EU RISK MANAGEMENT PLAN

Rytelo (imetelstat)

RMP version to be assessed as part of this application:

RMP Version number: 0.3

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QPPV name: Alma Christina Strom Moller

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation/Term	Definition
ADA	Anti-drug antibodies
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AEI	Adverse event of interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATG	Antithymocyte globulin
$AUC_{0-\infty}$	Area under the plasma concentration versus time curve from Time 0 to infinity
BIW	Twice per week
CNS	Central nervous system
C_{max}	Peak plasma concentration
$C_{max,u}$	Free/unbound maximum observed concentration in plasma
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CSA	Cyclosporine
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
C1D1	Cycle 1 Day 1
DEC-C	Decitabine and cedazuridine
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DRF	Dose range-finding
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EFD	Embryo-foetal development
EHA	European Hematology Association
EPAR	European public assessment report
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agent
ESMO	European Society for Medical Oncology
ET	Essential thrombocytopenia
EU	European Union
EU28	European Union (28 countries)
FDA	Food and Drug Administration
G-CSF	Granulocyte colony-stimulating factor
GD	Gestation day
GPRD	General Practice Research Database

Abbreviation/Term	Definition
HCT	Haematocrit
Hgb	Haemoglobin
hERG	Human ether-à-go-go-related gene
HI-E	Hematologic improvement-erythroid
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMA	Hypomethylating agent
HMRN	Haematological Malignancy Research Network
HNSTD	Highest non-severely toxic dose
HR-MDS	High-risk MDS
HSCT	Haematopoietic stem cell transplantation
hTERT	Human telomerase reverse transcriptase
hTR	Human telomerase RNA component
IC_{50}	Half maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INN	International nonproprietary name
IPSS	International prognostic scoring system
IPSS-R	Revised IPSS
IV	Intravenous(ly)
JAK	Janus kinase
LFT	Liver function test
LR-MDS	Lower risk MDS
MAA	Marketing authorisation application
MedDRA	Medical Dictionary for Regulatory Activities
MDS	Myelodysplastic syndromes
MDS-RS	Myelodysplastic syndrome with ring sideroblasts
MF	Myelofibrosis
MM	Multiple myeloma
MPN	Myeloproliferative neoplasms
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NOAEL	No-observed-adverse-effect-level
NPS	N3'→P5' thio-phosphoramidate
NYHA	New York Heart Association
OATP1	Organic anion transporting polypeptide 1
ODD	Orphan drug designation
ODN	Oligonucleotide
OS	Overall survival
P-gp	P-glycoprotein
PD	Pharmacodynamic(s)
PFS	Progression free survival
PK	Pharmacokinetic(s)
PL	Package leaflet
PNH	Paroxysmal nocturnal haemoglobinuria

Abbreviation/Term	Definition
PopPK	Population PK
PS	Phosphorothioate
PS ODN	Phosphorothioate oligonucleotide
PSUR	Periodic safety update report
PT	Preferred term
PV	Polycythemia vera
QoL	Quality of life
QPPV	Qualified Person Responsible for Pharmacovigilance
QTc	Corrected QT interval
Q4W	Every 4 weeks
RBC	Red blood cell
RMP	Risk management plan
RNA	Ribonucleic acid
RS	Ring sideroblasts
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA query
SOC	System organ class
TI	Transfusion independence
TPO-RA	Thrombopoietin receptor agonist
UGT1A1	UDP-glucuronosyltransferase 1A1
UK	United Kingdom
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

PART I PRODUCT OVERVIEW

Table 1: Product Overview

Active substance (INN or common name)	Imetelstat
Pharmacotherapeutic group (ATC Code)	Antineoplastic agents, Other antineoplastic agents (L01XX80)
Marketing Authorisation Applicant	Geron Netherlands B.V.
Medicinal products to which this RMP refers	One
Invented name in the European Economic Area (EEA)	Rytelo
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Oligonucleotide
	Summary of mode of action: Imetelstat is an oligonucleotide telomerase inhibitor that binds to the template region of the RNA component of human telomerase (hTR), which prevents telomere binding. Telomerase activity and human telomerase reverse transcriptase (hTERT) RNA expression are known to be significantly increased in MDS and malignant stem and progenitor cells. Imetelstat treatment leads to reduction of telomere length, inhibition of malignant stem and progenitor cell proliferation and induction of apoptotic cell death leading to reduction of malignant clones.
	Important information about its composition: Rytelo (imetelstat) powder for concentrate for solution for infusion is a white to off-white or slightly yellow lyophilised powder. Rytelo is provided in single-use vials and must be reconstituted and diluted prior to administration as an intravenous infusion.
Hyperlink to the Product Information	Rytelo Product Information (Module 1.3.1)
Indication in the EEA	Current: 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.
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended dose of Rytelo is 7.1 mg/kg body weight administered as an intravenous infusion once every 4 weeks.

	Proposed: Not applicable
Pharmaceutical form and strengths	Current: Powder for concentrate for solution for infusion (powder for concentrate). White to off-white or slightly yellow lyophilised powder. <u>Rytelo 47 mg powder for concentrate for solution for infusion</u> Each vial contains imetelstat sodium equivalent to 47 mg imetelstat. After reconstitution, 1 mL of the solution contains 31.4 mg imetelstat. <u>Rytelo 188 mg powder for concentrate for solution for infusion</u> Each vial contains imetelstat sodium equivalent to 188 mg imetelstat. After reconstitution, 1 mL of the solution contains 31.4 mg imetelstat.
	Proposed: Not applicable
Will the product be subject to additional monitoring in the EU?	Yes

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Imetelstat 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.

