearson CIs for the 2 treatment groups. Difference in TI and its 95% CI were presented using the Wilson Score method. The comparison was based on a stratified Cochran-Mantel-Haenszel test adjusting for the stratification factors at a 2-sided significance level of 0.05.

Sensitivity analyses were performed for the Phase 3 study to evaluate the robustness of the primary analysis and included:

- Cochran-Mantel-Haenszel test of 8-week RBC TI based on the modified intent-to-treat (mITT) analysis set in the case there were subjects who were dosed but did not receive any assigned treatment
- Cochran-Mantel-Haenszel test of 8-week RBC TI based on per-protocol (PP) analysis set
- Cochran-Mantel-Haenszel estimate of the odds ratio of 8-week RBC TI with the stratification factors and the associated 95% CI
- Comparison of 8-week RBC TI based on CMH test adjusted by values of prior RBC transfusion burden and IPSS risk group recorded on the eCRF
- Comparison of 8-week RBC TI based on CMH test without adjusting for the baseline stratification factors

Analysis of secondary endpoints

The 24-week RBC TI rates were summarized with frequencies and percentages along with 2-sided 95% exact Clopper-Pearson CIs for the 2 treatment groups. Difference in TI and its 95% CI were presented using Wilson Score method. The comparison was based on a stratified Cochran-Mantel-Haenszel test adjusting for the stratification factors at a 2-sided significance level of 0.05. Sensitivity analyses were performed to evaluate the robustness of the 24-week RBC TI endpoint and included:

- Cochran-Mantel-Haenszel test of 24-week RBC TI based on mITT analysis set in the case there were subjects who were dosed but didn’t receive any assigned treatment
- Cochran-Mantel-Haenszel test of 24-week RBC TI based on Per-protocol Analysis Set

The time to 8-week and 24-week RBC TI were summarized descriptively for the 2 treatment groups based on ITT 8-week and 24-week TI responder analysis sets, respectively. The Kaplan-Meier method was used to estimate the distribution of duration of RBC TI based on ITT 8-week and 24-week TI responder analysis sets, respectively, and were compared between the 2 treatment groups using stratified log rank test based on ITT 8-week responder analysis set. The distribution of the cumulative duration of RBC TI ≥ 8 weeks (sum of all durations of RBC TI ≥ 8 weeks) were estimated by the Kaplan-Meier method based on the ITT 8-week responder analysis set as well.

The proportion of subjects with haematologic improvement, CR, PR, or mCR per modified IWG 2006, and other binary endpoints were evaluated using the same statistical methods as for the endpoint of 24-week RBC TI rates. The 8-week RBC TI rate in the first 24 weeks and 48 weeks (proportion of subjects who had RBC TI ≥ 8 weeks in the first 24/48 weeks) was evaluated similarly.

The distribution of OS, PFS, and time to progression to AML were compared using a stratified log rank test for the ITT analysis set. The Kaplan-Meier method was used to estimate the distribution for each treatment. The treatment effect (hazard ratio) and its 2-sided 95% CIs were estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

Control of multiple testing

If the primary endpoint was significant, the first two secondary endpoints were tested sequentially at 0.05 (2-sided):

1. 24-week RBC TI
2. Rate of HI-E per modified IWG 2006

If both of these tests were significant, a Hochberg procedure was used to test PFS and OS.

Subgroup analysis

Subgroup analyses were performed to assess the consistency and robustness of the treatment benefit mainly for the rate of RBC TI and the rate of HI-E. Subgroup analysis could be performed for other selected efficacy and safety endpoints.

Interim analysis

No interim analysis was planned.

Missing data

No imputations for missing data were made for the primary and secondary efficacy endpoints. In order to be considered transfusion independent, a subject must have completed continuous transfusion assessments throughout the qualifying observation period where his/her transfusion independence was determined. An apparent transfusion-free period with 1 or more missing transfusion assessments was not considered a qualifying 8-week or 24-week TI period. Subjects with no qualifying observation periods were considered non-responders.

Results

- **Participant flow**

Table 5. Subject Disposition in Study MDS3001 (Phase 3, Intent-to-Treat Analysis Set)

	Imetelstat (N=118)	**Placebo (N=60)**	**Total (N=178)**
Subjects remaining on study, n (%)	76 (64.4%)	39 (65.0%)	115 (64.6%)
Discontinued from the study, n (%)	42 (35.6%)	21 (35.0%)	63 (35.4%)
Reason for discontinuation, n (%)			
Withdrawal by subject	20 (16.9%)	11 (18.3%)	31 (17.4%)
Death	19 (16.1%)	8 (13.3%)	27 (15.2%)
Lost to follow-up	3 (2.5%)	1 (1.7%)	4 (2.2%)
Adverse event	0	1 (1.7%)	1 (0.6%)
Time on study (months)[a]			
Mean (SD)	17.466 (8.1224)	16.572 (7.8735)	17.164 (8.0283)
Median[b]	19.483	17.511	18.497
Minimum, maximum	1.38, 36.17	0.72, 34.27	0.72, 36.17

a Defined as the interval between Study Day 1 (the date of randomization) and the date of death (censored) or last day on the study.
b Calculated based on Kaplan-Meier method.

At the time of the clinical cutoff (13 October 2022), treatment was ongoing in 22.9% of subjects in the imetelstat group and 23.7% of subjects in the placebo group. The proportion of subjects who discontinued from treatment was similar in the imetelstat and placebo groups (77.1% and 76.3% of subjects, respectively). The most common reasons for treatment discontinuation were lack of efficacy,

which was higher in the placebo group (42.4%) compared to the imetelstat group (23.7%), followed by subjects refusing further study treatment (16.9% and 13.6% subjects, respectively). No subjects in the placebo group discontinued treatment due to an AE compared to 16.1% of subjects in the imetelstat group. Discontinuations due to AEs in the imetelstat group were mainly due to cytopenias (8.5%). Treatment discontinuation due to disease relapse was higher in the imetelstat group (14.4%) compared to the placebo group (1.7%). Progressive disease accounted for treatment discontinuation in 5.9% and 8.5% subjects in the imetelstat and placebo groups, respectively, with very few subjects discontinuing due to transformation to AML (1.7% in both groups). Median time on treatment was longer for subjects in the imetelstat group (7.82 months; range: 0.03 to 32.5 months) compared to subjects in the placebo group (6.5 months; range: 0.03 to 26.7 months).

- **Recruitment**

Study initiation (first subject enrolled): 11 September 2019

Data Cutoff date: 13 October 2022

- **Conduct of the study**

The original protocol was amended 7 times. Phase 3 of the study started enrolling under Amendment 3.

Before the start of enrolment in Amendment 3, the planned primary efficacy and safety analysis was changed from 12 months to 15 months after the last subject had been randomised. In Amendment 7, this time point was restored to 12 months because it was believed to yield sufficient follow-up information.

After protocol amendment 7, transfusion data were only collected until the first post-treatment transfusion.

Major protocol deviations are summarised in **Table 6**.

Table 6. Major Protocol Deviations in Study MDS3001 (Phase 3, Intent-to-Treat Analysis Set)

	Imetelstat (N=118) n (%)	**Placebo (N=60) n (%)**	**Total (N=178) n (%)**
Major protocol deviations	55 (46.6%)	22 (36.7%)	77 (43.3%)
IP admin/study treat	38 (32.2%)	11 (18.3%)	49 (27.5%)
Correctness of study treatment administration[a]	35 (29.7%)	8 (13.3%)	43 (24.2%)
Study drug not administered according to the protocol schedule[b]	5 (4.2%)	4 (6.7%)	9 (5.1%)
Incorrect treatment assignment	1 (0.8%)	0	1 (0.6%)
Procedures/tests	21 (17.8%)	11 (18.3%)	32 (18.0%)
Incorrect stratification	15 (12.7%)	6 (10.0%)	21 (11.8%)
Haematology labs not done at scheduled visits	7 (5.9%)	5 (8.3%)	12 (6.7%)

Chemistry not done at scheduled visits	1 (0.8%)	1 (1.7%)	2 (1.1%)
AEs/SAEs	7 (5.9%)	2 (3.3%)	9 (5.1%)
AEI/SAE not reported as per protocol[c]	7 (5.9%)	2 (3.3%)	9 (5.1%)
Inclusion/exclusion criteria	3 (2.5%)	2 (3.3%)	5 (2.8%)
Exclusion criterion 5.3 met: subject has received an ESA or any chemotherapy, immunomodulatory, or immunosuppressive therapy within 4 weeks prior to study entry (8 weeks for long-acting ESAs)	1 (0.8%)	1 (1.7%)	2 (1.1%)
Exclusion criterion 18 met: subject with MDS/myeloproliferative neoplasm overlap syndrome	1 (0.8%)	0	1 (0.6%)
Exclusion criterion 5.1 met: prior treatment with a hypomethylating agent (eg, azacitidine, decitabine)	0	1 (1.7%)	1 (0.6%)
Exclusion criterion 5.2 met: prior treatment with lenalidomide	1 (0.8%)	0	1 (0.6%)
Prohibited medication: subject received a prohibited medication during the study[d]	1 (0.8%)	1 (1.7%)	2 (1.1%)

[a] *Included study treatment not held due to toxicity as per protocol, study treatment dose not reduced due to toxicity per protocol, treatment administered prior to availability of lab results, study treatment interruption lasting > 28 days, and treatment restarted without Sponsor approval.*

[b] *Study treatment was administered < 25 days from the prior dose.*

[c] *All AEIs/SAEs were reported later than required per protocol.*

[d] *Subject 300116 (placebo group) received prednisolone for 2.5 months, 40 mg daily. Subject 300244 (imetelstat group) received thromboreductin, which should have been discontinued prior to the study entry.*

AE = adverse event; AEI = adverse event of interest; ESA = erythropoietin stimulating agent; MDS = myelodysplastic syndromes; SAE = serious adverse event.

- **Baseline data**

Table 7. Demographic Characteristics in Study MDS3001 (Phase 3, Intent-to-Treat Analysis Set)

	Imetelstat (N=118)	**Placebo (N=60)**	**Total (N=178)**
Age (years)			
Mean (SD)	70.4 (8.82)	71.7 (8.95)	70.9 (8.86)
Median	71.5	73.0	72.0
Minimum, maximum	44, 87	39, 85	39, 87
Age group, n (%)			
< 65 years	27 (22.9%)	9 (15.0%)	36 (20.2%)
≥ 65 years	91 (77.1%)	51 (85.0%)	142 (79.8%)
<75 years	83 (70.3%)	37 (61.7%)	120 (67.4%)
≥ 75 years	35 (29.7%)	23 (38.3%)	58 (32.6%)

	Imetelstat (N=118)	Placebo (N=60)	Total (N=178)
Gender, n (%)			
Female	47 (39.8%)	20 (33.3%)	67 (37.6%)
Male	71 (60.2%)	40 (66.7%)	111 (62.4%)
Ethnicity, n (%)			
Hispanic or Latino	6 (5.1%)	5 (8.3%)	11 (6.2%)
Not Hispanic or Latino	100 (84.7%)	48 (80.0%)	148 (83.1%)
Unknown	1 (0.8%)	1 (1.7%)	2 (1.1%)
Not reported	11 (9.3%)	6 (10.0%)	17 (9.6%)
Race, n (%)			
White	95 (80.5%)	48 (80.0%)	143 (80.3%)
Black or African American	1 (0.8%)	2 (3.3%)	3 (1.7%)
Asian	8 (6.8%)	2 (3.3%)	10 (5.6%)
Other	1 (0.8%)	1 (1.7%)	2 (1.1%)
Unknown	1 (0.8%)	1 (1.7%)	2 (1.1%)
Not reported	12 (10.2%)	6 (10.0%)	18 (10.1%)
Region, n (%)			
North America	13 (11.0%)	12 (20.0%)	25 (14.0%)
European Union	80 (67.8%)	38 (63.3%)	118 (66.3%)
Rest of world	25 (21.2%)	10 (16.7%)	35 (19.7%)

Table 8. Disease and Other Baseline Characteristics in Study MDS3001 (Phase 3, Intent-to-Treat Analysis Set)

	Imetelstat (N=118)	Placebo (N=60)	Total (N=178)
Time since initial diagnosis (years)			
Mean (SD)	4.834 (4.3173)	3.825 (3.9462)	4.494 (4.2120)
Median	3.544	2.762	3.321
Minimum, maximum	0.10, 26.66	0.15, 25.68	0.10, 26.66
< 2 years, n%	31 (26.3%)	22 (36.7%)	53 (29.8%)
≥ 2 years, n%	87 (73.7%)	38 (63.3%)	125 (70.2%)
Prior RBC transfusion burden applied at randomisation[a], n (%)			
≤ 6 units	57 (48.3%)	28 (46.7%)	85 (47.8%)

> 6 units	61 (51.7%)	32 (53.3%)	93 (52.2%)
Prior RBC transfusion burden per modified IWG 2006			
Mean (SD)	7.3 (3.56)	6.9 (2.40)	7.2 (3.21)
Median	6.0	6.0	6.0
Minimum, maximum	4, 33	4, 13	4, 33
≤6 units, n%	62 (52.5%)	33 (55.0%)	95 (53.4%)
>6 units, n%	56 (47.5%)	27 (45.0%)	83 (46.6%)
WHO classification (2008)			
RS+ (RARS/RCMD-RS/MDS/MPN-RS-T)	73 (61.9%)	37 (61.7%)	110 (61.8%)
RS- (Others)	44 (37.3%)	23 (38.3%)	67 (37.6%)
RARS	50 (42.4%)	23 (38.3%)	73 (41.0%)
RCUD-RA	12 (10.2%)	7 (11.7%)	19 (10.7%)
RCUD-RT	1 (0.8%)	0	1 (0.6%)
RCMD	44 (37.3%)	27 (45.0%)	71 (39.9%)
RCMD-RS	23 (19.5%)	14 (23.3%)	37 (20.8%)
RAEB-1	5 (4.2%)	2 (3.3%)	7 (3.9%)
RAEB-2	1 (0.8%)	0	1 (0.6%)
MDS-U	4 (3.4%)	1 (1.7%)	5 (2.8%)
Missing	1 (0.8%)	0	1 (0.6%)
Local bone marrow blasts, n (%)			
≤5%	115 (97.5%)	58 (96.7%)	173 (97.2%)
>5%	3 (2.5%)	2 (3.3%)	5 (2.8%)
Central bone marrow blasts, n (%)			
≤5%	117 (99.2%)	56 (93.3%)	173 (97.2%)
>5%	1 (0.8%)	1 (1.7%)	2 (1.1%)
Missing	0	3 (5.0%)	3 (1.7%)
IPSS category applied at randomization[a], n (%)			
Low	80 (67.8%)	40 (66.7%)	120 (67.4%)
Intermediate-1	38 (32.2%)	20 (33.3%)	58 (32.6%)
IPSS category based on CRF[b], n (%)			
Low	80 (67.8%)	39 (65.0%)	119 (66.9%)

Intermediate-1	38 (32.2%)	21 (35.0%)	59 (33.1%)
IPSS-R prognostic risk category[c], n (%)			
Very low	3 (2.5%)	2 (3.3%)	5 (2.8%)
Low	87 (73.7%)	46 (76.7%)	133 (74.7%)
Intermediate	20 (16.9%)	8 (13.3%)	28 (15.7%)
High	1 (0.8%)	0	1 (0.6%)
Missing	7 (5.9%)	4 (6.7%)	11 (6.2%)
IPSS-R cytogenetic risk group[d], n (%)			
Very good	3 (2.5%)	2 (3.3%)	5 (2.8%)
Good	86 (72.9%)	45 (75.0%)	131 (73.6%)
Intermediate	22 (18.6%)	9 (15.0%)	31 (17.4%)
Missing	7 (5.9%)	4 (6.7%)	11 (6.2%)
Number of cytopenias, n (%)			
0-1	93 (78.8%)	49 (81.7%)	142 (79.8%)
2-3	25 (21.2%)	11 (18.3%)	36 (20.2%)
Serum erythropoietin (EPO) level (mU/mL)			
N	113	58	171
Mean (SD)	361.25 (556.018)	472.44 (763.935)	398.96 (634.147)
Median	174.86	277.00	184.10
Minimum, maximum	6.0, 4460.0	16.9, 5514.0	6.0, 5514.0
≤ 500 mU/mL, n (%)	87 (73.7%)	36 (60.0%)	123 (69.1%)
> 500 mU/mL, n (%)	26 (22.0%)	22 (36.7%)	48 (27.0%)
Missing, n (%)	5 (4.2%)	2 (3.3%)	7 (3.9%)
Prior treatment with, n (%)			
luspatercept	7 (5.9%)	4 (6.7%)	11 (6.2%)
ESA	108 (91.5%)	52 (86.7%)	160 (89.9%)
Weight (kg)			
Mean (SD)	75.53 (14.614)	75.28 (14.638)	75.44 (14.581)
Median	73.80	74.35	73.95
Minimum, maximum	47.7, 116.0	52.0, 112.0	47.7, 116.0
Height (cm)			
N	117	59	176

Mean (SD)	166.67 (9.299)	167.38 (8.652)	166.91 (9.069)
Median	167.00	167.80	167.60
Minimum, maximum	136.0, 190.0	146.0, 183.0	136.0, 190.0
ECOG score, n (%)			
0: Asymptomatic	42 (35.6%)	21 (35.0%)	63 (35.4%)
1: Symptomatic fully ambulatory	70 (59.3%)	39 (65.0%)	109 (61.2%)
2: Symptomatic in bed less than 50% of the day	6 (5.1%)	0	6 (3.4%)

[a] *Stratification factors.*

[b] *Final per investigator*

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

[d] *Derived by sponsor based on central lab cytogenetic data.*

CRF = case report form; ECOG = Eastern Cooperative Oncology Group; ESA = erythropoiesis-stimulating agent; FAB = French-American-British; HMA = hypomethylating agent; IPSS = International Prognostic Scoring System; IPSS-R = Revised International Prognostic Scoring System; MDS-u = myelodysplastic syndrome unclassifiable; RA = refractory anaemia; RAEB = RA with excess blasts; RARS = RA with ringed sideroblasts; RBC = red blood cell; RCMD = refractory cytopenia with multilineage dysplasia; RS = ring sideroblasts;

Transfusion history

Transfusion history was similar between the imetelstat and placebo groups. The median prior RBC transfusion burden was 6.0 units per 8 weeks (range: 4 to 33 and 4 to 13 for the 2 treatment groups, respectively), with almost half of the subjects in each of the groups having a prior RBC transfusion burden of > 6 units (47.5% and 45.0%, respectively).