Myelodysplastic syndromes (MDS) are a serious and life-threatening disease that constitute a heterogeneous group of haemopoietic clonal disorders that are characterised by ineffective haemopoiesis in which haematopoietic progenitor cells (HPCs) 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).

According to the European Society for Medical Oncology (ESMO) Guidelines for MDS, MDS should be classified according to the World Health Organization (WHO) criteria with prognosis established by the international prognostic scoring system (IPSS) or rather, its revised version (IPSS-R) (Fenaux, 2021). The IPSS classifies patients into low, intermediate-1, intermediate-2, and high-risk categories; patients with IPSS low/intermediate 1 risk or IPSS-R very low/low/intermediate MDS are often referred to as having 'lower-risk' disease (LR-MDS).

Incidence:

In Europe the annual incidence rate of MDS in the general population is 4 cases per 100,000 persons, which increases with age to an estimated incidence of 40-50 cases per 100,000 persons aged ≥ 70 years (Neukirchen, 2011). The Surveillance of Rare Cancers in Europe (RARECARE) project reports a crude incidence rate of 2.14 per 100,000 per year for MDS based on 33,542 observed cases from 83 cancer registries in 2000-2007, with an estimated 10,864 new cases in 2013 in EU28 (Gatta, 2017).

Data from other countries are broadly similar; age-adjusted annual incidence rates were estimated as 2.8 cases per 100,000 person-years in the Netherlands, 4.2 cases per 100,000 person-years in Germany, 4.8 cases per 100,000 person-years in Greece, 4.0 cases per 100,000 person-years in the US, and 4.8 cases per 100,000 person-years in Australia in 2015 (Zeidan, 2019). Using data from the Swedish population based MDS register, the yearly crude incidence rate of MDS in Sweden was 2.9 per 100,000 inhabitants (Moreno Berggren, 2018). In the UK, the annual incidence rate of MDS (from 2010-2019) reported by the Haematological Malignancy Research Network (HMRN) was 3.3 per 100,000 population (HMRN, 2022).

Prevalence:

Myelodysplastic syndromes have an estimated prevalence of approximately 2 in 10,000 based on recent reviews of orphan designations granted in the EU (EU Community Register of orphan medicinal products, 2023).

This is in line with the MDS prevalence of 1-9 per 100,000 of the Orphanet database (Orphanet, 2023).

Demographics of the population in the proposed indication - age, gender, racial and/or ethnic origin and risk factors for the disease:

The risk of MDS varies by age, sex and race. Age is known to be the most important risk factor, with incidence increasing significantly with age; there is a higher incidence in men than in women.

Myelodysplastic syndromes are among the most common haematologic malignancy in older people, with a median age at diagnosis of over 70 years old and less than 10% of patients are 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).

The aetiology of MDS is only known in 15% of cases. An inherited predisposition to MDS is seen in one-third of paediatric MDS patients, including Down syndrome, Fanconi anaemia and neurofibromatosis (Fenaux, 2020a). While it is less frequent in adults, point mutations of several genes including *DDX 41*, *GATA2*, *RUNX 1*, *ANKRD 26*, *ETV6* and telomerase complex genes (*TERC*, *TERT*) have been found in familial cases (Drazer, 2018). Almost 80% of patients with MDS carry at least one mutation in one gene (Papaemmanuil, 2013). Recurrently mutated genes include those involving RNA splicing, DNA methylation, histone modification, transcription regulation, DNA repair control, signalling, and the cohesin complex (Cazzola, 2020). *SF3B1*, *TET2*, *SRSF2*, *ASXL1*, *DNMT3A*, and *RUNX1* are mutated 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 acute myeloid leukaemia (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 disease and shorter overall survival (OS), with LR-MDS having fewer mutations than high-risk MDS (HR-MDS). Mutations in *SF3B1*, *TET2* and *ASXL1* occur more frequently in LR-MDS whereas mutations in *SRSF2*, *DNMT3A*, *RUNX1* and *TP53* are enriched in HR-MDS (Ogawa, 2019; Cazzola, 2020). The *SF3B1* mutation identifies a distinct subtype of MDS – MDS-RS+, that is characterised 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).

Environmental factors include previous exposure to chemotherapy, especially alkylating agents and purine analogues, radiotherapy or ionising radiation, and tobacco smoking Fenaux, 2021; Cardis, 2005; Iwanaga, 2011; Nisse, 2001). Recognised occupational factors include benzene and its derivatives, and more cases of MDS are reported among agricultural and industrial workers (Fenaux, 2021; Aksoy,1987; Nisse, 2001; Rigolin, 1998). Smoking was found to be significantly associated with MDS in a meta-analysis of 10 studies, while alcohol does not seem to play a major role in MDS aetiology (Du, 2010).

The main existing treatment options:

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 patient population who often have other complicating co-morbidities. Non-relapse mortality following HSCT represents a limiting factor especially in LR-MDS, and the survival rate differs significantly depending on age, disease risk, co-morbidities, conditioning intensity, and type of donor (Robin, 2020).

The aim of therapy in LR-MDS is to improve cytopenias, mainly anaemia (usually the predominant cytopenia), decrease transfusion needs, attempt to prolong OS, and reduce the risk of progression without compromising quality of life (QoL) (Fenaux, 2021; Platzbecker, 2021; Volpe, 2023). In patients where cytopenias are mild and asymptomatic, the approach is generally watchful observation. Eventually, ~40% of LR-MDS patients will become transfusion dependent.

The ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up for MDS, endorsed by the European Hematology Association (EHA) (van de Loosdrecht, 2022), provide a treatment algorithm supported by either evidence or expert opinions for LR-MDS (Figure 1).

Figure 1: Treatment algorithm for lower-risk MDS

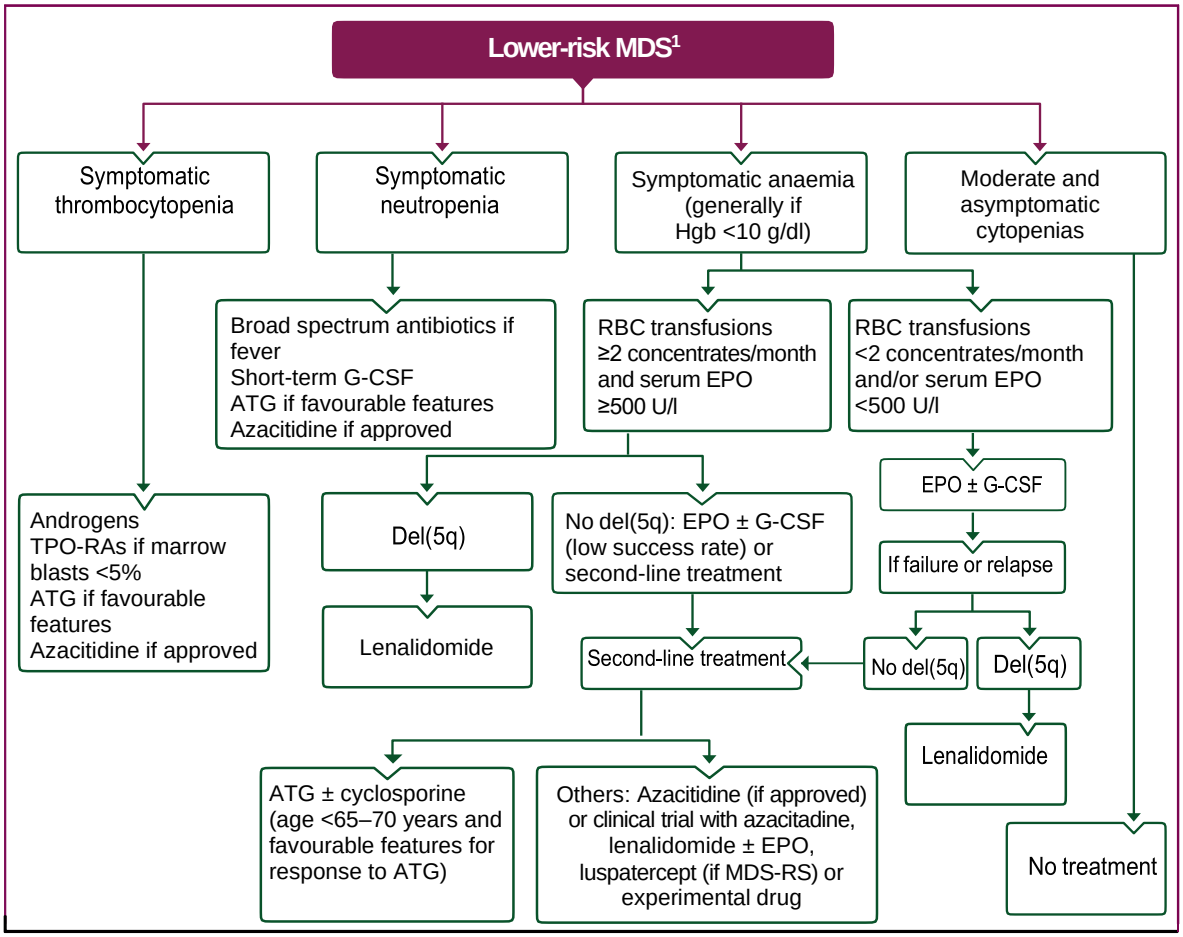

Figure adapted from ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of MDS (Fenaux, 2021).
ATG = antithymocyte globulin; EPO = erythropoietin; G-CSF = granulocyte colony-stimulating factor; Hgb = haemoglobin; IPSS-R = revised international prognostic scoring system; MDS = myelodysplastic syndromes; MDS-RS = myelodysplastic syndrome with ring sideroblasts; RBC = red blood cell; TPO-RA = thrombopoietin receptor agonist.
[1] IPSS-R very low-, low- and some intermediate-risk. For IPSS-R intermediate-risk MDS patients, whether they should initially receive treatment for lower-risk MDS or higher-risk MDS is also based on other factors including age, comorbidities, importance of cytopenias, somatic mutations, effect of first-line treatment, etc.