The median total number of RBC transfusion units in the 16 weeks prior to study entry was 10.0 units (range: 4 to 54 and 4 to 24, respectively) for the 2 treatment groups. Overall, a larger proportion of subjects in the imetelstat group (82.2%) were classified per IWG 2018 as having a high transfusion burden (≥ 8 RBC units in the 16 weeks prior to study entry in at least 2 transfusion episodes) compared to the placebo group (70.0%).

2006 IWG criteria suggest that transfusion-dependence (TD) should be defined as receiving 4 units over 8 weeks. This definition was challenged in 2018 with the aim of ensuring a more robust baseline assessment by requiring 16 weeks rather than 8 weeks for the baseline assessment:

Low and high transfusion burden were defined:

- Low high transfusion burden was defined as having received 3 to 7 RBCs within 16 weeks of screening

- High transfusion burden was defined as having received ≥8 RBCs in 16 weeks of screening

Notably, baseline transfusion burden according to the revised IWG 2018 criteria differed; 18% of patients had low transfusion burden in the imetelstat arm vs 30% in the placebo arm. Lower transfusion dependence in the placebo arm could potentially lead to a conservative bias in the evaluation of the primary endpoint.

Concomitant Medications

The use of concomitant medication was reported for the majority of subjects in the imetelstat group (98.3%) and all subjects (100%) in the placebo group. The most common concomitant medications in the imetelstat and placebo groups, respectively, were iron chelating agents (63.6% and 62.7%), proton pump inhibitors (39.8% and 42.4%), other viral vaccines (38.1% and 30.5%), colony stimulating factors (34.7% and 3.4%), sulfonamides, plain (28.0% and 25.4%), folic acid and derivatives (folic acid; 26.3% and 23.7%), beta blocking agents, selective (23.7% and 28.8%), and anilides (21.2% and 27.1%).

G-CSF was used concomitantly in 34.7% of patients in the imetelstat arm and in 3.4% of patients in the placebo arm.

Subsequent anticancer therapy

Subsequent anti-cancer therapy was reported for 33.9% of subjects in the imetelstat group and 42.4% subjects in the placebo group. The most common subsequent anti-cancer medications in the imetelstat and placebo groups, respectively, were other anti-anaemic preparations (23.7% and 27.1%; including luspatercept [22.0% and 23.7%]), pyrimidine analogues (7.6% and 11.9%), other antineoplastic agents (5.1% and 1.7%), and other immunosuppressants (lenalidomide, 2.5% and 6.8%). Four subjects in the imetelstat group and 2 subjects in the placebo group had a stem cell transplant in post treatment follow-up.

- **Numbers analysed**

- ITT Analysis Set: included all subjects randomized into the main study. This analysis set was used for all analyses of efficacy and PRO endpoints (except time to the 8- or 24- week RBC TI and duration of RBC TI), analyses of disposition, demographic, and baseline disease characteristics. Subjects were classified according to assigned treatment group, regardless of the actual treatment received.
- Modified ITT (mITT) Analysis Set: included all ITT subjects who received at least 1 dose of study drug according to assigned treatment group. This analysis set was used for sensitivity analyses for 8-week and 24-week RBC TI in the case there were subjects who were dosed but did not receive the assigned treatment.
- Per-protocol (PP) Analysis Set: was a subset of the ITT analysis set. Subjects with key protocol deviations were excluded from the PP analysis set. The categories and terms of the key protocol deviations leading to exclusion were defined in the project-specific Protocol Deviation Specification. Subjects in this analysis set were analysed according to the treatment to which they were randomized. This analysis set was used for sensitivity analysis for 8-week and 24-week RBC TI.
- Safety Analysis Set: included all subjects who received at least 1 dose of study drug. This analysis set was used for all safety analyses and analyses of exposure. All subjects were analysed according to the treatment which they actually received.
- Biomarker Analysis Set: included all subjects who received at least 1 dose of study drug and had at least 1 biomarker sample collected at baseline.
- PK Plasma Concentration Analysis Set: included all subjects who have received at least 1 dose of imetelstat and have at least 1 quantifiable imetelstat concentration, regardless of their inclusion in the PK Parameter Population.
- PK Parameter Analysis Set: included all subjects who had received at least 1 dose of imetelstat and who had sufficient data to calculate PK parameters for plasma imetelstat.

- Immunogenicity Analysis Set: included all subjects who had received at least 1 dose of imetelstat and had appropriate samples for detection of antibodies to imetelstat (i.e., subjects with at least 1 sample obtained after administration of at least 1 dose of imetelstat).
- PRO Analysis Set: included all subjects from the ITT population who had available FACIT-Fatigue data at baseline.

The number of subjects included in these analyses are summarised in **Table 9**.

Table 9. Study Population in Study MDS3001 (Phase 3, Intent-to-Treat Analysis Set)

	Imetelstat (N=118) n (%)	**Placebo (N=60) n (%)**	**Total (N=178) n (%)**
Analysis set: Intent-to-treat (ITT)	118	60	178
Modified ITT (MITT) analysis set	118 (100.0%)	59 (98.3%)	177 (99.4%)
Per-protocol (PP) analysis set	115 (97.5%)	59 (98.3%)	174 (97.8%)
Safety analysis set	118 (100.0%)	59 (98.3%)	177 (99.4%)
Biomarker analysis set[a]			
Telomerase Activity (TA)	41 (34.7%)	26 (43.3%)	67 (37.6%)
Telomere Length (TL)	93 (78.8%)	50 (83.3%)	143 (80.3%)
Human Telomerase reverse transcriptase (hTERT)	100 (84.7%)	51 (85.0%)	151 (84.8%)
Mutation	110 (93.2%)	55 (91.7%)	165 (92.7%)
Cytogenetic	111 (94.1%)	55 (91.7%)	166 (93.3%)
PRO analysis set[b]	118 (100.0%)	57 (95.0%)	175 (98.3%)

[a] *Biomarker analysis set included all the subjects who have received at least one dose of study drug and had baseline data available.*

[b] *PRO population included all ITT subjects who had available FACIT-Fatigue data at baseline. PRO = patient-reported outcome.*

- **Outcomes and estimation**

Results of Primary Endpoint Analyses

The study met the primary endpoint with a statistically significant and improvement in 8-week RBC TI rate in the imetelstat group compared to the placebo group (

Table 10).

Table 10. 8-Week Rate of RBC TI in Study MDS3001 (Phase 3, Intent-to-Treat Analysis Set)

	Phase 3 Total Population (N = 178)			
			Imetelstat vs Placebo	
	Imetelstat (N=118)	**Placebo (N=60)**	**% Difference (95% CI)[a]**	***P*-value[b]**
8-week RBC TI, n (%)	47 (39.8)	9 (15.0)	24.8 (9.90, 36.89)	<0.001
95% CI[c] for response rate (%)	(30.93, 49.25)	(7.10, 26.57)		

[a] The 95% CI was based on Wilson Score method.
[b] The *P* value was based on CMH controlling for prior RBC transfusion burden (≤6 vs >6 units RBC) and IPSS risk group (low vs intermediate-1) applied to randomization.
[c] Exact Clopper-Pearson CI.

Because the primary endpoint is difficult to interpret and potentially biased as the imetelstat group had more time to achieve transfusion independence, the following analyses were requested, with non-response imputation of any missing data:

a. Time to subsequent anti-cancer therapy for each treatment group (median, min, max).
b. 8-week RBC TI during the entire follow-up period, ignoring treatment discontinuations and use of new anti-cancer treatment (treatment policy strategy).
c. 8-week RBC TI until week 24, ignoring treatment discontinuations and use of new anti-cancer treatment (treatment policy strategy).
d. 8-week RBC TI until week 48, ignoring treatment discontinuations and use of new anti-cancer treatment (treatment policy strategy).
e. 24-week RBC TI until week 48, ignoring treatment discontinuations and use of new anti-cancer treatment (treatment policy strategy).

The applicant provided these analyses, are presented below (**Table 11**-**Error! Reference source not found.**).

Table 11. Summary of Time to Subsequent Anti-cancer Therapy; Part 2, Intent-to-Treat Analysis Set (Study MDS3001)

	Imetelstat (N=118)	**Placebo (N=60)**
Time to Subsequent Anti-cancer Therapy in Weeks		
Mean (SD)	55.27 (30.656)	45.85 (31.324)
Median* (Min, Max)	102.14 (0.1, 132.1)	64.14 (0.1, 146.1)

**Median is based on KM method, subjects without subsequent anticancer therapy are censord at last di sease evaluation date.*
Data cutoff date: 13 Oct 2022

Table 12. Rate of 8-week RBC TI During the Entire Follow-up Period (ignoring treatment discontinuations and use of new anti-cancer treatment); Part 2, Intent-to-Treat Analysis Set (Study MDS3001)

	Imetelstat (N=118)	**Placebo (N=60)**
8-week RBC TI (%)	50 (42.4%)	10 (16.7%)
95% CI for response rate (%) [a]	(33.33%, 51.81%)	(8.29%, 28.52%)
% Difference (95% CI) [b]	25.7% (10.49%, 38.06%)	
P-value [c]	< 0.001	

CI = confidence interval; RBC = red blood cell; TI = transfusion independence
[a] Exact Clopper-Pearson confidence interval.
[b] The 95% CI is based on Wilson score method.
[c] The p-value is based on Cochran-Mantel-Haenszel (CMH) controlling for prior RBC transfusion burden (≤ 6 vs > 6 units RBC) and IPSS risk group (low vs. intermediate-1) applied at randomization
Note: TI was derived regardless of start of subsequent therapy or last dose of treatment. For subjects who discontinued treatment, transfusion status and transfusion records after the first RBC transfusion post end of treatment were not considered for TI derivation.
Data cutoff date: 13 Oct 2022

Table 13. Rate of 8-week RBC TI in the first 24 weeks (ignoring treatment discontinuations and use of new anti-cancer treatment); Part 2, Intent-to-Treat Analysis Set (Study MDS3001)

	Imetelstat (N=118)	**Placebo (N=60)**
8-week RBC TI in the First 24 weeks (%)	36 (30.5%)	6 (10.0%)
95% CI for response rate (%) [a]	(22.37%, 39.66%)	(3.76%, 20.51%)
% Difference (95% CI) [b]	20.5% (6.79%, 31.47%)	
P-value [c]	0.002	

CI = confidence interval; RBC = red blood cell; TI = transfusion independence
[a] Exact Clopper-Pearson confidence interval.
[b] The 95% CI is based on Wilson score method.

Note: TI was derived regardless of start of subsequent therapy or last dose of treatment. For subjects who discontinued treatment, transfusion status and transfusion records after the first RBC transfusion post end of treatment were not considered for TI derivation.
Data cutoff date: 13 Oct 2022

Subgroup analyses

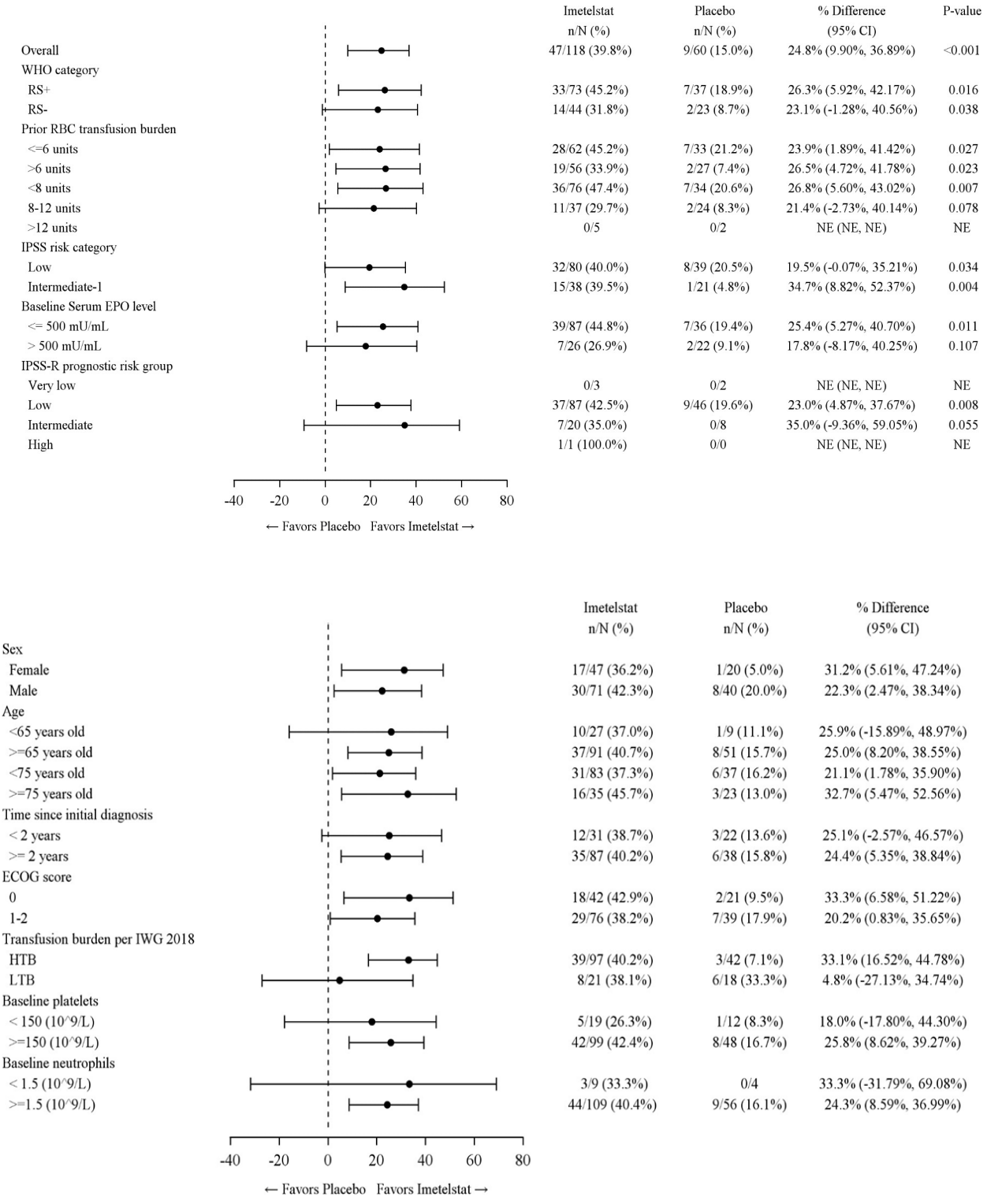


Figure 10. Subgroup Analysis of Rate of 8-week RBC TI in study MDS3001 (Phase 3, Intent-to-Treat Analysis Set)

Key Secondary Efficacy Variables

24-week RBC TI Rate

Table 14. Rate of 24-Week RBC TI in study MDS3001 (Phase 3, Intent-to-Treat Analysis Set)

	Phase 3 Total Population (N = 178)			
			Imetelstat vs Placebo	
	Imetelstat (N=118)	**Placebo (N=60)**	**% Difference (95% CI)[a]**	***P*-value[b]**
24-week RBC TI, n (%)	33 (28.0)	2 (3.3)	24.6 (12.64, 34.18)	<0.001
95% CI[c] for response rate (%)	(20.10, 36.98)	(0.41, 11.53)		

[a] The 95% CI was based on Wilson Score method.
[b] The P value was based on CMH controlling for prior RBC transfusion burden (≤6 vs >6 units RBC) and IPSS risk group (low vs intermediate-1) applied to randomization.
[c] Exact Clopper-Pearson CI.

1-year RBC TI Rate

Though not a secondary endpoint, 1-year RBC TI was achieved by 13.6% (16/118) of imetelstat-treated subjects versus 1.7% (1/60) of placebo-treated subjects, with the difference between the 2 treatment groups of 11.9% (95% CI: 1.86%, 19.87%, P = .012.

Duration of Red Blood Cell Transfusion Independence

Treatment with imetelstat resulted in statistically significant durability of RBC TI for subjects who achieved 8-week RBC TI. Additional evidence of long continuous TI achieved with imetelstat can be seen among the subjects who achieved 24-week RBC-TI (**Table 20**).