Currently available treatments for LR-MDS include:

- Erythropoiesis-stimulating agents (ESAs) have been well established as first-line treatment of anaemia in LR-MDS. However, patients with LR-MDS without del(5q) who have failed ESA treatment or do not respond or have short response to ESAs are at a higher risk of transformation to AML and poorer survival (median 36.7 vs. 54.3 months in patients with longer response to ESA (Kelaidi, 2013).
- Luspatercept is approved for the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS. The 8-week TI rate in RS+ patients who were refractory to or were unlikely to respond to ESAs was 38% with median duration of response of 30.6 weeks (Fenaux, 2020a). However, benefit was shown mostly in patients with a lower transfusion burden and limited data are available in RS- patients who are R/R to ESA.
- Lenalidomide is approved for the treatment of adult patients with transfusion-dependent anaemia due to low or intermediate-1 risk MDS associated with del(5q), which is observed in 10% to 15% of patients with MDS. Lenalidomide is not currently approved to treat MDS patients who are non-del(5q). The sub-set of patients with non-del(5q) MDS who are treated with lenalidomide do not respond or have responses of shorter duration.
- Hypomethylating agents (HMAs), specifically azacitidine, are primarily used in patients with higher risk (MDS intermediate 2 and high risk per IPSS) in the EU. 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) 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).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

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

Chronic anaemia is the major presentation of LR-MDS, leading to RBC transfusion dependency in approximately 40% of patients (Zeidan, 2013; Adès, 2014). Lower-risk patients with progressive cytopenias may become dependent on frequent RBC or platelet transfusions and may also experience repeated infections or bleeding events. Transfusion dependence and lower Hgb levels in patients with MDS have a significant negative correlation with survival and are associated with an increased likelihood of progression to AML (Malcovati, 2005; Platzbecker, 2012; Hellström-Lindberg, 2003; Fenaux, 2021). 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. 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).

Median survival in LR-MDS ranges from 32.0 months to 56.1 months (based on Surveillance, Epidemiology, and End Results [SEER] data from 2017; Zeidan, 2019). Patients with non-del(5q) LR-MDS who have failed ESA treatment, have a median overall survival (OS) of approximately 37 months (Kelaidi, 2013). Infection is the most common cause of death in LR-MDS, representing more than one-third of all disease-related deaths; leukaemic transformation and (mostly intracranial or gastrointestinal) bleeding complications are the cause of death in approximately 15% and 13% of LR-MDS patients, respectively (Zeidan, 2019).

Important co-morbidities:

Co-morbid conditions such as heart disease, mainly congestive heart failure, affect 18% and 25% of younger and older LR-MDS patients, respectively (Castelli, 2018). MDS patients experience an increased incidence of cardiovascular disease compared to matched non-cancer controls. This may be related to accelerated atherosclerosis and an inflammatory phenotype driven by common MDS mutations (*TET2*, *DNMT3A*) present in immune cells, notably monocytes/macrophages (Bazinet, 2022). These factors result in impaired QoL and most importantly shortened progression free survival (PFS) and OS (de Swart, 2020; Castelli, 2018; Platzbecker, 2021). Severe anaemia increases the negative effects of co-morbidities, such as heart and lung failure (Castelli, 2018).

Co-morbidity is recognised as a significant and independent determinant of MDS survival. A German study reported that the most frequent co-morbidities among a cohort of 504 MDS patients were cardiac diseases (37%), solid tumours (10%), and pulmonary (9%), renal (7%), and hepatic (4%) diseases (Zipperer, 2014). In this study, male patients had more co-morbidities than female patients ($P = 0.001$); cardiac and pulmonary diseases occurred with a greater frequency in males than in females (42% vs. 30% $P < 0.001$ and 11% vs. 6% $P = 0.002$, respectively). Furthermore, survival of male patients was worse than female patients in both the whole cohort and in the MDS-specific Comorbidity Index low-risk group ($P = 0.002$ and $P = 0.02$, respectively).

Another study evaluating 1,708 MDS patients (age ≥ 66 years) using SEER and Medicare data found that 51% of MDS patients had co-morbid conditions and that these patients had a significantly greater risk of death than those without co-morbidities (Wang, 2009). The most frequent co-morbidities included diabetes (21.8%), congestive heart failure (CHF) (20.8%), chronic obstructive pulmonary disease (COPD) (17.9%), cerebrovascular disease (8.0%), and peripheral vascular disease diagnosis (6.9%). MDS patients with CHF or COPD had significantly shorter survival than patients without those conditions, whereas diabetes did not appear to impact survival.

PART II: MODULE SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

Imetelstat is a 13-mer N3'→P5' thio-phosphoramidate (NPS) oligonucleotide (ODN) with a palmitoyl lipid covalently attached by an aminoglycerol linker to the 5' thio-phosphate of the first nucleotide. It has a complementary nucleotide sequence that binds to the template region of the RNA component of human telomerase (hTR), which lies in the active or catalytic site of human telomerase reverse transcriptase (hTERT), resulting in competitive inhibition of hTERT enzymatic activity which prevents telomere binding (Asai, 2003; Herbert, 2005). While sharing some structural similarity with other ODN classes, the mechanism of action of 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.

Consistent with the SmPC Guideline 2009, study drug doses are expressed as milligrams of imetelstat (the active moiety) in the following sections that summarise data from nonclinical studies, while in the nonclinical study reports and summary sections included in the marketing authorisation application (MAA), study drug doses are expressed as milligrams of imetelstat sodium (the active substance), a salt of imetelstat. To convert a quantity of imetelstat salt to the equivalent quantity of imetelstat, a factor of 0.9416 based on relative molar mass of the free acid form (4610 g/mol) to the sodium salt (4896 g/mol; 4610/4896 = 0.9416) is applied (i.e., 1 mg imetelstat sodium = 0.9416 mg imetelstat).

The safety profile of imetelstat was evaluated in a comprehensive programme of toxicology studies in rodents (mice and rats), rabbits, and non-human primates (cynomolgus monkeys) to support its use as a systemically administered therapy for patients with haematologic and solid tumour malignancies. These species were selected based on sequence homology to the template region of the RNA component of hTR and expected relevant pharmacologic action of imetelstat across species, from human to monkey to rabbit to rodent, as well as species-specific sensitivities to known oligonucleotide class effects. The studies included single-dose toxicity studies, repeat-dose toxicity studies, and a battery of genotoxicity studies, reproductive and embryo-foetal developmental toxicity studies, and immunotoxicity and phototoxicity assessments.

Safety pharmacology studies conducted included two in vitro studies to assess potential QTc prolongation effects on human ether-à-go-go-related gene (hERG) potassium channels. In addition, a single-dose study in monkeys was conducted to assess imetelstat effects on the central nervous system (CNS), cardiovascular and respiratory systems.

The potential for PK drug-drug interactions was evaluated in a series of in vitro studies using human biomaterials. The inhibitory potential of imetelstat on human drug transporters was assessed in Caco-2, HEK293 and MDCKII cells, and membrane vesicles. In addition, the inhibitory or induction potential of imetelstat on activities of cytochrome P450 (CYP) enzymes was assessed in human hepatocytes and liver microsomes, and one study evaluating the inhibitory potential of imetelstat on UDP-glucuronosyltransferase 1A1 (UGT1A1) enzyme activity was assessed in human liver microsomes.

Key safety findings from nonclinical studies and relevance to human usage are summarised as follows:

Key Safety findings (from nonclinical studies)	Relevance to human usage
Toxicity	
Acute or repeat-dose toxicity studies Early toxicity studies In the initial nonclinical toxicity studies, imetelstat doses were given at very high doses that ranged from 4.7 to 1158 mg/kg in mice and from 4.7 to 122.4 mg/kg in monkeys (by bolus intravenous [IV] injection and IV infusion). Consequently, the high IV doses of imetelstat given to animals in the early studies (i.e., ≥ 69.5 mg/kg) were poorly tolerated, resulting in the following adverse findings: • Haemorrhage in multiple tissues leading to mortality at imetelstat doses ≥ 69.5 mg/kg in mice (GS04-059; Module 2.6.6, Section 2.1), consistent with the inhibition of the intrinsic coagulation pathway by high doses/exposures observed with phosphorothioate oligonucleotides (PS ODNs). • In monkeys, single imetelstat doses ≥ 75.3 mg/kg administered as a 2-hour infusion led to mortality, observed within 8 to 20 hours after the end of infusion (GS04-062; Module 2.6.6, Section 2.2). Extensive multifocal haemorrhage was observed in multiple tissues, including heart, lung, skeletal muscle, gastrointestinal tract, and spleen. Coagulopathy, as characterised by prolongation of activated partial thromboplastin time (aPTT) and prothrombin time and marked reductions in fibrinogen and platelet counts, and activation of complement were the most prominent effects and were considered the main causes leading to deaths. • In contrast to the findings in the monkey study described above, in the IND-enabling 8-week monkey study (GS04-071; Module 2.6.6, Section 3.8) there were increases in plasma Bb levels (indicative of alternative pathway activation), but no increase in the C5a split product at any dose level, indicating the absence of any potential for adverse downstream sequelae from complement activation at the 14.1 mg/kg/week dose administered by 6-hour infusion. In addition, while > 3-fold prolongation in aPTT was observed at a mean plasma concentration (C_{max}) that was approximately 3- to 4-fold higher than the C_{max} in MDS patients at the recommended clinical dose, there was no evidence of clinical sequelae from clotting abnormalities seen in this study.	Nonclinical findings that could have relevance for use in humans include known ODN class effects, including cytopenias (most notably thrombocytopenia), complement activation, and coagulation abnormalities. Complement activation and coagulation abnormalities were related to the plasma concentration of imetelstat and reflect the well-characterised toxicity profile of the related PS ODN class (Frazier, 2015; Henry, 1997a; Henry, 1997b; Henry, 2002; Henry, 2008; Henry, 2016; Sheehan, 1998). Early toxicity studies involving imetelstat given by bolus IV injection, and/or at very high doses (e.g., up to 122.4 mg/kg in monkeys), are not reflective of the proposed dosing regimen for MDS patients, i.e., 7.1 mg/kg (equivalent to 7.5 mg/kg imetelstat sodium) administered by a 2-hour IV infusion, and produced exposures of imetelstat that were well above the range that is known to produce life-threatening toxicity with PS ODNs. Importantly, the mean plasma concentration levels achieved with such high doses of imetelstat in monkeys in GS04-062 (1,527.5 µg/mL for the 75.3 mg/kg dose and 2,628.3 µg/mL for the 122.4 mg/kg dose; Module 2.6.6, Section 2.2) exceeded C_{max} in MDS patients by approximately 17- to 29- fold following the administration of the recommended clinical dose. Such early toxicity studies served to elucidate the potential toxicities that are produced under excessive exposure conditions, and data from those studies provided evidence that the toxicity profile of imetelstat depended on factors in addition to dose, such as the mode and duration of IV administration (i.e., IV bolus vs. infusion) and species tested. In the clinical development programme, thrombocytopenia and neutropenia, including Grade 3/4 thrombocytopenia treatment-emergent adverse events (TEAEs) and Grade 3/4 neutropenia TEAEs, occurred in the majority of subjects treated with imetelstat (Section SVII.1.1). Based on nonclinical toxicology findings that showed aPTT prolongations and bleeding, in the Phase 1 imetelstat studies serial aPTT was measured following infusion, and transient Grade 1 and 2 aPTT prolongations were observed in subjects treated with imetelstat. The