The swimmer plot of subjects achieving 8-Week RBC TI Intervals is shown in

Table 15. Summary of Duration of RBC TI in study MDS3001 (Phase 3, Intent-to-Treat Analysis Set)

	Phase 3 Total Population (N = 178)			
	Imetelstat (N=47)	**Placebo (N=9)**	**Imetelstat vs Placebo**	
			Hazard Ratio (95% CI)[a]	***P*-value [b]**
Subjects who achieved 8-week RBC TI	47	9	-	
Number censored, n (%)	17 (36.2)	1 (11.1)		
Number of events, n (%)	30 (63.8)	8 (88.9)		
Duration of RBC TI (weeks)				

	Phase 3 Total Population (N = 178)			
	Imetelstat (N=47)	Placebo (N=9)	Imetelstat vs Placebo	
			Hazard Ratio (95% CI)[a]	*P*-value [b]
Median (95% CI)[c]	51.6 (26.86, 83.86)	13.3 (8.00, 24.86)	0.23 (0.091, 0.571)	<0.001
Minimum, maximum	8.0+, 136.9	8.0, 111.3+		
Subjects who achieved 24-week RBC TI	33	2	-	
Number censored (%)	15 (45.5)	1 (50.0)		
Number of events (%)	18 (54.5)	1 (50.0)		
Duration of RBC TI (weeks)				
Median (95% CI) [c]	80.0 (51.57, NE)	NE (24.86, NE)	0.59 (0.069, 5.103)	0.655
Minimum, maximum	24.9, 136.9	24.9, 111.3+		

[a] Hazard ratio and 95% CI are from the Cox proportional hazard model, stratified by prior RBC transfusion burden (≤ 6 vs > 6 units RBC) and IPSS risk group (low vs intermediate-1), with treatment as the only covariate.
[b] P-value (2-sided) for superiority of imetelstat versus placebo in hazard ratio, using stratified log-rank test.
[c] Based on Kaplan-Meier product limit estimates.
Number assessed refers to responders; the table only includes responders.
Phase 3: ITT 8-week and 24-week TI Responder Analysis Set

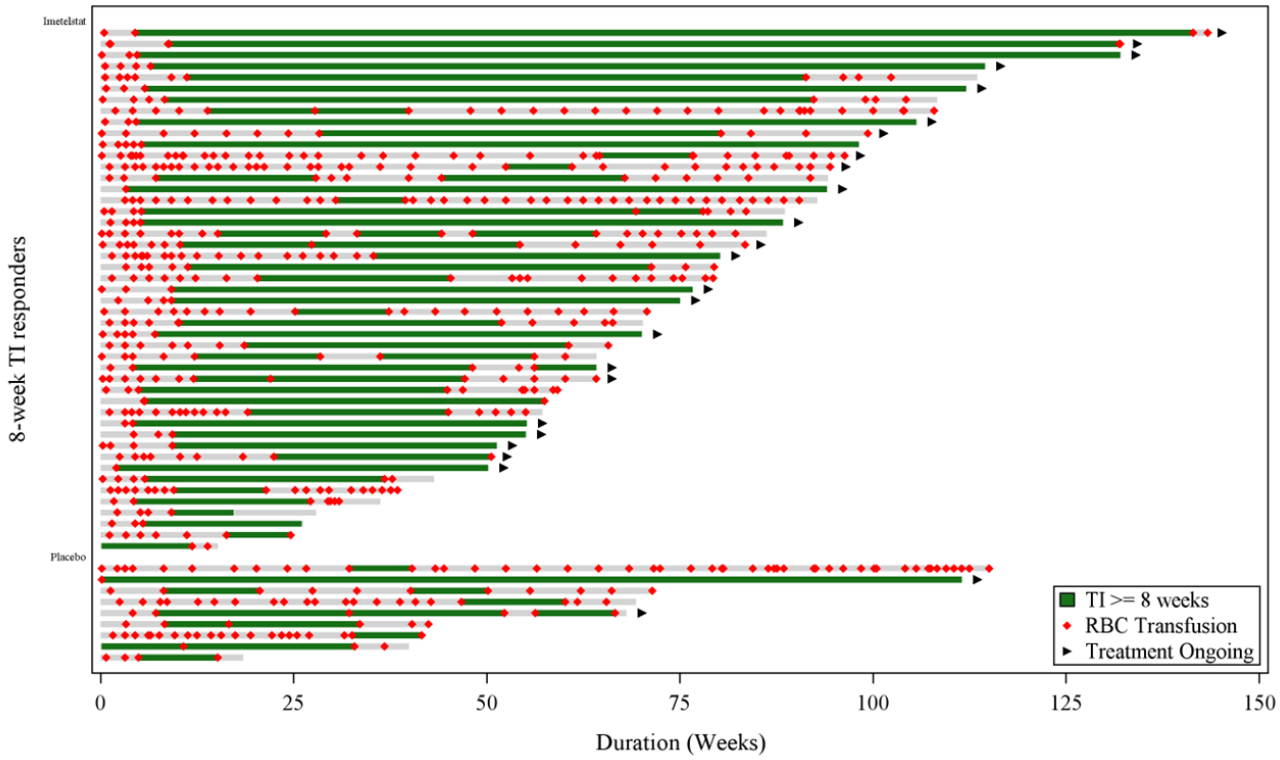


Figure 11. Swimmer Plot of 8-Week RBC TI Intervals in Phase 3 (Intent-to-Treat 8-Week TI Responder Analysis Set)

There was 1 long-term 8-week RBC TI responder in the placebo group. This subject had a pretreatment Hb of 6.2 g/dL with transfusion burden of 5 units/8 weeks before study start, including receiving a transfusion of 1 unit prior to randomization for a Hb of 7 g/dL. However, on-study Hb was < 6.5 g/dL during the majority of the TI period, yet no transfusions were given after randomization. Hb = haemoglobin; TI = transfusion independence; RBC = red blood cell.

Rate of HI-E Per Modified IWG 2006

Haematologic improvement-erythroid response was defined as (1) a Hb rise of at least 1.5 g/dL above the pretreatment level and lasting at least 8 weeks, or (2) reduction of at least 4 units of RBC /8 weeks compared with the prior RBC transfusion burden (criterion adapted from the modified IWG 2006 [Cheson, 2006]). Baseline pretreatment Hb level was defined as the average of all the Hb values in the 8 weeks prior to C1D1, including the value on C1D1 and excluding values that were within 14 days after transfusion (thus considered to be influenced by transfusion). If there were no Hb values that met this definition of not being influenced by transfusions, then the baseline value was used.

The HI-E rate based on IWG 2006 criteria was 63.6% in the imetelstat group compared with 51.7% in the placebo group ($P = 0.112$). Hb increase ≥ 1.5 g/dL above pretreatment and lasting ≥ 8 weeks favoured imetelstat (33.9%) compared with 10.0% in the placebo group ($P < 0.001$). Transfusion reduction by ≥ 4 units/8 weeks was achieved by 60.2% of subjects in the imetelstat group compared with 50.0% in the placebo group ($P = 0.175$). While acknowledging the high rate of transfusion reduction by ≥ 4 units/8 weeks by placebo-treated subjects, this reduction was not sustained over time. Further analysis showed that only 13% of placebo responders continued to have transfusion reduction in the 8-week interval after the best 8-week interval, while 77% of imetelstat responders continued to have durable transfusion reduction in the subsequent 8-week interval, thus further validating the use of a 16-week interval according to the IWG 2018 criteria.

No HI-P response was observed for any subject in the imetelstat or placebo treatment groups. Due to the protocol inclusion criterion of ANC 1.5×10^9/L, no subjects could be considered eligible for haematologic improvement-neutrophil response.

Rate of HI-E Per Revised IWG 2018

After the start of the study, new criteria for HI-E response were established (revised IWG 2018 criteria [Platzbecker, 2019]). An analysis using the IWG 2018 criteria was also performed. which is considered more clinically relevant in MDS than the previous IWG 2006 criteria as it emphasizes durability of response over a 16-week interval versus an 8-week interval used by the 2006 IWG criteria. HI-E per IWG 2018 criteria was 42.4% in subjects treated with imetelstat vs. 13.3% with placebo ($p < 0.001$), reflecting the increased durability of the RBC-TI response with imetelstat.

Among low transfusion burden subjects (who received 3 to 7 RBC units in the 16 weeks prior to study entry), the HI-E response rate was 33.3% and 22.2% in imetelstat and placebo subjects, respectively ($p = 0.562$). Among high transfusion burdens subjects (who received ≥ 8 RBC units in the 16 weeks prior to study entry), 30.9% of imetelstat subjects and none in the placebo group had a major HI-E response ($p < 0.001$) and 44.3% of the imetelstat-treated subjects compared to 9.5% of the placebo-treated subjects had a minor HI-E response ($p < 0.001$).

Assessment of Transfusion Practices

Per protocol, transfusions were administered as needed per investigator discretion and according to local standard practices. The protocol did not outline transfusion parameters, such as Hb level threshold for administering transfusion. Analysis performed evaluating the Hb levels prior to receiving RBC transfusions on study demonstrated a median Hb of 7.4 g/dL on imetelstat and 7.5 g/dL on

placebo. Pre-study baseline Hb levels leading to transfusions were also compared to on-study Hb levels resulting in transfusions.

Change in Haemoglobin Level

Imetelstat treatment led to a significant and sustained increase in Hb levels (based on central laboratory results) compared to placebo treatment, with the median Hb rise from pretreatment in the longest TI period for 8-week RBC TI responders of 3.6 g/dL in the imetelstat group compared to 0.8 g/dL in the placebo group. Median Hb peak in the longest RBC TI interval was 11.3 g/dL in the imetelstat group compared to 8.9 g/dL in the placebo group. The median average Hb rise from pretreatment during the longest TI interval was 2.4 g/dL in the imetelstat groups and 0.4 g/dL in the placebo group, with a median average Hb level of 10.0 g/dL and 8.7 g/dL, respectively.

Disease Progression and Progression to AML

With a median follow-up of 19.48 and 17.51 months in the imetelstat and placebo groups, respectively, 12 (10.2%) subjects in the imetelstat group and 6 (10.0%) subjects in the placebo group had disease progression, including 2 (1.7%) and 1 (1.7%) subjects, respectively, who had transformation to AML during follow-up. Of note, 1 of the subjects on imetelstat with disease progression who subsequently transformed to AML was found to have MDS/MPN overlap on study (an exclusion criterion that was reported as a major protocol deviation). Three additional subjects (2 in the imetelstat group and 1 in the placebo group) progressed to AML but were censored from the analysis of progression to AML because they received subsequent anticancer therapy before progression to AML.

The majority of subjects had disease progression based on a ≥ 50% increase in blasts to > 5% blasts. Given that subjects were transfusion-dependent at time of study entry, most subjects with transfusion-dependence as a reason for disease progression also had either evidence of disease progression by blasts or reduction in Hb.

Progression-free Survival

In Phase 3, with a median follow-up of 19.48 and 17.51 months in the imetelstat and placebo groups, respectively, the median estimated PFS was NE in both treatment groups. The Kaplan-Meier estimate of the proportion of subjects without a PFS event for the imetelstat and placebo groups, respectively, was 83.6% (95% CI: 74.06%, 89.81%) and 82.6% (95% CI: 66.06%, 91.60%) at 12 months.

The PFS data are considered preliminary, and subjects are still in follow-up.

Approximately 80% of both the imetelstat and placebo treatment groups were censored from PFS analysis due to being still at risk (35.6% and 28.3%, respectively), discontinuation from study (15.3% and 20.0%, respectively), or subsequent anti-cancer therapy study (29.7% and 35.0%, respectively).

Overall Survival

After a median follow-up of 19.48 months in the imetelstat group and 17.51 months in the placebo group, median OS was not reached in either treatment group.

After an additional 15 months of follow up, with a median follow-up time of ~31 months, the number of subjects who were alive (censored) was 83 (70.3%) in the imetelstat groups and 45 (75.0%) in the placebo group. Results from the primary and updated analyses are summarised in

Table 21.

Table 16. Summary of Overall Survival (MDS3001 Phase 3, ITT Analysis Set)

	Primary Analysis [c]		Updated Analysis [d]	
	Imetelstat (N=118)	**Placebo (N=60)**	**Imetelstat (N=118)**	**Placebo (N=60)**
Number assessed	118	60	118	60
Number censored (%)	99 (83.9%)	52 (86.7%)	83 (70.3%)	45 (75.0%)
Number of events (%)	19 (16.1%)	8 (13.3%)	35 (29.7%)	15 (25.0%)
Hazard Ratio (95% CI)[a]	1.07 (0.459, 2.476)		0.98 (0.526, 1.823)	
P-value [b]	0.882		0.949	
OS (months)				
25th percentile (95% CI)	25.3 (20.44, NE)	NE (14.42, NE)	28.5 (20.86, 31.84)	22.5 (14.78, NE)
Median (95% CI)	NE (29.31, NE)	NE (NE, NE)	40.4 (37.06, NE)	NE (32.16, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
OS rate, % (95% CI)				
12-months	92.5 (85.49, 96.17)	94.7 (84.49, 98.27)	92.4 (85.38, 96.14)	94.7 (84.49, 98.27)
24-months	77.1 (64.56, 85.73)	80.3 (62.88, 90.19)	77.6 (67.94, 84.67)	73.8 (59.03, 83.95)
36-months	66.0 (45.38, 80.31)	NE (NE, NE)	62.6 (50.69, 72.33)	66.7 (49.76, 79.05)

CI = confidence interval; NE = non evaluable; OS = overall survival.
[a] Hazard ratio and 95% CI are from the Cox proportional hazard model, stratified by prior RBC transfusion burden (≤ 6 vs. > 6 units RBC) and IPSS risk group (low vs. intermediate-1), with treatment as the only covariate
[b] P-value (two-sided) for superiority of imetelstat versus placebo in hazard ratio, using stratified log-rank test.
[c] Data cutoff date: 13 Oct 2022
[d] Data cutoff date: 05 Jan 2024
Note: Survival rate and 95% CI are based on Kaplan-Meier method.

- **Ancillary analyses**

Mutation Status at Baseline and Change Over Time

Mutation analysis was performed by Next Generation Sequencing in the MDS gene panel, which includes 36 genes that are frequently mutated in MDS. Analysis based on baseline mutation status demonstrated that imetelstat had consistently superior 8-week RBC TI rates compared to placebo treatment regardless of numbers of mutations harboured or presence of poor prognosis mutations (*ASXL1, RUNX1, TP53, EZH2, ETV6;* Bejar, 2011).

SF3B1 is one of the most frequent mutations found in MDS and is associated with the RS subtype (Malcovati, 2015; Tang, 2019; Jafari, 2020). It is also significantly associated with lower Hb values, consistent with a high degree of ineffective erythropoiesis, higher neutrophil and platelet counts, and lower bone marrow blasts in LR-MDS patients (Malcovati, 2020). A total of 116 subjects had the SF3B1 mutation detected at baseline and at least 1 post-treatment mutation assessment, including 78 and 38

subjects in imetelstat and placebo group, respectively. The imetelstat group had sustained reduction of SF3B1 VAF over time compared to the placebo group, with 29.5% (23/78) of imetelstat-treated subjects versus 2.6% (1/38) of placebo-treated subjects achieving ≥ 50% reduction in SF3B1 VAF (*P* = .001).

In addition, compared to placebo treatment, a higher percentage of subjects in the imetelstat group achieved ≥ 50% VAF reduction in the mutation biomarkers TET2 (34.3% [12/35] versus 8.3% [1/12], DNMT3A (11.1% [2/18] versus 0/8, and ASXL1 (40.0% [4/10] versus 16.7% [1/6] genes, which are also highly prevalent in MDS patients and some associated with poorer outcomes (Thol, 2011; Liang, 2019). Reduction in mutation burden across multiple gene mutations characteristic of MDS supports the potential disease modifying activity of imetelstat.

Time to the 8-week and 24-week RBC TI

Median time to the start of 8-week RBC TI was similar in the imetelstat group (9.29 weeks [range: 0.1 to 64.7]) and placebo group (8.29 weeks [range: 0.1 to 46.9]). Median time to the start of 24-week RBC TI was 8.43 weeks (range: 2.1 to 35.4 weeks) in the imetelstat group and 3.79 weeks (range: 0.3 to 7.3 weeks) in the placebo group.

Median time to the start of 8-week RBC TI was similar between treatment groups. These medians were presumably calculated on responders only and is thus not a randomized comparison.

Improvement in Fatigue

The proportion of subjects who experienced any episode of sustained, meaningful improvement in fatigue (defined ≥3-point increase on the FACIT-Fatigue Scale for ≥2 consecutive non-missing treatment cycles) in the PRO population was higher (50%) in the imetelstat group than in the placebo group (40.4%). Evaluating meaningful improvement for at least one cycle, 67.8% of imetelstat-treated subjects versus 59.6% of placebo-treated subjects experienced meaningful improvement.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17. ***Summary of Efficacy for trial MDS3001 - Phase 3***

Title: A study to evaluate imetelstat (GRN163L) in transfusion-dependent subjects with IPSS low or intermediate-1 risk myelodysplastic syndrome (MDS) that is relapsed/refractory to erythropoiesis-stimulating agent (ESA) treatment		
Study identifier	63935937MDS3001 Phase 2/3 ClinicalTrials.gov identifier: NCT02598661 EudraCT number: 2015-002874-19	
Design	Phase III, blinded, randomized, two treatment arms, multi-centre	
	Duration of main phase:	~3 years First patient randomized: 11 Sep 2019 Last patient randomized: 15 Sep 2021 Data cut-off date: 13 Oct 2022
	Duration of Run-in phase:	not applicable

Hypothesis	Superiority		
Treatments groups	Imetelstat		Randomized: N = 118 Treated: N = 118 IV; starting dose: 7.1 mg/kg q4w
	Placebo		Randomized: N = 60 Treated: N = 59 IV; starting dose: 7.1 mg/kg q4w
Endpoints and definitions	Primary endpoint	8-week red blood cell (RBC) transfusion independence (TI) Rate	The proportion of subjects without any RBC transfusion during any consecutive 8 weeks starting from randomization
	Key secondary endpoint	24-week RBC TI Rate	The proportion of subjects without any RBC transfusion during any consecutive 24 weeks starting from randomization
	Secondary endpoint (not controlled for type 1 error)	Duration of RBC TI	Duration of RBC TI for subjects who achieved 8-week RBC TI
Database lock	Data cut-off date for the primary analysis: 13 Oct 2022		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population	**Intent-to-Treat (ITT) Analysis Set:** N = 178 (imetelstat: 118; placebo: 60)		
	Treatment group	Imetelstat	Placebo
	Number of subjects	N = 118	N = 60
Primary endpoint 8-week RBC TI (%)	Number of responders	n = 47	n = 9
	Response rate (%)	39.8	15.0
	95% CI for response rate (%)	(30.93, 49.25)	(7.10, 26.57)
	% Difference (95% CI)	24.8 (9.90, 36.89)	
	P-value	< 0.001	
Key secondary endpoint 24-week RBC TI (%)	Number of responders	n = 33	n = 2
	Response rate (%)	28.0	3.3

	95% CI for response rate (%)	(20.10, 36.98)	(0.41, 11.53)
	% Difference (95% CI)	24.6 (12.64, 34.18)	
	P-value	< 0.001	
Secondary endpoint Duration of RBC TI (weeks)	Subjects who achieved 8-week RBC TI	n = 47	n = 9
	Median duration of RBC TI (weeks)	51.6	13.3
	95% CI for duration of RBC TI (weeks)	(26.9, 83.9)	(8.0-24.9)
	HR (95% CI)	0.23 (0.091, 0.571)	
	P-value	nominal P < 0.001	

2.6.5.3. Clinical studies in special populations

Study MDS3001	**Age 65-74** N (%)	**Age 75-84** N (%)	**Age 85+** N (%)
Controlled Trial (N=178) Phase 3 (Part 2)	84 (47.2%)	50 (28.1%)	8 (4.5%)
Imetelstat (N=118)	56 (47.5%)	29 (24.6%)	6 (5.1%)
Placebo (N=60)	28 (46.7%)	21 (35.0%)	2 (3.3%)
Non-Controlled Trials (N=57) Phase 2 (Part 1)	25 (43.9%)	18 (31.6%)	0

Data cutoff date: 13 Oct 2022

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.6.5.6. Supportive study

Study MDS3001—Phase 2

The Phase 2 part of Study MDS3001 was a multicentre open-label single-arm study to evaluate the efficacy and safety of imetelstat in transfusion-dependent subjects with MDS who were R/R or ineligible for ESA. All subjects in Phase 2 were treated with imetelstat at a starting dose of 7.5 mg/kg IV every 4 weeks.