Key Safety findings (from nonclinical studies)	Relevance to human usage
• Other findings in studies conducted up to a duration of 8 weeks included a variable degree of thrombocytopenia in repeat-dose studies, most pronounced in mice (GR05-031). In some rodent (GR05-031, GS03-030) and monkey (GS04-062, GS03-044) studies, there was also a reduction in the indicators of circulating red blood cell (RBC) mass (RBC counts, haemoglobin [Hgb] concentration and haematocrit [HCT]), typically accompanied by a reduction in circulating reticulocytes (new RBCs), and consistent with underproduction in the marrow (Module 2.6.6, Sections 2.2, 3.1, 3.5, 3.6 and 9).	aPTT prolongations did not have significant clinical sequelae. While aPTT and prothrombin time were not routinely measured in the Phase 2 studies, no bleeding events associated with coagulation abnormalities were reported in these studies. In Phase 3 study MDS3001, in the imetelstat group, most subjects were within normal range at baseline for aPTT and prothrombin international normalised ratio (INR) (92.8% and 76.6%, respectively) and remained within normal range during treatment (75.3% and 84.0%, respectively) (Table tlab06g, Table tlab02g). A maximum CTCAE grade of Grade 3 for aPTT or prothrombin INR was only reported for 1 subject each in the imetelstat group and there were no associated bleeding events (MDS3001 CSR [Phase 3]/ Listing lsflb07_p1; Listing lsflb07_p2; Listing lsfae03_p1; Listing lfsae03_p2). Similarly in the placebo group, most subjects were within normal range at baseline for aPTT and prothrombin INR (90.0% and 73.9%, respectively) and remained within normal range during treatment (82.0% and 71.7%, respectively). Grade 3 aPTT and Grade 3 prothrombin time were reported for 2 subjects and 1 subject, respectively, in the placebo group and there were no associated bleeding events (MDS3001 CSR [Phase 3]/ Listing lsflb07_p1; Listing lsflb07_p2; Listing lsfae03_p1; Listing lfsae03_p2). Similar trends in aPTT levels over time were observed in both the imetelstat and placebo groups, with an early increase followed by relative stabilization above baseline with some peaks over the course of the study (Module 2.7.4, Section 3.1.2.1). In the imetelstat group, there was a corresponding trend toward early decrease in prothrombin international normalised ratio (INR) levels followed by recovery to within normal range. Similar trends in aPTT and prothrombin time levels over time were observed in the Phase 2 and Phase 3 imetelstat groups in Group B (Module 2.7.4, Section 3.1.2.2) and across dose groups in the overall Group C pool (Module 2.7.4, Section 3.1.2.3).
Chronic pivotal toxicity studies In the 6-month mouse study conducted with dose levels up to 18.8 mg/kg given twice per week (BIW) by slow-bolus IV injection (003-TOX-2008; Module 2.6.6, Section 3.4), there was no	The most relevant toxicity studies to the intended clinical use of imetelstat based on duration of dosing in both species, as well as the mode of administration employed (i.e., 2-hour IV infusion in monkeys), are the chronic pivotal toxicity