Results

Study Subjects and Exposure

A total of 57 subjects were enrolled, including 38 subjects who met the target population criteria of having neither prior HMA nor lenalidomide use and no del(5q) in karyotype at baseline.

All 57 subjects received study treatment, and all subjects had discontinued treatment at the time of the clinical cutoff and primary analysis. The most common reasons for discontinuing treatment were an AE (most commonly cytopenia, which per protocol required study treatment discontinuation after 2 dose reductions) and lack of efficacy (29.8% each), followed by disease progression (12.3%). Median time on treatment for all subjects was 7.43 months.

Most subjects were White (80.7%) and not Hispanic or Latino (84.2%). Just over half the subjects were male (56.1%). The median age was 71.0 years; 75.4% of all subjects were ≥ 65 years old, and 31.6% of all subjects were ≥ 75 years old.

Most baseline disease characteristics were similar for subjects in the target population and the total population, including ≤ 5% bone marrow blasts at baseline (92.1% and 91.2%, respectively), proportions of subjects with IPSS low and intermediate-1 category (63.2% and 36.8% for both the target population and for all subjects overall), and proportions of subjects with 2 to 3 cytopenias (10.5% and 14.0% for the 2 populations, respectively). Per WHO classification, 61.4% of subjects overall were RS+ and 38.6% were RS-. Most subjects (91.2%) had a baseline ECOG score of ≤ 1.

Most subjects had a high transfusion burden at baseline (median of 8.0 units per 8 weeks and up to 14 units per 8 weeks for the target population or median of 7.0 units per 8 weeks for the overall subjects population), with approximately half of the subjects having a prior RBC transfusion burden of > 6 units. Most subjects (approximately 90%) were classified per IWG 2018 as having a HTB (≥ 8 RBC units in the 16 weeks prior to study entry in at least 2 transfusion episodes).

Most subjects had prior ESA treatment, and approximately one-third of subjects had serum EPO > 500 mU/mL at baseline, indicating a low likelihood to respond to or be candidates for further ESA therapy.

Median duration of treatment was 32.3 weeks (or 7.4 months); 61.4% of subjects completed 24 weeks of treatment, and 38.6% of subjects completed 48 weeks of treatment. Median dose intensity was 6.8 mg/kg/cycle in both the target population and the overall subject population. Twenty-one (36.8%) subjects remained on treatment at 1 year.

Efficacy

Efficacy results of imetelstat in 57 subjects with transfusion-dependent LR-MDS (median follow-up of 57.3 months), including 38 subjects who were non-del(5q) and HMA and lenalidomide-naive (target population; median follow-up of 57.0 months) can be summarized as follows:

Primary Endpoint

The rate of 8-week RBC TI in the target population was 42.1%. Among all subjects overall, the 8-week RBC TI rate was 36.8%.

Imetelstat demonstrated comparable clinical benefit across most subgroups in the target population, including RS status (44.4% [RS+] and 36.4% [RS-]), baseline transfusion burden (47.1% [≤ 6 units] and 38.1% [> 6 units]), and baseline serum EPO levels (48.0% [≤ 500 mU/mL] and 33.3% [> 500 mU/mL]).

Key Secondary Efficacy Endpoints

The rate of 24-week RBC TI in the target population was 31.6%. Among all subjects, the 24-week RBC TI rate was 24.6%.

Median duration of RBC TI among the 16 subjects in the target population who achieved 8-week RBC TI was 74.5 weeks. Among the 21 subjects in the overall subject population who achieved 8-week RBC TI, median duration of RBC TI was 69.6 weeks. Median duration of RBC TI among both the 12 subjects in the target population and the 14 subjects in the overall subject population who achieved 24-week RBC TI was 85.9 weeks.

Imetelstat treatment led to a sustained increase in Hb levels. The median Hb rise from pretreatment in the longest RBC TI period for 8-week RBC TI responders was 3.96 g/dL in the target population and 3.75 g/dL in the overall subject population. Median Hb peak in the longest RBC TI interval was 11.6 g/dL in the target population and 11.4 g/dL in the overall subject population.

Median relative change from baseline in RBC transfusion burden during the best 8-week interval was -77.8% in the target population and -66.7% in the overall subject population.

The rate of haematologic improvement per revised IWG 2018 among subjects in the target population the HI-E response rate was 50.0%. Among low-transfusion burden subjects (n = 4), the HI-E response rate was 50.0%. Among high-transfusion burden subjects (n = 34), 32.4% of subjects had a major HI-E response, and 50% of subjects had a minor HI-E response. HI-E rates were similar in the overall subject population.

The rate of HI-E per modified IWG 2006 criteria in the target population was 65.8%. Among all subjects overall, the rate of HI-E was 61.4%.

Other Secondary Efficacy Endpoints

Median OS was 55.2 months in the target population and 55.3 months in the overall subject population.

Median estimated PFS was 34.2 months in both the target population and the overall subject population. Eleven (28.9%) subjects in the target population and 13 (22.8%) subjects in the overall subject population had disease progression.

With post-treatment follow-up, 4 subjects, all in the target population, had reported progression to AML as of the cutoff date. Median estimated time to progression to AML was 44.2 months in the target population. In the overall subject population, the median estimated time to progression to AML was not reached.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The multi-centre, placebo-controlled, double-blind, randomised, phase 3 part of study MDS3001 represents the pivotal study for the intended label and the phase 2 part of study MDS3001 provides supportive efficacy and safety results.

Study population

The study population consisted of patients with IPSS low and intermediate-1 risk MDS. Diagnosis of MDS was based on the WHO classification. MDS diagnosis for screening (bone marrow biopsy, bone marrow aspirate, and peripheral blood samples) was centrally reviewed. In view of the primary endpoint, i.e. the evaluation of transfusion independence, baseline transfusion data must be clearly determined and the population be selected on this basis. Indeed, patients had to be transfusion dependent at baseline to be eligible for the study, defined as requiring at least 4 RBC units transfused over an 8-week period during the 16 weeks prior to randomization; pre-transfusion Hb should be ≤ 9.0 g/dL to count towards the 4 units total.

A further precondition was that patients were refractory or intolerant to, or ineligible for (baseline EPO >500 U/L) prior ESA treatment. The definition of 'refractory' to ESA therapy is not entirely in agreement with current clinical treatment guidelines, which recommend higher maximum doses than the ones suggested by the inclusion criterion, but this does not challenge external validity.

Patients with MDS associated with del(5q) cytogenetic abnormality were not included.

Overall, the study population as defined by the in- and exclusion criteria is representative for the target population that is to be treated. Stratification factors are endorsed.

The initially applied for indication by the applicant was "treatment of transfusion-dependent anaemia in adults with low- to intermediate-1 risk myelodysplastic syndromes (MDS) who have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA). "

CHMP requested that the indication should be revised for "treatment of adult patients with transfusion-dependent anaemia due to very low, low or intermediate risk myelodysplastic syndromes (MDS) and who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy" in accordance with the terminology of the Revised International Prognostic Scoring System (IPSS-R) and to be consistent with other approved products in the same indication; this was accepted by the applicant.

During the procedure, the applicant further elected to restrict the indication to patients without an isolated deletion 5q cytogenetic (non-del 5q) abnormality. The final approved indication therefore for imetelstat is: for the treatment of adult patients with transfusion-dependent anaemia due to very low, low or intermediate risk myelodysplastic syndromes (MDS) without an isolated deletion 5q cytogenetic (non-del 5q) abnormality and who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.

Objectives

The goals of therapy comparing lower and high-risk disease patients are slightly different: in patients with lower risk disease, treatment is focused on improving cytopenia (a large proportion of patients develop anaemia and become transfusion-dependent). Further, improvement of quality of life is a treatment goal, which is impaired not only by the symptoms related to cytopenia, but also by the chronic need of RBC transfusion in transfusion-dependent patients. In contrast, treatment in higher risk disease patients rather aims at modifying the disease course.

In this respect, the primary objective of the study, i.e., the evaluation of transfusion independence, is considered clinically relevant. According to the expert group statement on proposals for revised IWG 2018 haematological response criteria (Platzbecker et al., Blood 2019), a response lasting for at least 16 weeks would be considered clinically relevant. Scientific advice by the CHMP stated that the primary endpoint of 8-week TI rate was acceptable if supported by 24-week TI rate as a key secondary endpoint.

Endpoints

The primary efficacy endpoint was the rate of RBC TI lasting at least 8 weeks. The starting date of 8-week RBC TI duration was between Study Day 1 and the date of last dose of study drug + 30 days or End of Treatment Visit whichever occurred first, thus the primary endpoint was a *while on treatment* estimand. The 8-week period was also required to finish before the start of any new anti-cancer therapy.

The applicant did not use the estimand framework to describe how intercurrent events were handled. However, the definition of the primary endpoint implies that treatment discontinuations were handled using a type of while-on-treatment strategy, use of new anti-cancer treatment using a 'while-untreated' strategy, and deaths using a while-alive strategy. Use of prohibited medication other than

anti-cancer treatment and the use of allowed medications were in practice handled using a treatment policy strategy.

Handling deaths using a while-alive strategy is acceptable because it is reasonable to classify a deceased patient as a responder if he or she achieved transfusion independence before dying.

Use of prohibited medication other than anti-cancer treatment using a treatment policy strategy was considered acceptable, as only one patient in each group used prohibited medication. It is also acceptable to handle allowed concomitant medications using a treatment policy strategy.

However, it is inappropriate to handle treatment discontinuations using a while-on-treatment strategy because this strategy gives an advantage in terms of longer follow-up (more time to achieve transfusion independence) to the study group with fewer treatment discontinuations, which in this case was the imetelstat group. Results using a treatment policy, ignoring treatment discontinuations and use of new anti-cancer treatment is not merely as a sensitivity analysis in support of efficacy by normalising observation time across arms but a measure of providing a bias-free metric of efficacy. Therefore, the CHMP requested that it should be presented in the SmPC as the primary efficacy result.

The secondary endpoints were 'progression to AML' and 'OS', which are considered appropriate and relevant.

Sample size, randomisation, and statistical methods

The study was designed to enrol 170 patients. With this sample size, the study was estimated to have 88% power to detect an increase in RBC TI rate from 7.5% with placebo to 30% with imetelstat using a Chi-square test at the 5% level, assuming 10% dropout. This sample size and power calculation is acceptable.

Patients were randomly assigned 2:1 to receive either imetelstat or placebo. Randomisation was stratified by RBC transfusion burden ≤6 or > 6 units RBC) and by IPSS risk group (low versus intermediate-1). This randomisation procedure is acceptable.

With respect to the proposed double-blinded design, it should be taken into consideration that imetelstat has a safety profile with the potential of 'unblinding' the study (e.g., severe thrombocytopenia/neutropenia requiring dose modification/interruption and supportive treatment).

Efficacy data and additional analyses

In the phase 3 part of study MDS3001 a total of 317 subjects was screened, of whom 178 were randomized in a 2:1 ratio to the imetelstat (n = 118) or placebo (n= 60) treatment groups. In total, 177 subjects were treated (118 subjects received imetelstat and 59 subjects received placebo).

Loss to follow up from the study was uncommon: 2.5% in the imetelstat arm vs 1.7% in the placebo arm. Withdrawal from the study by the subject was somewhat more frequent in the placebo arm (16.9% in the imetelstat arm vs 18.3% in the placebo arm).

Twenty-three and 24% respectively for imetelstat- and placebo-treated patients were still on treatment at data cut-off. Median time on treatment was 7.8 and 6.5 months for imetelstat- and placebo-treated patients respectively.

There was a difference between arms in treatment discontinuation due to lack of efficacy and disease relapse (lack of efficacy: 23.7% in the imetelstat arm and 42.2% in the placebo arm, disease relapse: 14.4% in the imetelstat arm and 1.7% in the placebo arm). Because of these differences, there were concerns that investigators' decisions were biased due to functional unblinding.

As evidence against functional unblinding, the applicant argued that the median duration of treatment was similar in the two arms (33.9 weeks in the imetelstat arm and 28.3 weeks in the placebo arm).

The applicant also argued that functional unblinding was unlikely because the treatments were identical in appearance, had similar reconstitution characteristics, were administered in the same way, and both required premedication. Both groups also received supportive care.

The applicant's efforts to blind the study were acknowledged, and while functional unblinding in the study could not be ruled out, the CHMP considered that it was unlikely to strongly influence the reported results.

Changes in the conduct of the study

The original protocol was amended 7 times. Phase 3 of the study started enrolling under Amendment 3. The addition of an extension phase to evaluate long-term safety is acknowledged.

Before the start of enrolment in Amendment 3, the planned primary efficacy and safety analysis was changed from 12 months to 15 months after the last subject had been randomized. In Amendment 7, this time point was returned to 12 months because it was believed to yield sufficient follow-up information.

Baseline characteristics

Disease and other baseline characteristics were similar in the 2 treatment groups. Median age was 71 years (range 39-87) with 80% of subjects ≥65 years, and 62% were male. The imetelstat group was slightly younger compared to the placebo group with 77% versus 85% of subjects being ≥ 65 years old. The imetelstat arm included fewer men (60% in the imetelstat arm vs 67% in the placebo arm).

All included patients had IPSS low or intermediate-1 risk, which was in line with the inclusion criteria. Both the IPSS and IPSS-R stratify patients with MDS into risk categories based on blast percentage, number of cytopenias, and cytogenetic profile. 75% of patients in the imetelstat group and 78% of patients in the placebo group were classified as good or very good IPSS-R cytogenetic risk group.

The important characteristic of transfusion burden at baseline was similar in the 2 treatment groups. The median 8-week RBC transfusion volume over the 16 weeks prior to study entry was 10.0 units in both groups (range 4-54 for the active treatment arm and 4-24 for the placebo arm).

Twenty-two percent of the patients in the imetelstat arm vs 37% in the placebo arm had a baseline EPO > 500 mU/mL. The subgroup analysis showed that imetelstat might be less efficient in patients with EPO >500 and thus the difference in baseline EPO might lead to an anti-conservative bias. An analysis of the primary endpoint stratified at EPO ≤ or > 500 mU/mL, did however show consistent findings.

Prior ESA therapy was an important baseline characteristic and most patients had previously used ESAs. Since ESAs can influence baseline RBC requirement and were allowed until 4 weeks prior to randomisation, further information was requested on proportions of patients in each treatment group receiving ESAs during the 8 weeks before randomisation. The proportions were similar between arms, and the median time since the last ESA treatment was ~ 1 month in both groups, which is expected given that a 4-week washout window was required per protocol. Accordingly, it was ruled out that prior ESA treatment affected outcomes.

There were no noteworthy differences between subjects in the imetelstat and placebo groups for median baseline value of pretreatment haemoglobin (79.2 g/L and 78.0 g/L, respectively).

Outcomes

Primary endpoint

The primary endpoint, 8-Week Rate of RBC TI, showed statistically significantly higher response rates in the imetelstat treatment group compared with placebo (39.8 and 15.0%; p<0.001). Presented subgroup results of the primary endpoint showed an overall consistent treatment effect.

Key secondary endpoint

The key secondary endpoint, 24-week rate of RBC TI, showed statistically significantly higher response rates in the imetelstat treatment group compared with placebo (28.0 and 3.3%; p<0.001).

Analysis of the primary outcome measure

The primary endpoint can be difficult to interpret because it was not assessed over a fixed time period. The time period was shorter if a patient discontinued their randomised treatment or started new anti-cancer treatment. Since both treatment discontinuation and use of new anti-cancer treatment were less common in the imetelstat group than in placebo group, the imetelstat group had more time to achieve transfusion independence. This raised concerns that the results were biased in favour of imetelstat, so the applicant was asked to provide additional analyses ignoring treatment discontinuations and use of new anti-cancer treatment.

The 8-week TI rate including the entire follow-up period regardless of treatment discontinuation or initiation of subsequent therapy was similar to the primary Analysis and remained significantly higher for imetelstat-treated subjects compared with placebo (% difference: 25.7% [10.49%, 38.06%]; p-value < 0.001).

Similar results were also obtained when the RBC TI rate is evaluated over a fixed time period (the first 48 week of follow-up). Therefore, although the definition of the primary endpoint had an inherent limitation, with an obvious risk for bias in favour of the imetelstat group, the supplementary analyses provided by the applicant confirmed a robust effect.

Other secondary endpoints

Treatment with imetelstat resulted in statistically significant durability of RBC TI for subjects who achieved 8-week RBC TI, with a median duration of 51.6 weeks (95% confidence interval [CI]: 26.86, 83.86) in the imetelstat group versus 13.3 weeks (95% CI: 8.00, 24.86) in the placebo group.

However, as the comparison of the longest response is limited to responders, durability of RBC TI is a non-randomized comparison and the number of patients in the placebo arm is low, the results should be interpreted with caution. In addition, this analysis is not type-1-error controlled.

A specific molecular mechanism of resistance has not been identified by the applicant, however the SmPC indicates when to discontinue treatment in case of no response

Haematologic improvement-erythroid (HI-E) response was defined as (1) a Hb rise of at least 1.5 g/dL above the pretreatment level and lasting at least 8 weeks, or (2) reduction of at least 4 units of RBC /8 weeks compared with the prior RBC transfusion burden. The type I error-controlled endpoint of HI-E based on modified IWG 2006 criteria was not met. The HI-E rate based on IWG 2006 criteria was 63.6% in the imetelstat group compared with 51.7% in the placebo group (P = 0.112). Hb increase ≥ 1.5 g/dL above pretreatment and lasting ≥ 8 weeks favoured imetelstat (33.9%) compared with 10.0% in the placebo group (P < 0.001). Transfusion reduction by ≥ 4 units/8 weeks was achieved by 60.2% of subjects in the imetelstat group compared with 50.0% in the placebo group (P = 0.175).

An analysis of HI-E was also performed using the revised 2018 IWG criteria, which is considered more clinically relevant in MDS than the previous IWG 2006 criteria (Platzbecker, 2019), as it emphasizes durability of response over a 16-week interval versus an 8-week interval used by the 2006 IWG

criteria. HI-E per IWG 2018 criteria was 42.4% in subjects treated with imetelstat vs. 13.3% with placebo (nominal $p < 0.001$).

Transfusions were given at the investigators' discretion. There was no notable difference in investigators' transfusion practice between treatment groups on study.

After a median follow-up of 19.48 months in the imetelstat group and 17.51 months in the placebo group, median OS was not reached in either treatment group. As of the cutoff date for the primary analysis, the proportion of subjects who died was roughly similar between the 2 treatment groups (16.1% [19 subjects] in the imetelstat group and 13.3% [8 subjects] in the placebo group, HR = 1.07; 95% CI: 0.459, 2.476). In an updated analysis (05 Jan 2024) after an additional 15 months of follow up, with a median follow-up time of ~31 months, the number of subjects who were alive (censored) was 83 (70.3%) in the imetelstat groups and 45 (75.0%) in the placebo group, with a HR of 0.98 (95% CI: 0.526, 1.823)

Supportive study

The supportive, open label, phase part of study MDS3001 recruited 57 subjects, out of which 38 subjects were identified with similar disease and baseline characteristics as the phase 3 population (neither prior HMA nor lenalidomide use and no del(5q) in karyotype at baseline). The efficacy outcomes observed were consistent with the phase 3 results and are supportive to the phase 3 data.

2.6.7. Conclusions on the clinical efficacy

Available clinical data demonstrate clinically relevant efficacy and support the use of imetelstat in the treatment of transfusion-dependent anaemia in patients with very low, low- or intermediate risk MDS without an isolated deletion 5q cytogenetic (non-del 5q) abnormality who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

The applicant has submitted an integrated analysis of pooled safety data from five imetelstat monotherapy studies in haematologic malignancy indications ranging from Phase 2 to Phase 3, including the pivotal, Phase 3, placebo-controlled study titled MDS3001, performed in transfusion-dependent patients with IPSS Low- or Intermediate- 1 Risk MDS that is relapsed/refractory to ESA Treatment. The cut-off date for the pivotal study MDS3001 occurred on 13 October 2022; selected clinical safety data from the additional 1-year follow-up (Final Analysis, cutoff date 13 October 2023) has also been submitted.

The data from these 5 studies were analysed in 3 analysis pools as follows:

Table 18. Pooled Data Grouping to Support MDS MAA

Group	Classification	Number of Treated Subjects	Studies Included
A	MDS: imetelstat vs placebo treated; Phase 3	118 imetelstat vs 59 placebo	MDS3001 Phase 3
B	MDS: all imetelstat treated; Phase 2 and 3	175 imetelstat	MDS3001 Phase 2 and 3

C	Haematologic malignancies (MF, blastic MF, MDS/MPN overlap, MM, ET, and PV): monotherapy imetelstat; all Phase 2 and 3	391 imetelstat	MDS3001 Phase 2 and 3 CP14B015 (Phase 2) CP14B019 (Phase 2) MYF2001 (Phase 2) CP14B013 (Phase 2)[a]
Total number of subjects		391 imetelstat 59 placebo 450 total	

[a] *Four subjects who received imetelstat in combination with lenalidomide are not included in the safety analyses.*

ET = essential thrombocythemia; MDS = myelodysplastic syndrome; MF = myelofibrosis; MM = multiple myeloma; MPN = myeloproliferative neoplasms; PV = polycythaemia vera.

Since Group C, concerns imetelstat monotherapy studies in indications not proposed for licensure, data from that group is not further discussed in this report.

Group A - Study MDS3001: Phase 3 Imetelstat Versus Placebo

Table 19*:* Summary of Treatment Exposure - Study MDS3001 - Phase 3 Imetelstat Versus Placebo (Group A Treated Population)

	Imetelstat	**Placebo**
	Phase 3 (N=118)	**Phase 3 (N=59)**
Treatment duration (weeks)		
Mean (SD)	46.75 (34.304)	39.60 (29.196)
Median	33.93	28.29
Minimum, maximum	0.1, 141.1	0.1, 116.1
Number of treatment cycles received		
Mean (SD)	11.5 (8.14)	10.6 (7.08)
Median	8.0	8.0
Minimum, maximum	1, 34	1, 30
1-3 cycles, n (%)	15 (12.7%)	6 (10.2%)
4-6 cycles, n (%)	27 (22.9%)	12 (20.3%)
7-12 cycles, n (%)	28 (23.7%)	24 (40.7%)
≥13 cycles, n (%)	48 (40.7%)	17 (28.8%)
Dose interval (days)[a]		
Mean (SD)	31.2 (7.74)	28.7 (5.20)
Median	28.0	28.0
Minimum, maximum	21, 128	21, 133
Average dose intensity (mg/kg/cycle)		
Mean (SD)	6.787 (0.8844)	7.373 (0.3463)
Median	7.308	7.469
Minimum, maximum	4.80, 7.76	5.40, 7.88

Relative dose intensity with respect to planned dose		
Mean (SD)	99.608 (1.9243)	99.164 (2.2788)
Median	99.817	99.679
Minimum, maximum	84.49, 103.45	94.71, 105.10
Relative dose intensity with respect to the starting dose (7.5 mg/kg) (%)		
Mean (SD)	90.495 (11.7921)	98.301 (4.6170)
Median	97.437	99.583
Minimum, maximum	64.02, 103.42	71.96, 105.10
Subjects completing 24 weeks of treatment, n (%)	81 (68.6%)	41 (69.5%)
Subjects completing 48 weeks of treatment, n (%)	53 (44.9%)	17 (28.8%)

a Dose interval is defined as the days between two consecutive dosing dates across all cycles.
SD = standard deviation.

Study MDS3001 - Phase 2

In the Phase 2 imetelstat group (N = 57), median duration of treatment was 32.29 weeks (range: 0.1 to 260.1 weeks). Subjects received a median of 8 cycles of treatment and 36.8% of subjects received more than 13 cycles. In Phase 2, 61.4% of subjects completed 24 weeks of treatment, and 38.6% of subjects, respectively, completed 48 weeks of treatment.

2.6.8.1. Adverse events

Table 20: Overview of Treatment-emergent Adverse Events – Study MDS3001 – Phase 3 Imetelstat Versus Placebo (Group A Treated Population)

Subjects with ≥ 1:	**Imetelstat**	**Placebo**
	Phase 3 (N=118) n (%)	**Phase 3 (N=59) n (%)**
TEAE[a]		
Any	117 (99.2%)	59 (100.0%)
Grade 3/4	107 (90.7%)	28 (47.5%)
Grade 5 (fatal)	1 (0.8%)	1 (1.7%)
Study drug-related TEAE[b]		
Any	97 (82.2%)	20 (33.9%)
Grade 3/4	85 (72.0%)	6 (10.2%)
Grade 5 (fatal)	0	0
Treatment-emergent SAE	38 (32.2%)	13 (22.0%)
Study drug-related treatment-emergent SAE	6 (5.1%)	0
TEAE leading to treatment discontinuation	17 (14.4%)	0
Study drug-related TEAE leading to treatment discontinuation	11 (9.3%)	0
TEAEs leading to infusion interruption/abortion	7 (5.9%)	0
TEAEs leading to dose reduction or cycle delays	83 (70.3%)	14 (23.7%)

a Treatment-emergent AEs are defined as events that occur or worsen after the first dose of study drug. Treatment emergent events that were identified for each individual study are used for the pooled analyses.
b Study drug relationship is based on investigator assessment.
SAE = serious adverse event; TEAE = treatment-emergent adverse event.

TEAEs of any grade showed similar frequency in the imetelstat group compared to the placebo group (99.2% vs 100%, respectively), most of which in the imetelstat group were Grade 3/4 (90.7% vs 47.5%, respectively). TEAEs lead predominantly to dose reduction or cycle delays (70.3% vs 23.7%, respectively). A total of 14.4% of subjects discontinued treatment due to a TEAE in the imetelstat arm, compared to no subjects in the placebo. The pattern of TEAEs recorded in Phase 2 were generally consistent with the data presented from Phase 3.

Common adverse events

Table 21. Treatment-emergent Adverse Events Reported in ≥ 5% in Any Group (Treated Population) - Study MDS3001 - Phase 3 Imetelstat Versus Placebo (Group A Treated Population)

	Imetelstat	**Placebo**
Preferred Term	**Phase 3 (N=118)**	**Phase 3 (N=59)**
Subjects with ≥ 1 TEAE	117 (99.2%)	59 (100.0%)
Thrombocytopenia	89 (75.4%)	6 (10.2%)
Neutropenia	87 (73.7%)	4 (6.8%)
Anaemia	24 (20.3%)	6 (10.2%)
Asthenia	22 (18.6%)	8 (13.6%)
COVID-19	18 (15.3%)	4 (6.8%)
Headache	15 (12.7%)	3 (5.1%)
Alanine aminotransferase increased	14 (11.9%)	4 (6.8%)
Diarrhoea	14 (11.9%)	7 (11.9%)
Oedema peripheral	13 (11.0%)	8 (13.6%)
Leukopenia	12 (10.2%)	1 (1.7%)
Aspartate aminotransferase increased	11 (9.3%)	4 (6.8%)
Fatigue	11 (9.3%)	5 (8.5%)
Hyperbilirubinemia	11 (9.3%)	6 (10.2%)
Arthralgia	10 (8.5%)	2 (3.4%)
Back pain	10 (8.5%)	4 (6.8%)
Dyspnoea	10 (8.5%)	5 (8.5%)
Constipation	9 (7.6%)	7 (11.9%)
Pyrexia	9 (7.6%)	7 (11.9%)
Abdominal pain	7 (5.9%)	2 (3.4%)
Epistaxis	7 (5.9%)	0
Nausea	7 (5.9%)	3 (5.1%)
Pruritus	7 (5.9%)	1 (1.7%)
Urinary tract infection	7 (5.9%)	2 (3.4%)
Atrial fibrillation	6 (5.1%)	1 (1.7%)
Dizziness	6 (5.1%)	4 (6.8%)
Haematoma	6 (5.1%)	0
Myalgia	5 (4.2%)	3 (5.1%)

Abdominal pain upper	2 (1.7%)	4 (6.8%)
Blood creatinine increased	2 (1.7%)	3 (5.1%)
COVID-19 pneumonia	2 (1.7%)	3 (5.1%)
Chest pain	1 (0.8%)	5 (8.5%)
Contusion	1 (0.8%)	3 (5.1%)
Hyperkalaemia	1 (0.8%)	4 (6.8%)
Iron overload	1 (0.8%)	3 (5.1%)
Pain in extremity	0	4 (6.8%)

Note: Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0.
ALT = alanine aminotransferase; PT = preferred term; TEAE = treatment-emergent adverse event.

The most commonly reported TEAEs by PT in the imetelstat group was thrombocytopenia (75.4%) and neutropenia (73.7%), followed by anaemia (20.3%). In the placebo group, the most commonly reported TEAEs by PT were asthenia and oedema peripheral (13.6% each), followed by diarrhoea, constipation, and pyrexia (11.9% each). Relatively consistent results of type and frequency of the most common TEAEs were reported in the Phase 2 Imetelstat group.

Grade 3 or 4 Adverse Events

Table 22. Treatment-emergent Adverse Events with Worst Severity of Grade 3 or Grade 4 Reported in ≥ 5% of Subjects in Any Group – Study MDS3001 – Phase 3 Imetelstat Versus Placebo (Group A Treated Population)

Preferred Term	**Imetelstat**	**Placebo**
	Phase 3 (N=118) n (%)	**Phase 3 (N=59) n (%)**
Subjects with any Grade 3 or Grade 4 TEAE	107 (90.7%)	28 (47.5%)
Neutropenia	80 (67.8%)	2 (3.4%)
Thrombocytopenia	73 (61.9%)	5 (8.5%)
Anaemia	23 (19.5%)	4 (6.8%)
Leukopenia	9 (7.6%)	0
COVID-19 pneumonia	2 (1.7%)	3 (5.1%)

Note: Medical Dictionary for Regulatory Activities (MedDRA) v25.0 was used for TEAE coding.
PT = preferred term; TEAE = treatment-emergent adverse event.

The most common Grade 3/4 TEAEs reported in the Phase 3 imetelstat, and placebo arms were neutropenia (80 [67.8%] vs 2 [3.4%] subjects, respectively), thrombocytopenia (73 [61.9%] vs 5 [8.5%] subjects, respectively) and anaemia (23 [19.5%] and 4 [6.8%] subjects, respectively).

More than half of the Grade 3/4 neutropenia (69 [58.5%] vs 2 [3.4%] subjects, respectively), and thrombocytopenia (64 [54.2%] vs 2 [3.4%] subjects, respectively) reported in the Phase 3 imetelstat and placebo arms were related to treatment. One third of the anaemia cases (6.8%) and almost all cases of leukopenia (5.9%) were related to treatment.

The type and frequencies of the Grade 3/4 TEAEs in Phase 2 were generally consistent with the Phase 3 results.

2.6.8.2. Serious adverse event/deaths/other significant events

Serious adverse events

Table 23. Treatment-emergent Serious Adverse Events Reported in 2 or More Subjects in Any Group – Study MDS3001 – Phase 3 Imetelstat Versus Placebo (Group A Treated Population)

Preferred Term	Imetelstat	Placebo
	Phase 3 (N=118) n (%)	Phase 3 (N=59) n (%)
Subjects with ≥1 treatment-emergent SAE	38 (32.2%)	13 (22.0%)
Anaemia	3 (2.5%)	0
Cardiac failure	3 (2.5%)	0
Pneumonia	3 (2.5%)	1 (1.7%)
Atrial fibrillation	2 (1.7%)	0
COVID-19 pneumonia	2 (1.7%)	3 (5.1%)
Femur fracture	2 (1.7%)	1 (1.7%)
Pyrexia	2 (1.7%)	0
Sepsis	2 (1.7%)	0
Syncope	2 (1.7%)	0
Urinary tract infection	2 (1.7%)	0
Abscess limb	0	2 (3.4%)
Note: Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0. SAE = serious adverse event.		

Treatment-related SAEs were reported in 6 (5.1%) subjects in the imetelstat group. No subjects in the placebo group had a treatment-related SAE.

In the Phase 2 group, treatment-emergent SAEs were reported in 27 (47.4%) subjects.

Deaths

Table 24*:* Summary of Deaths and Causes of Deaths – Study MDS3001 – Phase 3 Imetelstat Versus Placebo (Group A Treated Population)

	Imetelstat (N=118) n (%)	Placebo (N=59) n (%)
Overall deaths on study	19 (16.1%)	8 (13.6%)

Deaths during treatment (≤ 30 days after last dose or > 30 days if death due to related TEAE)	1 (0.8%)	1 (1.7%)
Grade 5 TEAE	1 (0.8%)	1 (1.7%)
Deaths in post-treatment follow-up (> 30 days after last dose)[a]	18 (15.2%)	7 (11.9%)
Non-treatment-emergent adverse events	6 (5.1%)	2 (3.4%)
Progressive disease	1 (0.8%)	3 (5.1%)
Other	11 (9.3%)	2 (3.4%)

The most common reason of death in the post-treatment follow-up in the imetelstat group was "other" (11 [9.3%] vs 2 [3.4%] deaths, respectively), while in the placebo arm was progressive disease (1 [0.8%] vs 3 [5.1%] deaths, respectively).

During treatment, two deaths were reported (one death in each arm) due to sepsis in the imetelstat arm and aortic stenosis in the placebo arm. Regarding the event of sepsis in the imetelstat arm it is noted that following the last imetelstat dose, grade 4 neutropenia was reported 11 days prior to onset of the event; no ANC was provided on the day of the event.

Overall death rate in the Phase 2 imetelstat group was 27 (47.4%). Five Grade 5 TEAEs during treatment were reported in the Phase 2 group (5 [8.8%]), due to one of the following events: cerebrovascular accident, neurodegenerative disorder, thrombosis mesenteric vessel, femur fracture, and COVID-19 pneumonia.

Other significant adverse events

Treatment-emergent Adverse Events Leading to Dose Reduction

TEAEs led to dose reduction were reported in 58 (49.2%) subjects in the imetelstat group versus 4 (6.8%) subjects in the placebo group. Most common TEAEs were neutropenia (39 [33.1%] vs 1 [1.7%]) and/or thrombocytopenia (27 [22.9%] vs 1 [1.7%]). Consistent results in frequency and type were reported in the Phase 2 group.

Treatment-emergent Adverse Events That Led to Infusion Interruption

TEAEs leading to infusion interruption were reported in 7 (5.9%) subjects in the imetelstat group and in no subjects in the placebo group. Most common TEAEs leading to infusion interaction were due to headache (1.7%) and infusion site-related issues (administration site extravasation and infusion site extravasation, 0.8% each). The IRR frequency reported in the Phase 2 Group was10.5%.

Treatment-emergent Adverse Events That Led to Cycle Delay

Cycle delays were reported in 81 (68.6%) subjects in the imetelstat group versus 14 (23.7%) in the placebo group. Half of the imetelstat-treated subjects had a cycle delay due to neutropenia (50.8%) and thrombocytopenia (46.6%), whereas the frequency of both TEAEs in the placebo group was low (1.7% each). Consistent frequencies and type of TEAEs leading to cycle delay were reported in the Phase 2.