Key Safety findings (from nonclinical studies)	Relevance to human usage
imetelstat-related mortality. The primary effects included: • Mild decreases in RBC parameters at dose levels ≥ 14.1 mg/kg; • Increases in mixed inflammatory cell foci in the liver and increases in hepatic Kupffer cells and/or histiocytic aggregates containing brown and/or blue pigment, likely indicative of the basophilic granulation that reflects the uptake of the ODN into the endosomal compartment of these cells that is considered a benign histomorphologic alteration (Levin, 1998); • Local injection site reactions at 18.8 mg/kg, which correlated with microscopic observations of necrosis/inflammation and vascular/perivascular fibrosis; however, these findings are not clinically relevant due to the small tail vein vessels in mice and the likelihood of local extravasation of the imetelstat dose, as well as the bolus injection mode of administration; • Increases in spleen weight at ≥ 4.7 mg/kg and in liver and kidney weights at 18.8 mg/kg in males. All of these dose-related effects showed evidence of recovery following the 8-week treatment-free period. The systemic no-observed-adverse-effect-level (NOAEL) of imetelstat administered BIW for 26 weeks was 18.8 mg/kg/dose due to the low severity and reversibility of the imetelstat-related effects. The NOAEL for local (tail vein injection site) toxicity was 4.7 mg/kg based on the vascular irritation observed at ≥ 14.1 mg/kg/dose, but it was not considered clinically relevant. In the 9-month chronic toxicity study in monkeys with once-weekly dosing via 2-hour IV infusion (002-TOX-2008; Module 2.6.6, Section 3.9), dose levels up to 14.1 mg/kg/week were generally well tolerated. Salient test article-related changes included: • Systemic toxicity that consisted mainly of mild decreases in RBC parameters at ≥ 9.4 mg/kg. • Platelet counts were highly variable but were mildly lower at 9.4 and 14.1 mg/kg, and lower platelet counts were occasionally associated with higher mean platelet volume. • Evidence of erythroid hyperplasia at 14.1 mg/kg based on evaluation of bone marrow smears, usually associated with the poorly-regenerative mild to moderate anaemia.	studies, i.e., the 6-month study in mice (003-TOX-2008; Module 2.6.6, Section 3.4) and the 9-month study in monkeys (002-TOX-2008; Module 2.6.6, Section 3.9). As demonstrated in the 9-month toxicity study in monkeys, the degree and potential adverse sequelae of coagulation abnormalities and complement activation can be mitigated by administering imetelstat over a 2-hour IV infusion, even at doses that produced exposures (C_{max}) in animals that are 6-7 x higher than those in human plasma at the proposed clinical dose. Cytopenias are also a class effect of polyanionic ODNs, the aetiology of which is not entirely certain, but is widely believed to stem from the known immunostimulatory properties of PS and related ODNs, i.e., direct effect of cytokines on stem cell maturation leading to underproduction of platelets in the bone marrow (Levin, 1998; Levin, 1999). The on-target effect of imetelstat on haematopoietic progenitor cells may also account for one of the potential mechanisms of imetelstat-induced, reversible thrombocytopenia. The degree of haematological effects, particularly decreases in platelets, observed in toxicity studies of imetelstat was variable, with mild to moderate decreases seen in the 9-month toxicity study in monkeys. Importantly, while cytopenias are the most frequently observed TEAEs in imetelstat clinical studies, specifically Grade 3/4 thrombocytopenia and neutropenia, they are easily monitored in patients, can be managed with dose modifications, and the majority have been reversible with limited clinical consequences. The imetelstat summary of product characteristics (SmPC) provides guidance on how to manage thrombocytopenia and neutropenia in clinical practice through monitoring, dose modifications, and provision of supportive care by healthcare professionals who are experienced at treating thrombocytopenia and neutropenia in patients with MDS. Additional toxicities observed in these studies that may have relevance to humans included ODN class-related effects on the liver (deposition in Kupffer cells) and kidney (mesangial thickening, glomerulonephritis/sclerosis, deposition in interstitium, renal tubular haemorrhage, protein casts, and regeneration) (Levin, 1998). Minimal-to-moderate telangiectasis (dilation of small blood vessels) in the liver was also observed in

Key Safety findings (from nonclinical studies)	Relevance to human usage
• Initial activation of complement that was immediate and driven by the alternative pathway (Bb). For longer-term treatment beyond 6 months, the Bb diminished but was still significantly high, with some of the animals exceeding 20 µg/mL. Chronic treatment caused depletion of classical pathway activity (CH50), with individual cases of complete depletion of the CH50 activity. Although some of the C5a levels at 14.1 mg/kg rose about 2.5-fold above their baseline, they remained within the normal range for cynomolgus monkeys (4.2 to 13 ng/mL). During the recovery period, the values for all complement parameters remained only slightly elevated over baseline and showed reversal. Complement activation is a dynamic process and seldom involves only one pathway of activation. In this case, it seems that direct activation of the alternative pathway by imetelstat in the naïve monkeys was gradually followed by involvement of both pathways at the later timepoints and shifted the activation mechanism to the classical pathway. • Following chronic treatment, liver and kidney weights were increased with microscopic correlates of mild to moderate changes in the kidney (mesangial thickening, glomerulonephritis/ sclerosis, deposition in interstitium, renal tubular haemorrhage, protein casts, and regeneration) and in the liver (telangiectasis, brown pigment deposition in Kupffer cells). Importantly, there were no degenerative changes or alterations in clinical pathology parameters indicative of hepatic dysfunction or injury (i.e., no substantial elevations in serum transaminases, bilirubin, or alkaline phosphatase [ALP]), nor were there any remarkable changes in parameters of kidney function. • In addition, changes were noted in the uterus (atrophy of the endometrium), choroid plexus (minimal lymphoid follicle formation and mononuclear cellular infiltration), and general systemic arteritis, including at the injection site. The uterine endometrial atrophy was only noted after chronic dosing of female monkeys at 14.1 mg/kg and was absent following a 14-week recovery period which is suggestive of complete reversibility. • There were no gross or histological changes noted at any dose up to 14.1 mg/kg for the male reproductive tissues, which is consistent with a	some animals. Importantly, there were no degenerative changes or alterations in clinical pathology parameters indicative of hepatic dysfunction or injury (i.e., no substantial elevations in serum transaminases, bilirubin, or ALP), nor were there any remarkable changes in parameters of kidney function, which is consistent with the clinical experience. In the clinical development programme, the majority of hepatic TEAEs were non-serious, Grade 1 or Grade 2 in severity, and resolved within 2 weeks (Section SVII.1.2). No subjects met Hy's law criteria. Hepatic enzyme elevations can be managed in clinical practice through monitoring and dose modifications based on severity grade and occurrence. In the clinical development programme imetelstat was not found to cause renal toxicity (Table tae02a; Table tae02b; Table tae02c). Reversible uterine endometrial atrophy was noted after chronic dosing of female monkeys at high doses and therefore imetelstat may impair female fertility. There were no gross or histological changes noted at any dose for the male reproductive tissues. The imetelstat SmPC informs healthcare professionals that based on findings in animals, imetelstat may impair fertility in females of reproductive potential. No human data on the effect of imetelstat on fertility are available.