Hepatic TEAEs

Table 25*:* Treatment-emergent Adverse Events of Interest Per Protocol Criteria: Hepatic Event – Study MDS3001 – Phase 3 Imetelstat Versus Placebo (Group A Treated Population)

Category Preferred Term	Imetelstat – Phase 3 (N=118) n (%)			Placebo – Phase 3 (N=59) n (%)		
	Any Grade	Grade 3/4	SAE	Any Grade	Grade 3/4	SAE
Subjects with ≥1 hepatic TEAE	34 (28.8%)	8 (6.8%)	1 (0.8%)	10 (16.9%)	3 (5.1%)	0
Alanine aminotransferase increased	14 (11.9%)	3 (2.5%)	0	4 (6.8%)	2 (3.4%)	0
Aspartate aminotransferase increased	11 (9.3%)	0	0	4 (6.8%)	0	0
Hyperbilirubinemia	11 (9.3%)	1 (0.8%)	0	6 (10.2%)	1 (1.7%)	0
Blood alkaline phosphatase increased	5 (4.2%)	0	0	1 (1.7%)	0	0
Gamma-glutamyltransferase increased	4 (3.4%)	0	0	2 (3.4%)	1 (1.7%)	0
Ascites	2 (1.7%)	0	0	0	0	0
Hepatic steatosis	2 (1.7%)	0	0	0	0	0
Portal hypertension	2 (1.7%)	0	0	0	0	0
Biliary cyst	1 (0.8%)	0	0	0	0	0
Bilirubin conjugated increased	1 (0.8%)	1 (0.8%)	0	0	0	0
Cholelithiasis	1 (0.8%)	0	0	0	0	0
Hepatic cirrhosis	1 (0.8%)	0	0	0	0	0
Hepatitis	1 (0.8%)	1 (0.8%)	0	0	0	0
Hepatomegaly	1 (0.8%)	0	0	0	0	0
Hepatotoxicity	1 (0.8%)	1 (0.8%)	0	0	0	0
International normalised ratio increased	1 (0.8%)	0	0	0	0	0
Jaundice hepatocellular	1 (0.8%)	0	0	0	0	0
Oesophageal varices haemorrhage	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Prothrombin time prolonged	1 (0.8%)	0	0	0	0	0
Transaminases increased	1 (0.8%)	0	0	0	0	0
Varices oesophageal	1 (0.8%)	0	0	0	0	0
Hypoalbuminemia	0	0	0	1 (1.7%)	0	0

Note: Medical Dictionary for Regulatory Activities (MedDRA) v25.0 was used for TEAE coding.
SAE = serious adverse event; TEAE = treatment-emergent adverse event.

The median time to onset of hepatic TEAE was longer in the imetelstat group (198 days [range: 1 to 633 days] vs 113 days [range: 85 to 330], respectively).

No subjects discontinued study treatment due to hepatic TEAEs in both arms. One (0.8%) subject had a dose modification due to Grade 2 hepatic enzyme increase in the imetelstat group versus two (3.4%) subjects due to Grade 2/3 hepatic enzyme increase in the placebo group.

At Final Analysis of MDS3001 Study (13 October 2023), the incidence of hepatic TEAEs was 28.0% (33 subjects) with imetelstat versus 18.6% (11 subjects) with placebo overall, and Grade 3/4 events incidence was 9.3% (11 subjects) with imetelstat versus 5.1% (3 subjects) with placebo.

Exposure-adjusted incidence rates (EAIR) per 100 patient-years for hepatic TEAEs overall in the imetelstat and placebo groups respectively was 30.0 and 20.6 at Primary Analysis, and 24.9 and 20.8 at Final Analysis.

Liver function test abnormalities

Few subjects (approximately 5%) met the protocol-defined criteria for Liver function test abnormalities. The frequencies for ALT, AST and Bilirubin Grade ≥3 events showed similar frequencies between the two arms.

Two cases in the imetelstat group were reported to meet the criteria for Hy's law. However, these could not be confirmed due to alternative aetiologies, which in the first case concerned a positive de-challenge and rechallenge with the iron chelating agent deferasirox, and in the second, the high RBC transfusion burden and the overall medical history of the subject.

Worsening toxicity grades during treatment in the imetelstat and placebo arms were reported for ALT (46/117 [39.3%] vs 22/59 [37.3%] subjects, respectively), ALP (53/118 [44.9%] vs 7/59 [11.9%] subjects, respectively), AST (57/118 [48.3%] vs 13/59 [22.0%] subjects, respectively), and bilirubin (46/118 [39.0%] vs 23/59 [39.0%] subjects, respectively).

The frequency of subjects who had worsening to Grade 3 was relatively low across all LFTs, with the most frequent to be ALT worsening to Grade 3 (3.4% vs 5.1% in the imetelstat and placebo groups respectively); no ALP worsening to Grade 3 was reported. No LFT worsening to Grade 4 was reported.

In 4/5 subjects in the imetelstat arm and 2/2 subjects in the placebo arm, who had Grade ≥ 3 LFT abnormalities, the events were related to treatment. No action was taken with treatment in the imetelstat group whereas the dose was reduced in both placebo-treated subjects.

Grade 3 laboratory LFTs in the imetelstat and placebo groups resolved to Grade ≤ 2 in less than 4 weeks in all but one cases.

Results in the Phase 2 imetelstat group for hepatic TEAEs were generally consistent with Phase 3. TEAEs of any grade were reported in 18 (31.6%) subjects in Phase 2, of which Grade 3 events were reported in 7 (12.3%) subjects. One subject in the Phase 2 group met the Hy's law criteria, but the LFT elevations were considered to be due to sepsis.

The updated data from the MDS3001 Phase 3 study Final Analysis (cutoff date 13 October 2023) were in line with the Primary Analysis. More specifically, no changes were observed for Grade 3/4 incidence rate of laboratory abnormalities (laboratory testing). Regarding TEAEs, 3 subjects had additional Grade 3/4 events in the imetelstat group (PTs: Gamma- glutamyltransferase increased [2 subjects] and cholestasis [1 subject]). The 2 events of gamma- glutamyltransferase increased were reported as Grade 3, non-serious and not related to imetelstat. The cholestasis event was reported as Grade 3, non-serious and probably related to imetelstat.

Thrombocytopenia

Thrombocytopenia TEAEs of any grade in the imetelstat and placebo groups was reported in 89 [75.4%] versus 6 [10.2%] subjects, respectively. Most of the events (80/89 subjects) in the imetelstat arm and half of the events (3/6 subjects) in the placebo group were considered related to treatment. Grade 3/4 thrombocytopenia was reported in 73 (61.9%) versus 5 (8.5%) subjects, respectively.

No Grade 5 events or SAE were reported in any of the treatment arms.

Half of the imetelstat group (55 [46.6%] subjects) had a cycle delay and 27 [22.9%] subjects had a dose reduction due to thrombocytopenia, versus 1 [1.7%] subject each in the placebo group. Treatment discontinuation was reported in 4 [3.4%] subjects in the imetelstat group, whereas no subject discontinued treatment in the placebo group due to thrombocytopenia.

The time interval data showed a decreasing frequency of thrombocytopenia over time, which in the case of Grade 3/4 TEAEs, has decreased from 39% in the first trimester to 19.2% after the three first months of treatment.

Based on the laboratory data provided, most subjects in the imetelstat and placebo groups (83.9% vs 81.4%, respectively) had no thrombocytopenia at baseline, and 13.6% vs 18.6% of subjects, respectively, had Grade 1 thrombocytopenia.

Worsening thrombocytopenia from baseline while on treatment was reported in 113 (95.8%) subjects in the imetelstat group compared to 20 (33.9%) subjects in the placebo group. In the imetelstat group, 47/118 (39.8%) subjects worsened by 3 grades and 19 (16.1%) subjects worsened by 4 grades during the study.

The profile of thrombocytopenia TEAEs was generally consistent between Phase 2 and Phase 3; thrombocytopenia of any grade was reported in 35 (61.4%) versus 89 (75.4%) subjects in Phase 2, and 31 (54.4%) subjects had Grade 3/4 thrombocytopenia. No Grade 5 events of thrombocytopenia were reported.

Bleeding events

Bleeding TEAEs of any grade were reported in 25 (21.2%) versus 7 (11.9%) subjects in the imetelstat and placebo groups, respectively. Grade 3/4 events were reported in 3 (2.5%) versus 1 (1.7%) subjects and SAEs in 3 (2.5%) vs 1 (1.7%) subjects, respectively. The most common events in the imetelstat group were epistaxis (5.9%), and haematoma (5.1%), whereas in the placebo group were contusions (5.1%).

In the imetelstat group, one subject had a Grade 3 SAE event of haematuria and 2 subjects had Grade 4 SAE events of gastrointestinal haemorrhage and oesophageal varices haemorrhage. In the placebo group, one subject had 2 events of Grade 3 SAE of small intestinal haemorrhage. No Grade 5 events were reported in any of the two arms.

Out of the 77 (65.3%) subjects in the imetelstat group with Grade 3/4 decreased platelets based upon laboratory results, while on treatment, 9 (7.6%) reported Grade 1/2 bleeding events within +/- 7 days of the laboratory result, whereas none of the subjects in the placebo group had bleeding events associated with Grade 3/4 decreased platelets.

The exposure-adjusted incidence rates (EAIR) per 100 patient-years for bleeding events was in line with the Primary Analysis and the Final Analysis (cutoff date 13 October 2023) of the MDS3001 Phase 3 study in each treatment group (Table 36).

Table 26. Exposure-Adjusted Incidence Rate for Treatment-emergent Adverse Events by MedDRA SMQ Haemorrhages; Phase 3, Treated Analysis Set (Study MDS3001) – Primary Analysis and Final Analysis

SMQ[a]	Imetelstat – Phase 3 (N=118)		Placebo – Phase 3 (N=59)	
	Primary Analysis n (EAIR)	Final Analysis n (EAIR)	Primary Analysis n (EAIR)	Final Analysis n (EAIR)
Bleeding events	25 (22.1)	27 (20.4)	7 (14.4)	7 (13.2)

[a] *MedDRA SMQ Haemorrhages*

*EAIR is presented as exposure-adjusted patient incidence rate per 100 patient-years, which is calculated defined as (the total number of patients with the TEAE divided by total treatment exposure in patient-years) *100.*

PY = The last dose date + 30 days or initiation date of subsequent anti-cancer therapy or end of study date or death date, whichever occurs first) - first dose date + 1, divided by 365.25.

EAIR =- exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; PY = patient-year; SMQ = standardized MedDRA query; SOC = system organ class; TEAE = treatment-emergent adverse event.

Neutropenia

Neutropenia TEAEs of any grade was reported in 87 (73.7%) subjects in the imetelstat group versus 4 (6.8%) in the placebo group; treatment-related neutropenia was reported in 76 (64.4%) vs 3 (5.1%) subjects, respectively.

Grade 3/4 neutropenia events reported in (80 [67.8%] vs 4 [6.8%] subjects, respectively. No Grade 5 events or SAE were reported in any of the treatment arms.

One case of serious Grade 3 febrile neutropenia is reported in the imetelstat group versus no cases in the placebo group.

Half of the imetelstat group (60 [50.8%] subjects) had a cycle delay and 39 [33.1%] subjects had a dose reduction due to neutropenia, versus 1 [1.7%] subject each in the placebo group. Treatment discontinuation was reported in 6 [5.1%] subjects in the imetelstat group, whereas no subject discontinued treatment in the placebo group due to neutropenia.

The time interval data show a decreasing frequency of thrombocytopenia over time, which in the case of Grade 3/4 TEAEs, has decreased from 52.5% in the first trimester to 25.0% after the three first months of treatment.

Based on the laboratory data provided, most subjects in the imetelstat and placebo groups (82.2% vs 83.2%, respectively) had no neutropenia at baseline.

Based on the laboratory data provided, median time to onset of Grade 3 or Grade 4 neutropenia was 4.43 weeks (range: 1.0 to 81.0 weeks) with a median duration of 1.86 weeks (range: 0.0, 15.9) in the imetelstat group and 13.00 weeks (range: 3.0 to 23.0 weeks) with a median duration of 2.21 weeks (range: 1.0, 4.6) in the placebo group.

In the imetelstat and placebo groups, a total of 226 (81.0%) versus 3 (50.0%) Grade 3/4 neutropenia events, respectively, resolved to Grade ≤ 2, and 49 (90.7%) versus 1(100%) events of Grade 4 neutropenia events, respectively, resolved to Grade ≤ 3 in under 4 weeks.

A total of 40 (14.3%) vs 2 (33.3%) events, respectively, resolved in ≥ 4 weeks whereas 13 (4.7%) vs 1 (16.7%) events, respectively were ongoing as of the cut-off date.

Neutropenia TEAEs showed generally consistent frequencies between Phase 2 and Phase 3, with most events being Grade 3/4. In both groups, the majority of subjects had neutropenia with rates decreasing over time.

Infections

Table 27. Treatment-emergent Adverse Events of Interest: Infections Reported in ≥ 5% of Either Group or Reported Serious in Any Subject – Study MDS3001 – Phase 3 Imetelstat Versus Placebo (Group A Treated Population)

Preferred Term	Imetelstat – Phase 3 (N=118) n (%)			Placebo – Phase 3 (N=59) n (%)		
	Any Grade	Grade 3/4	SAE	Any Grade	Grade 3/4	SAE
Subjects with any infection TEAE	50 (42.4%)	12 (10.2%)	14 (11.9%)	20 (33.9%)	8 (13.6%)	8 (13.6%)
COVID-19	18 (15.3%)	0	0	4 (6.8%)	0	0
Urinary tract infection	7 (5.9%)	2 (1.7%)	2 (1.7%)	2 (3.4%)	0	0
Pneumonia	4 (3.4%)	3 (2.5%)	3 (2.5%)	2 (3.4%)	1 (1.7%)	1 (1.7%)
Gastroenteritis	3 (2.5%)	0	0	2 (3.4%)	1 (1.7%)	1 (1.7%)
COVID-19 pneumonia	2 (1.7%)	2 (1.7%)	2 (1.7%)	3 (5.1%)	3 (5.1%)	3 (5.1%)
Erysipelas	2 (1.7%)	0	1 (0.8%)	0	0	0
Sepsis	2 (1.7%)	1 (0.8%)	2 (1.7%)	0	0	0
Clostridium difficile infection	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Enterococcal sepsis	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Gastroenteritis clostridial	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Infection	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Neutropenic sepsis	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Pneumonia bacterial	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Pseudomembranous colitis	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Abscess limb	0	0	0	2 (3.4%)	2 (3.4%)	2 (3.4%)
Arthritis bacterial	0	0	0	1 (1.7%)	1 (1.7%)	1 (1.7%)
Listeriosis	0	0	0	1 (1.7%)	1 (1.7%)	1 (1.7%)

Note: Medical Dictionary for Regulatory Activities (MedDRA) v25.0 was used for TEAE coding.
SAE=serious adverse event; TEAE = treatment-emergent adverse event.

Five subjects had sepsis events in the imetelstat group, of which two were Grade 3, two Grade 4 and one Grade 5. One of the Grade 4 sepsis events was considered related to treatment and led to treatment discontinuation. One grade 4 infection and no Grade 5 events were reported in the placebo group.

In the imetelstat group, 9 (7.6%) out of 85 (72.0%) subjects with Grade 3 or Grade 4 decreased neutrophils while on treatment had an infection within ±7 days of the laboratory result, compared to 1 (1.7%) out of 4 (6.8% subjects) in the placebo group.

Three subjects with sepsis events had Grade 3/4 infections associated with Grade 3/4 neutropenia: Grade 4 enterococcal sepsis, Grade 3 Escherichia sepsis and Grade 3 neutropenic sepsis, all of which were reported as SAEs and one was considered related to imetelstat, leading to dose reduction.

In the Phase 2 imetelstat group, the rate of treatment-emergent infections reported was 57.9%. The rate of reported Grade 3/4 infections was 21.1% and of SAE infections 17.5%.

The exposure-adjusted incidence rates (EAIR) per 100 patient-years for infections was in line with the Primary Analysis and the Final Analysis (cutoff date 13 October 2023) of the MDS3001 Phase 3 study in each treatment group (**Table 33**). Additional events of infections reported at Final Analysis with imetelstat were all Grade 1/2. None occurred in context of (±7 days) Grade 3/4 neutropenia. Additional events of infections reported at Final Analysis with placebo included 1 fatal event of pneumonia.

Table 28. Exposure-Adjusted Incidence Rate for Treatment-emergent Adverse Events by System Organ Class (SOC); Phase 3, Treated Analysis Set (Study MDS3001)

SOC	Imetelstat – Phase 3 (N=118)		Placebo – Phase 3 (N=59)	
	Primary Analysis n (EAIR)	Final Analysis n (EAIR)	Primary Analysis n (EAIR)	Final Analysis n (EAIR)
Infections and infestations	50 (44.2)	56 (42.3)	20 (41.2)	20 (37.8)

*EAIR is presented as exposure-adjusted patient incidence rate per 100 patient-years, which is calculated defined as (the total number of patients with the TEAE divided by total treatment exposure in patient-years) *100.*
PY = The last dose date + 30 days or initiation date of subsequent anti-cancer therapy or end of study date or death date, whichever occurs first) - first dose date + 1, divided by 365.25.
EAIR =- exposure-adjusted incidence rate; PY = patient-year; SOC = system organ class; TEAE = treatment-emergent adverse event.

TEAEs related to COVID-19 infection

COVID-19 related TEAEs were reported in 22 (18.6%) subjects in the imetelstat group versus 8 (13.6%) subjects in the placebo group. One non-TEAE Grade 5 event was reported in each group and both occurred in follow up (>30 days after the last dose of study treatment).

Infusion-related reactions

Table 29. Treatment-emergent Adverse Events: Infusion Related Reaction Events – Study MDS3001 – Phase 3 Imetelstat Versus Placebo (Group A Treated Population)

Category Preferred Term	Imetelstat-Phase 3 (N=118) n (%)			Placebo – Phase 3 (N=59) n (%)		
	Any Grade	Grade 3/4	SAE	Any Grade	Grade 3/4	SAE
Any IRR TEAE	9 (7.6%)	2 (1.7%)	1 (0.8%)	2 (3.4%)	0	0
Headache	5 (4.2%)	0	0	0	0	0
Abdominal pain	1 (0.8%)	0	0	0	0	0
Arthralgia	1 (0.8%)	0	0	0	0	0
Asthenia	1 (0.8%)	0	0	0	0	0
Back pain	1 (0.8%)	0	0	0	0	0

Bone pain	1 (0.8%)	0	0	0	0	0
Diarrhoea	1 (0.8%)	0	0	0	0	0
Erythema	1 (0.8%)	0	0	0	0	0
Hypertensive crisis	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Malaise	1 (0.8%)	0	0	0	0	0
Non-cardiac chest pain	1 (0.8%)	1 (0.8%)	0	0	0	0
Pruritus	1 (0.8%)	0	0	0	0	0
Urticaria	1 (0.8%)	0	0	0	0	0
Chest pain	0	0	0	1 (1.7%)	0	0
Cough	0	0	0	1 (1.7%)	0	0
Pyrexia	0	0	0	1 (1.7%)	0	0

Note: Medical Dictionary for Regulatory Activities (MedDRA) v25.0 was used for TEAE coding.
IRR = infusion-related reaction; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Median time to onset of the Grade 3 events was 106.5 days (range: 85 to 128 days) in the 2 subjects with Grade 3 IRRs.

Overall, treatment interruption was reported in 5 (4.2%) subjects in the imetelstat group due to IRRs and 1 subject (0.8%) discontinued treatment due to an IRR of Grade 2 pruritus. There were no Grade 4 or Grade 5 IRR events.

In the Phase 2 imetelstat group, IRRs of any grade were reported in 6 (10.5%) subjects and of Grade 3/4 events in 4 (7.0%) subjects.

Adverse drug reactions

Based on the size of the population treated in the MDS3001 Phase 3 study, TEAEs occurring at an incidence of ≥ 5% in the imetelstat group and occurring at an incidence of ≥2% higher in the imetelstat group compared to the placebo group were initially assessed for inclusion as ADRs. In addition, TEAEs occurring at an incidence of < 5% but ≥ 2% were reviewed and assessed for inclusion based on severity and relevance. All Grade ≥ 3 TEAEs and serious TEAEs occurring in the imetelstat group were also reviewed.

Additional ADRs were identified from the pooled MDS3001 Phase 2 and Phase 3 studies. TEAEs were reviewed regardless of frequency for consideration for inclusion as ADRs. The frequency of ADRs, whether identified from MDS3001 Phase 3 or MDS3001 Phase 2, was based on the total incidence in the pooled studies, regardless of causality assessment of individual cases.

Based on this approach the following ADRs and frequencies were identified:

Table 30. Adverse reactions in low to intermediate-1 risk MDS patients treated with Rytelo in Phase 2 and 3 MDS3001 study

System organ class	Adverse reaction	Frequency (all grades)	All grades (N = 175)	Grades ≥ 3 (N = 175)
Infections and infestations	Urinary tract infection	Very common	12%	2.3%
	Sepsis	Common	4.0%	4.0%
Blood and lymphatic system disorders	Thrombocytopenia	Very common	94%	63%
	Neutropenia	Very common	92%	69%
	Leukopenia	Very common	93%	56%
Immune system disorders	Infusion-related reactions	Common	8.6%	3.4%
Nervous system disorders	Headache	Very common	16%	1.7%
	Syncope	Common	4.6%	1.7%
Cardiac disorders	Atrial fibrillation	Common	3.4%	1.1%
Vascular disorders	Haematoma	Common	5.7%	0.6%
Respiratory, thoracic and mediastinal disorders	Epistaxis	Common	5.1%	0
Gastrointestinal disorders	Gastrointestinal bleeding	Common	6.3%	1.7%
Hepatobiliary disorders	Aspartate aminotransferase increased	Very common	48%	2.3%
	Alanine aminotransferase increased	Very common	42%	4.0%
	Alkaline phosphatase increased	Very common	41%	0
Skin and subcutaneous tissue disorders	Pruritus	Common	5.1%	0
Musculoskeletal and connective tissue disorders	Arthralgia	Common	6.9%	0
Renal and urinary disorders	Haematuria	Common	4.6%	1.1%
General disorders and administration site conditions	Asthenia	Very common	26%	0.6%

2.6.8.3. Laboratory findings

Haematology

The mean laboratory values change from baseline over time showed increased mean haemoglobin through Cycle 11 (Weeks 41 to 44) in the imetelstat arm.

An initial decrease was shown in neutrophils and leukocytes after start of treatment with subsequent recovery back to normal range. Platelet counts were decreased early in the study and stabilised at a lower level compared to the normal range.

Similar trends of changes over time are observed in all values between Phase 2 and Phase 3 imetelstat groups.

Individual Subject Changes and Clinically Significant Abnormalities

Haemoglobin that worsened from baseline during treatment was reported at the same rate of subjects in imetelstat and placebo groups: 64.4% of patients had Grade 3 Decreased haemoglobin in both treatment arms. The results reported in Group B are consistent with those observed in Phase 3.

Coagulation

aPTT levels over time were similar in the Phase 3 imetelstat and placebo groups, with an early increase followed by relative stabilization above baseline with some peaks over the course of the study.

An early decrease in prothrombin INR levels was observed in the imetelstat group which tends to recover within normal range over the course of the study.

Results in Phase 2 were consistent with Phase 3, except for a greater initial decrease observed in aPTT levels in the Phase 2 imetelstat group.

Chemistry

The mean clinical chemistry values change from baseline over time showed increased ALP and AST values. No notable trends could be observed in mean values over time for any of the other LFTs. Consistent results were reported in Phase 2.

Vital signs – ECGs

No major differences were identified in vital signs between the imetelstat and placebo groups in the Phase 3 study, consistent with the results reported in Phase 2.

Proarrhythmic potential

The potential for imetelstat to prolong the QT interval was assessed with an integrated assessment composed of results from the *in vitro* human ether-à-go-go-related gene (hERG) assay, the non-clinical *in vivo* QT assessments conducted in safety pharmacology studies, a summary of clinical cardiac safety data.

Four events (1.0%) of ECG QT prolonged were reported across the pooled population in haematology imetelstat monotherapy studies (Group C - N=391), with 2 subjects experiencing non-serious Grade 3 events and 2 subjects experiencing a Grade 1 event. ECG QT Prolongation associated events were reported in 8 subjects (6.8%%) in the Phase 3 imetelstat group versus no subjects in the placebo group, including 5 (4.2%) subjects with events of syncope.

Two Grade 5 Cardiac arrest events were reported in one MDS/MPN patient (Group C) following an esophagogastroduodenoscopy for Grade 3 upper gastrointestinal haemorrhage 26 days after the last dose of imetelstat, and one MF subject in the setting of disease progression and Grade 4 sepsis 31 days after the first and last dose. The Grade 5 cardiac arrest events followed Grade 3 and 4 events of severe bleedings and severe infections.

2.6.8.4. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.5. Safety in special populations

MedDRA Terms	Age <65 years n (%)		Age 65-74 years n (%)		Age 75-84 years n (%)		Age 85+ years n (%)	
	Imetelstat (N=27)	Placebo (N=9)	Imetelstat (N=56)	Placebo (N=27)	Imetelstat (N=29)	Placebo (N=21)	Imetelstat (N=6)	Placebo (N=2)
Total AEs	26 (96.3%)	9 (100.0%)	56 (100.0%)	27 (100.0%)	29 (100.0%)	21 (100.0%)	6 (100.0%)	2 (100.0%)
Serious AEs – Total	5 (18.5%)	1 (11.1%)	19 (33.9%)	3 (11.1%)	13 (44.8%)	9 (42.9%)	1 (16.7%)	0
-Fatal	0	0	1 (1.8%)	0	0	1 (4.8%)	0	0
-Hospitalization/prolong existing hospitalization	5 (18.5%)	1 (11.1%)	19 (33.9%)	3 (11.1%)	12 (41.4%)	9 (42.9%)	1 (16.7%)	0
-Life-threatening	1 (3.7%)	0	1 (1.8%)	0	2 (6.9%)	3 (14.3%)	0	0
-Disability/incapacity	0	0	0	0	1 (3.4%)	0	0	0
-Other (medically significant)	0	0	1 (1.8%)	0	1 (3.4%)	0	0	0
AE leading to drop-out	0	0	12 (21.4%)	0	5 (17.2%)	0	0	0
Psychiatric disorders	3 (11.1%)	0	1 (1.8%)	2 (7.4%)	4 (13.8%)	4 (19.0%)	0	0
Nervous system disorders	8 (29.6%)	3 (33.3%)	14 (25.0%)	4 (14.8%)	11 (37.9%)	7 (33.3%)	1 (16.7%)	0
Accidents and injuries	3 (11.1%)	2 (22.2%)	4 (7.1%)	2 (7.4%)	8 (27.6%)	5 (23.8%)	1 (16.7%)	0
Cardiac disorders	1 (3.7%)	1 (11.1%)	10 (17.9%)	1 (3.7%)	4 (13.8%)	6 (28.6%)	1 (16.7%)	0
Vascular disorders	6 (22.2%)	0	3 (5.4%)	1 (3.7%)	6 (20.7%)	5 (23.8%)	2 (33.3%)	0
Cerebrovascular disorders	0	0	0	0	0	0	0	0
Infections and infestations	6 (22.2%)	0	27 (48.2%)	8 (29.6%)	16 (55.2%)	11 (52.4%)	1 (16.7%)	1 (50.0%)
Anticholinergic syndrome	4 (14.8%)	2 (22.2%)	8 (14.3%)	6 (22.2%)	7 (24.1%)	7 (33.3%)	1 (16.7%)	0
Quality of life decreased (Sum of impaired quality of life, quality of life decreased)	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	3 (11.1%)	1 (11.1%)	7 (12.5%)	3 (11.1%)	7 (24.1%)	2 (9.5%)	1 (16.7%)	0
Other AE appearing more frequently in older patients (Sum of asthenia, thrombocytopenia, anaemia, back pain, urinary tract infection, atrial fibrillation, hyperserotonaemia, syncope)	20 (74.1%)	2 (22.2%)	51 (91.1%)	10 (37.0%)	27 (93.1%)	9 (42.9%)	6 (100.0%)	1 (50.0%)

2.6.8.6. Immunological events

In the MDS3001 study, ADA developed in 28 (16.9%) imetelstat-treated subjects. ADA-positive subjects exhibited a slightly higher rate of drug-related TEAEs compared to the ADA-negative (92.9% vs. 84.1%) and similar drug-related Grade ≥3 TEAEs (75.0% vs. 74.6%).

ADA-positive subjects showed increased frequency of IRRs compared to ADA-negative subjects (17.9% vs. 7.3%).

2.6.8.7. Safety related to drug-drug interactions and other interactions

Based on the clinical evidence reported, the risk of clinically relevant drug-drug interactions for imetelstat is considered low.

2.6.8.8. Discontinuation due to adverse events

In the imetelstat group, 17 (14.4%) subjects discontinued study treatment due to a TEAE, whereas no treatment discontinuations were reported in the Placebo arm. The most common TEAE leading to study treatment withdrawal was neutropenia (6 [5.1%] subjects), followed by thrombocytopenia (4 [3.4%] subjects).

Discontinuation rates due to a TEAE were reported in 28.1% subjects in Phase 2. The most commonly reported TEAE leading to study treatment withdrawal was thrombocytopenia (7 [12.3%] subjects), followed by neutropenia (5 [8.8%] subjects).

Treatment-emergent Adverse Events Leading to Dose Reduction

TEAEs led to dose reduction were reported in 58 (49.2%) subjects in the imetelstat group versus 4 (6.8%) subjects in the placebo group. Most common TEAEs were neutropenia (39 [33.1%] vs 1 [1.7%]) and/or thrombocytopenia (27 [22.9%] vs 1 [1.7%]). Consistent results in frequency and type were reported in the Phase 2 group.

Treatment-emergent Adverse Events That Led to Infusion Interruption

TEAEs leading to infusion interruption were reported in 7 (5.9%) subjects in the imetelstat group and in no subjects in the placebo group. Most common TEAEs leading to infusion interaction were due to headache (1.7%) and infusion site-related issues (administration site extravasation and infusion site extravasation, 0.8% each). The IRR frequency reported in the Phase 2 Group was10.5%.

Treatment-emergent Adverse Events That Led to Cycle Delay

Cycle delays were reported in 81 (68.6%) subjects in the imetelstat group versus 14 (23.7%) in the placebo group. Half of the imetelstat-treated subjects had a cycle delay due to neutropenia (50.8%) and thrombocytopenia (46.6%), whereas the frequency of both TEAEs in the placebo group was low (1.7% each). Consistent frequencies and type of TEAEs leading to cycle delay were reported in the Phase 2.

2.6.8.9. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

The assessment of safety is focused on pooled data from the pivotal, placebo-controlled Phase 3 MDS3001 study using the dose of 7.5 mg/kg Q4W proposed in the SmPC, combined with the supporting database from Phase 2, open-label, single-arm part of MDS3001 study.,

Phase 2 and Phase 3 pooled data from the MDS3001 study provides a safety database of 175 patients treated with Imetelstat, which while of limited size, is considered adequate for safety assessment, based on the orphan status assigned to imetelstat. A total of 57 patients in Phase 2 and 118 patients in Phase 3 have been exposed to imetelstat.

The median duration of imetelstat treatment is 32.29 weeks (range: 0.1 to 260.1 weeks) and 33.93 weeks (range: 0.1 to 141.1 weeks) in the Phase 2 and Phase 3 groups respectively. The median time on study including follow-up was 57.3 months (range: 3.9 to 79.1 months) in Phase 2 and 19.5 months (range: 1.4 to 36) in the Phase 3 groups.

The patient population enrolled in the MDS3001 study is considered representative for the target population in terms of age, with a median age of 71 years (range 39-87) and 80% of subjects ≥65 years. The Phase 3 imetelstat group was slightly younger compared to the placebo group with 77% versus 85% of subjects being ≥ 65 years old.

Overall Safety Profile

TEAEs of any grade showed similar frequency between the imetelstat and placebo groups (99.2% vs 100%, respectively), most of which being Grade 3/4 (90.7% vs 47.5%, respectively) in the imetelstat group. No fatal study drug related TEAEs were reported.

The most common TEAEs by PT in the Phase 3 imetelstat group were thrombocytopenia (75.4%) and neutropenia (73.7%), followed by anaemia (20.3%), whereas in the placebo arm were asthenia and oedema peripheral (13.6% each).

Consistent results were observed across the two safety analysis groups (Phase 3 and pooled Phase 2 and 3).

Grade 3/4 Adverse Events

Among the Grade 3/4 events reported in the Phase 3 imetelstat and placebo groups, the most common were neutropenia (67.8% vs 6.8% subjects, respectively), thrombocytopenia (61.9% vs 8.5% subjects, respectively) and anaemia (19.5% and 6.8% subjects, respectively).

Neutropenia (33.1%) and thrombocytopenia (22.9%) were the most common of the TEAEs leading to dose reduction, while 50.8% of neutropenia and 46.6% of thrombocytopenia TEAEs led to cycle delays in the Phase 3 imetelstat group. In total, 49.2% of the subjects experienced a TEAE that led to dose reduction and 68.6% of the subjects experienced a TEAE that led to cycle delay.

Deaths

The most updated survival data (data cut off: 05 January 2024) with a median follow up of ~31 months show a (HR = 0.98; 95% CI: 0.526, 1.823). While data remain immature due to the prognosis of low risk patients, the median follow up time of 31 months in the MDS condition provide reassurance on the overall safety profile of imetelstat.

Serious Adverse Events

SAEs were reported in 38 (32.2%) subjects in the imetelstat group and 13 (22.0%) subjects in the placebo group.

The most common SAEs reported in the imetelstat group were anaemia, cardiac failure, and pneumonia (3 [2.5%] subjects each), while in the placebo group were COVID-19 pneumonia (3 [5.1%] subjects) and abscess limb (2 [3.4%] subjects).

Treatment-related SAEs were reported in 6 subjects in the imetelstat group: Anaemia, Atrial fibrillation, Febrile Neutropenia, Hypertensive Crisis, Neutropenic Sepsis, Pneumonia bacterial, Pyrexia and Sepsis, with the same frequency (1 subject each). No treatment-related SAEs were reported in the placebo group.

In the Phase 2 imetelstat group SAEs were reported in 27 (47.4) subjects, with the most common to be femur fracture (3 [5.3%] subjects), cardiac failure, pneumonia, and thrombocytopenia in 2 (3.5%) subjects. Nine subjects in total had SAEs that were considered related to treatment.

Discontinuation due to AEs

Overall, the treatment discontinuation rate due to a TEAE in the imetelstat arms was high in all three safety analysis pools (14.4% in Group A, 18.9% in Group B and 17.1% in Group C). The most frequently reported AEs leading to discontinuation in the three safety pools were thrombocytopenia and neutropenia.

Adverse Events of Clinical Interest (AECI)

- *Hepatic Adverse Events and LFT Elevations*

  Hepatic TEAEs of grade 3/4 hepatic TEAEs were reported with similar frequency of Grade 3/4 TEAEs between the two Phase 3 arms (8 [6.8%] vs 3 [5.1%] subjects).

  No firm conclusion could be drawn from the assessment of the program-wide summary of all events fulfilling Hy's law provided, due to confounding factors in all reported cases. The available data show that the incidence for hepatic TEAEs was similar between the imetelstat and placebo groups. Severe hepatotoxicity is listed as an important potential risk in the RMP and will be closely monitored via routine pharmacovigilance and further characterised in Study MDS3001 Extension Phase.

- *Bleeding Events*

  Bleeding TEAEs of any grade were reported in 25 (21.2%) versus 7 (11.9%) subjects in the Phase 3 imetelstat and placebo groups, respectively, of which 3 (2.5%) versus 1 (1.7%) were Grade 3/4 and 3 (2.5%) vs 1 (1.7%) were SAEs, respectively. In the imetelstat group, one subject had a Grade 3 SAE event of haematuria and 2 subjects had Grade 4 SAE events of gastrointestinal haemorrhage and oesophageal varices haemorrhage. No Grade 5 events were reported in any of the two arms.

- *Anaemia*

  Anaemia, while also being reported with a higher rate of TEAEs in the imetelstat group (24 subjects [20.3%]) compared to placebo (6 subjects [10.2%], has been excluded from the ADR table based on the similarity in changes in haemoglobin levels between the two arms and given the baseline anaemia in all patients.

- *Thrombocytopenia*

Based on haematology laboratory measures, thrombocytopenia occurred in 94.3% of patients receiving imetelstat in Phase 2 and Phase 3 pooled data. Incidences of Grade 3 or Grade 4 thrombocytopenia were 62.9%. Median time to first onset of ≥ Grade 3 events was 5 (range: 1.7, 89.7) weeks. Median duration of thrombocytopenia for ≥ Grade 3 events was 1.4 (range: 0.1, 15.0) weeks. (see sections 4.2 and 4.4). Thrombocytopenia (treatment-emergent adverse events of any Grade) led to dose reduction or cycle delay in 24.6% and 44.6% of patients, respectively. Treatment was permanently discontinued in 6.3% of patients.

- *Neutropenia and infections*

Based on haematology laboratory measures, neutropenia occurred in 92.0% of patients receiving imetelstat in Phase 2 and Phase 3 pooled data. Incidences of Grade 3 or Grade 4 neutropenia were 69.1%. Median time to first onset of ⩾ Grade 3 events was 4.3 (range: 1.0, 118.6) weeks. Median duration of neutropenia for ⩾ Grade 3 events was 2.0 (range:0.0, 16.7) weeks. Neutropenia (treatment emergent adverse events of any Grade) led to dose reduction or cycle delay in 36.6% and 50.3% of patients, respectively. Treatment was permanently discontinued in 6.3% of patients.

Complete blood cell counts should be monitored prior to each dose of imetelstat, weekly following administration of the first two doses, and for any case of Grade 3 or Grade 4 neutropenia. Patients with Grade 3 or Grade 4 neutropenia should be monitored for infections, including sepsis as a precaution. Granulocyte-colony stimulating factors and anti-infective therapies should be administered as clinically indicated. Patients should be advised to report any signs or symptoms of neutropenia, such as fever or infection immediately. The next dose should be delayed and resumed at the same or reduced dose as recommended in the SmPC.

- *Infusion-related reactions*

Infusion-related reactions occurred in 8.6% of patients receiving imetelstat in Phase 2 and Phase 3 pooled data. Incidences of Grade 3 or Grade 4 infusion-related reactions were 3.4%. Infusion related reactions usually occurred during or shortly after the end of the infusion (see sections 4.2 and 4.4). Infusion related reactions led to dose reduction or cycle delay in 0.6% of patients or in temporary interruption or termination of the infusion in 5.7% of patients. Treatment was permanently discontinued in 0.6% of patients.

The most common symptoms were headache and back pain. Other notable adverse reactions were Grade 3 hypotension, hypertension, hypertensive crisis, and non-cardiac chest pain. Patients usually experienced an infusion-related reaction during or shortly after the end of the infusion.

Patients should receive premedication at least 30 minutes prior to dosing with Rytelo to reduce the risk of experiencing infusion-related reactions. Patients should be monitored for adverse reactions for at least one hour after the infusion has been completed.

Symptoms of infusion-related reactions should be managed with supportive care and consideration given to interrupting the infusion, decreasing the infusion rate, or discontinuing treatment based on the severity and frequency of occurrence as recommended.

- *Electrocardiogram*

Overall, based on the clinical data presented, imetelstat-arms showed a low frequency of QT prolongation. However, the results from the ongoing ventricular repolarization sub study for MDS3001, for which no results have been provided to date, could be of relevance to confirm the limited effect that imetelstat is suggested to have on ECG parameters; thus, the applicant is recommended to submit the results when available.

Safety in special groups

The analysis of safety in special populations with the regard to the age subgroups showed that the AE profile was generally similar between both age groups. AEs were reported more frequently in subjects ≥ 65 years old compared with those < 65 years old, in both imetelstat and placebo arms. Similarly, AE were more frequent in subjects ≥ 75 years old than those < 75 years in both arms.

Regarding the subgroups analysed based on renal function and hepatic function, no consistent trend of worse toxicity is observed in in increasingly renally or hepatically impaired subjects.

No dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance [CrCL] 30 to < 90 mL/min). There is insufficient data in patients with severe renal impairment (CrCL 15 to < 30 mL/min) or end-stage renal disease to support a dose recommendation.

No dose adjustment is required in patients with mildly to moderately abnormal liver function tests (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or total bilirubin > 1× to 1.5× ULN (Grade 1) and any AST) or (total bilirubin > 1.5× to 3× ULN (Grade 2) and any AST). There is insufficient data in patients with severely abnormal liver function tests (total bilirubin > 3× ULN (Grade 3) and any AST) to support a dose recommendation.

Long-term safety concerns

Based on the mechanism of action of imetelstat and the on target adverse reactions that have been observed, a concern has been raised on the potential effect of imetelstat on telomere length and genomic instability of the normal Haematopoietic Stem Cells (HSCs) pool, which could prompt AML progression and secondary malignancies. Nevertheless, the limited literature data and the immature clinical data available on the AML progression rates between the imetelstat and placebo arms (1.7% vs 3.3%, FU: 32.2 months in the imetelstat group and 28.4 in the placebo group) do not show a concerning pattern against imetelstat. Additionally, the preclinical data indicate that imetelstat does not pose a risk for mutagenicity or clastogenicity.

Long-term safety is included in the safety concerns as missing information in the RMP and will be further characterised during the extension phase of MDS3001 study.

2.6.10. Conclusions on the clinical safety

The safety profile of imetelstat monotherapy in patients with MDS is based on the phase 2/3 study MDS3001 and is mainly characterised by neutropenia and thrombocytopenia. These may be associated with febrile neutropenia and serious bleeding. While overall survival data remain immature due to the prognosis of low-risk patients, the median follow up time of 31 months in the MDS condition provide reassurance on the overall safety profile of imetelstat, which is deemed manageable and acceptable in the context of proposed use. Long term effects are expected to be further characterised in the extension phase of the pivotal study.

The safety information and recommendations included in the product information are considered sufficient, to adequately minimise the known risks associated with its use.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	Severe bleeding Severe infections
Important potential risks	Severe hepatotoxicity Embryo-foetal toxicity
Missing information	Long-term safety

2.7.2. Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
Study MDS3001 Extension Phase A Study to Evaluate Imetelstat (GRN163L) in Transfusion-Dependent Subjects with IPSS Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) that is Relapsed/ Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment Ongoing	To evaluate the long-term safety in transfusion dependent subjects with low- or immediate-1 risk to MDS that is relapsed/refractory to ESA treatment receiving imetelstat.	Severe bleeding Severe infections Severe hepatotoxicity Long-term safety	Study initiation:	Q4 2023
			Study completion:	Q4 2026
			Final study report:	Q4 2027

2.7.3. Risk minimisation measures

Safety concern	**Risk minimisation measures**
Severe bleeding (Important identified risk)	Routine risk minimisation measures: • *Instructions for blood cell count monitoring and recommendations for delaying treatment, reducing the dose or stopping treatment in SmPC sections 4.2 and 4.4* • *Guidance on blood tests and possible delays to infusions, dose reductions or stopping treatment in PL sections 2 and 3* • *Recommendation to assess the need for platelet transfusions in SmPC section 4.4*

Safety concern	Risk minimisation measures
	• *Warning to monitor patients with severe thrombocytopenia for bleeding events in SmPC section 4.4 and PL section 2* • *Warning for the patient to talk to their doctor or nurse before they are given Rytelo if they recently had bleeding or bruising in PL section 2* • *Warning for patients to report any signs or symptoms of bruising or bleeding immediately in SmPC section 4.4 and PL section 4* • *Adverse reactions in SmPC section 4.8 and PL section 4* • *Legal status: Restricted medical prescription* Additional risk minimisation measures: • *None*
Severe infections (Important identified risk)	Routine risk minimisation measures: • *Instructions for blood cell count monitoring and recommendations for delaying treatment, reducing the dose or stopping treatment in SmPC sections 4.2 and 4.4* • *Guidance on blood tests and possible delays to infusions, dose reductions or stopping treatment in PL sections 2 and 3* • *Recommendation to administer granulocyte-colony stimulating factors and anti-infectives in SmPC section 4.4* • *Warning to monitor patients with severe neutropenia for infections in SmPC section 4.4 and PL section 2* • *Warning for the patient to talk to their doctor or nurse before they are given Rytelo if they have signs of an infection in PL section 2* • *Warning for patients to report any signs or symptoms of infection immediately in PL section 4* • *Adverse reaction in SmPC section 4.8 and PL section 4* • *Legal status: Restricted medical prescription* Additional risk minimisation measures: • *None*
Severe hepatotoxicity (Important potential risk)	Routine risk minimisation measures: • *Instructions for liver function test monitoring and recommendations for delaying treatment, reducing the dose or stopping treatment in SmPC section 4.2* • *Guidance on liver function tests and possible delays to infusions, dose reductions or stopping treatment in PL sections 2 and 3* • *Legal status: Restricted medical prescription* Additional risk minimisation measures: • *None*
Embryo-foetal toxicity (Important potential risk)	Routine risk minimisation measures: • *Warning for healthcare professionals to advise pregnant women of the potential risk to a foetus based on findings in animals in SmPC section 4.4*

Safety concern	Risk minimisation measures
	• *Warning that imetelstat is not recommended during pregnancy and in women of childbearing potential not using contraception in SmPC section 4.6 and PL section 2* • *Warning for patients to tell their doctor straight away if they become pregnant during treatment in PL section 2* • *Warning to use effective contraception in SmPC sections 4.4 and 4.6 and PL section 2* • *Guidance to perform a pregnancy test before starting treatment in SmPC section 4.6 and PL section 2* • *Information on nonclinical findings in SmPC sections 4.4, 4.6, and 5.3* • *Legal status: Restricted medical prescription* Additional risk minimisation measures: • *None*
Long-term safety (Missing information)	Routine risk minimisation measures: • *None* Additional risk minimisation measures: • *None*

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 6 June 2024. The new EURD list entry will therefore use the {EBD} {IBD} to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Rytelo (imetelstat) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

3.1. Therapeutic context

3.1.1. Disease or condition

The approved indication is the treatment of transfusion dependent anaemia in adult patients with very low, low or intermediate risk MDS without an isolated deletion 5q cytogenetic abnormality and who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.

Myelodysplastic syndromes are characterized by ineffective haematopoiesis in which haematopoietic progenitor cells have a reduced ability to differentiate and an increased likelihood of apoptosis. This manifests in abnormal "dysplastic" cell morphology and the development of peripheral cytopenias.

3.1.2. Available therapies and unmet medical need

First line treatment in patients with lower risk MDS-associated symptomatic anaemia, no del(5q) mutation and serum EPO level ≤500 mU/mL is treatment with erythropoiesis-stimulating agents (ESAs). Despite an initial response to ESA treatment, approximately 70% of patients become unresponsive to ESAs at some point during therapy.

Luspatercept is also approved for the treatment of transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes.

Second line treatment options include immunomodulatory agents such as off-label lenalidomide (which is approved for lower risk MDS patients with an isolated deletion 5q) and off-label azacitidine (a hypomethylating agent, which is approved in higher risk MDS patients).

In summary, an unmet medical need exists in transfusion-dependent patients with symptomatic anaemia who are ineligible for ESA or become unresponsive to ESA treatment.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is the phase 3 part of study MDS3001, a multicentre, randomized, double-blind study of imetelstat or placebo in transfusion-dependent subjects with IPSS low or intermediate-1 risk MDS that is relapsed/refractory (R/R) to or ineligible for ESA treatment.

3.2. Favourable effects

The pivotal phase 3 part of study MDS3001 showed statistically significant results in favour of imetelstat in the primary and the hierarchically tested key secondary endpoint. However, the study design favours imetelstat as follow-up of patients was terminated at the first transfusion in patients that discontinued study treatment, which in the study occurred more frequently in the placebo treated patients. Consequently, patients treated with imetelstat were followed-up longer thus having a higher chance to achieve the defined transfusion independence. Importantly, in an analysis of transfusion independence in the first 24 weeks of treatment and ignoring treatment discontinuations which allows for equal observation periods for the two arms, 8-Week Rate of RBC TI, was shown to be statistically significantly higher in the imetelstat treatment group compared with placebo (30.5% and 6%; p=0.002).

The key secondary endpoint, 24-week rate of RBC TI, showed statistically significantly higher response rates in the imetelstat treatment group compared with placebo (28.0 and 3.3%; p<0.001).

Presented subgroup results of the primary endpoint showed an overall consistent treatment effect, lending further evidence of the efficacy of imetelstat in the claimed indication.

3.3. Uncertainties and limitations about favourable effects

Treatment with imetelstat resulted in statistically significant durability of RBC TI for subjects who achieved 8-week RBC TI, with a median duration of 51.6 weeks (95% confidence interval [CI]: 26.86, 83.86) in the imetelstat group versus 13.3 weeks (95% CI: 8.00, 24.86) in the placebo group.

As the comparison of the longest response is limited to responders, durability of RBC TI is a non-randomized comparison and the number of patients in the placebo arm is low, the results should be interpreted with caution. In addition, this analysis was not type-1-error controlled, hence no inference can be made.

3.4. Unfavourable effects

The safety database is focused on data from the MDS3001 pivotal study A supporting database from the Phase 2, open-label, single-arm part of MDS3001 study was pooled with the Phase 3 data providing a safety analysis set of 175 patients treated with imetelstat.

The most commonly reported AEs with imetelstat reported in the Phase 3 study were thrombocytopenia (75.4% with imetelstat, vs 10.2% with placebo) and neutropenia (73.7% with imetelstat, vs 6.8% with placebo), followed by anaemia (20.3% with imetelstat, vs 10.2% with placebo). Moreover, pre-defined AEs of Clinical Interest (AECIs) included bleeding events (21.2% vs 11.9%), infections (42.4% vs 33.9%), IRRs (7.6% vs 3.4%) and hepatic AEs & LFT elevations (28.8% vs 16.9%).

Grade $\geq$3 AEs occurred in 90.7% with imetelstat versus 47.5% with placebo in the Phase 3 Group. Neutropenia (67.8% vs 3.4% subjects), thrombocytopenia (61.9% vs 8.5% subjects) and anaemia (19.5% vs 6.8% subjects) were the most commonly reported grade $\geq$3 AEs in the Phase 3 imetelstat and placebo groups.

A higher incidence of SAEs was reported in the Phase 3 imetelstat group compared to the placebo (32.2% vs 22%). Anaemia, cardiac failure, and pneumonia (2.5% subjects each) were the most frequently reported SAEs with imetelstat.

Death rates on study in the imetelstat and placebo arms were (16.1% vs 13.6%, respectively), with one death on treatment being reported in each arm (0.8% vs 1.7%, respectively) due to sepsis in the imetelstat arm and aortic stenosis in the placebo arm.

3.5. Uncertainties and limitations about unfavourable effects

The main uncertainties on unfavourable effects relate to the potentially increased risk of infections and bleeding complications in the MDS patients treated with imetelstat due to imetelstat induced neutropenia and thrombocytopenia.

Hepatotoxicity was seen across studies in the imetelstat program. Given the relatively small safety database, the incidence of hepatotoxicity could be underestimated and thus, it should be monitored during the long-term follow up**.** Severe hepatotoxicity is listed as an important potential risk in the RMP and will be closely monitored via routine pharmacovigilance and further characterised in Study MDS3001 Extension Phase.

PK data are very limited, and no recommendations on appropriate amendments to the posology in special populations such individuals with impaired organ function can be made

The data on the long-term impact of telomerase inhibition on the target population is limited; however, the data observed so far in MDS patients do not suggest a contributory role of imetelstat in disease progression, secondary malignancies or progression to AML. Long-term safety is included in RMP as missing information and should be further characterized during the extension phase of MDS3001 study and monitored through routine pharmacovigilance.

The latest available survival analysis is at the time considered neutral with a slightly lower HR of 0.98 (0.526, 1.823). Due to the slow accrual of events, these data are still immature. However, the median follow-up time of 31 months in patients with MDS provides acceptable reassurance regarding potential detrimental effects.

3.6. Effects Table

Table 31. Effects Table for Rytelo for the treatment of transfusion-dependent anaemia due to very low, low or intermediate risk MDS without an isolated deletion 5q cytogenetic abnormality (data cut-off: 13 October 2022).

Effect	Short Description	Unit	Imetelstat	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
			N=118	N=60		
RBC-TI ≥ 8 weeks	Proportion of subjects without any RBC transfusion in the first 24 weeks (ignoring treatment discontinuations and use of new anti-cancer treatment)	% (95% CI)	30.5 (22.37, 39.6)	6 (3.76.20.51)	SoE: p=0.002 Consistent results with primary and secondary endpoint of the trial and subgroup analyses	MDS3001, phase 3
Unfavourable Effect						
			N=175	N=59		
Thrombo-cytopenia Neutropenia	Incidence Any grade (Grade ≥3)	%	75.4 (61.9) 73.7(67.8)	10.2 (8.5) 6.8 (3.4)		MDS3001, phase 2 and 3

Abbreviations: MDS: myelodysplastic syndrome; RBC: red blood cell; TI: transfusion independence; CI: confidence interval; SoE: strength of evidence

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In lower-risk MDS, the risk of AML progression is lower and survival longer compared to patients with higher-risk disease. The aim of therapy in LR MDS is to improve cytopenias, mainly anaemia (usually the predominant cytopenia), and improve QoL. In patients with mild and asymptomatic cytopenias, the approach is generally watchful observation. Eventually, ~40% of LR MDS patients will become transfusion dependent. Iron overload due to RBC transfusions may be deleterious to various organs (Fenaux, 2021).

As such, transfusion independence is an important objective, and this was evaluated in the pivotal phase III trial. The primary and key secondary efficacy endpoints show a statistically significant result in favour of imetelstat. Sensitivity analyses showed that the results are statistically robust.

In terms of safety, the frequencies of reported AEs, Grade 3/4 and SAEs are high and are characterized mainly by neutropenia and thrombocytopenia, being the most common TEAEs leading to dose reductions, cycle delays and treatment discontinuation. As these events can lead to serious infections and haemorrhagic events, supportive measures, such as colony stimulating factors and platelet transfusions are described in the product information to minimise these risks.

3.7.2. Balance of benefits and risks

The observed benefit of imetelstat in reducing the requirement for red blood cell transfusion subjects with very low, low or intermediate risk MDS patients is considered to outweigh the haematological toxicity associated with its use.

3.8. Conclusions

The overall benefit/risk balance of Rytelo is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Rytelo is not similar to Reblozyl within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety, and efficacy, the CHMP considers by consensus that the benefit-risk balance of Rytelo is favourable in the following indication(s):

Rytelo is indicated as monotherapy for the treatment of adult patients with transfusion-dependent anaemia due to very low, low or intermediate risk myelodysplastic syndromes (MDS) without an isolated deletion 5q cytogenetic (non-del 5q) abnormality and who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New active substance status

Based on the CHMP review of the available data, the CHMP considers that imetelstat is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.