Key Safety findings (from nonclinical studies)	Relevance to human usage
lack of such findings in the 6-month mouse study (003-TOX-2008; Module 2.6.6, Section 3.4). • No test article-related changes were observed in electrocardiography, blood pressure, and respiratory rate, which is consistent with the findings in the safety pharmacology study of imetelstat conducted in monkeys (GS04-072; Module 2.6.2, Section 4.2). Most changes showed evidence of recovery after a 14-week drug-free period. Because test article-related adverse changes were observed at all dose levels, this study did not identify a NOAEL. The absence of mortality and absence of clear or pronounced clinical signs of toxicity or substantial changes in body weight at any dose level suggests that 14.1 mg/kg/week could be regarded as the highest non-severely toxic dose (HNSTD).	
Reproductive/developmental toxicity The embryo-foetal developmental (EFD) toxicity studies were conducted with imetelstat in mice (004-TOX-2008, 006-TOX-2008; Module 2.6.6, Sections 6.1 and 6.2) and rabbits (005-TOX-2008, 007-TOX-2008; Module 2.6.6, Sections 6.3 and 6.4), species typically used for such assessment of ODNs (Cavagnaro, 2014). Imetelstat was administered by IV bolus injection at doses of 4.7, 9.4, 14.1 or 28.2 mg/kg/day on gestation days (GD) 6, 9 and 12 in mice, or by 2-hour IV infusion at doses of 4.7, 14.1 or 28.2 mg/kg on GD 6 and 13 in 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, a dose deemed to be maternally toxic based on decreases in mean gestation weight. Embryo-lethal effects were observed at 28.2 mg/kg in both species, noted as increased post-implantation loss due to an increase in early resorptions, resulting in a decrease in viable foetuses and litter size per animal. These effects were observed at a dose that produced exposures (based on AUC) that are approximately 3.4-times (mice) or 26.4-times (rabbits) the human exposure at the recommended clinical dose. 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. In mice, while there were no maternal or developmental toxicities observed at the doses tested in the definitive EFD study (up to	In embryo-foetal developmental toxicity studies, imetelstat was not teratogenic. The embryo-lethal effects observed following administration of 28.2 mg/kg imetelstat (the highest dose) to pregnant mice and rabbits were observed at maternal exposures (based on AUC) that are approximately 3.4-times (mice) or 26.4-times (rabbits) the human exposure at the recommended clinical dose (Module 2.6.6, Section 9). Based on findings in animal studies, imetelstat may cause embryonic or foetal loss when administered to a pregnant woman. In the clinical development programme, there was no imetelstat exposure during pregnancy (Section SIV.3). The imetelstat SmPC informs healthcare professionals that imetelstat is not recommended during pregnancy and in women of childbearing potential not using contraception. Healthcare professionals are requested to verify the pregnancy status of females of reproductive potential before starting treatment with imetelstat. 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. Healthcare professionals are informed that it is unknown whether imetelstat is excreted in human milk. There is no data on the presence of imetelstat in human milk, the effects on the breastfed child, or the effects on milk production. A risk to the breast-feeding child cannot be excluded. Women should be advised not to breastfeed during treatment with imetelstat and

Key Safety findings (from nonclinical studies)	Relevance to human usage
28.2 mg/kg/dose) (006-TOX-2008), embryo-lethality was observed at 28.2 mg/kg/dose in the dose range-finding (DRF) study (004-TOX-2008). Therefore, those results are taken into consideration in the assessment of the margin-to-effect values in relation to human exposure. In rabbits, doses of 14.1 and 28.2 mg/kg were considered to be maternally toxic based on a decrease in mean gestation body weight observed in a single study interval (GD 13-16) out of 11 study intervals assessed for the 14.1 mg/kg/dose group, and a statistically significant decrease in mean gestation body weight change observed during the length of the study period (GD 0-29) for the 28.2 mg/kg/dose group, such effects occurring at exposures that are 13.0- and 26.4-times, respectively, the human exposure at the recommended clinical dose. These data are in line with other fertility, foetal development, and development and reproductive function studies in mice, rats, and rabbits that found little evidence for uptake of polyanionic ODNs by the placenta or transfer into the foetus (Soucy, 2006; Module 2.6.6 Section 9).	for 1 week after the last dose because of the potential for adverse reactions in breast-fed children. Embryo-foetal toxicity is an important potential risk (Section SVII.1.2).
Genotoxicity No genotoxic effects were observed in the in vitro bacterial mutagenicity assay (Ames test) in the standard strains of *S. typhimurium* and *E. coli* at imetelstat concentrations up to 5000 µg/plate and the mammalian cell clastogenicity assays in cultured human lymphocytes at imetelstat concentrations up to 2450 µg/mL (Module 2.6.6, Sections 4.1 and 4.2). In addition, imetelstat did not induce a biologically relevant increase in micronucleated polychromatic erythrocytes in a mouse in vivo micronucleus assay at IV dose levels up to 103.6 mg/kg, which was the maximum tolerated dose (Module 2.6.6, Section 4.3). Therefore, imetelstat does not pose a risk for mutagenicity or clastogenicity.	Imetelstat does not pose a risk for mutagenicity or clastogenicity. These genotoxicity studies, together with the embryo-foetal developmental toxicity studies, substantiate that imetelstat is not teratogenic.
Carcinogenicity A weight of evidence assessment supports the conclusion that imetelstat has a low risk of carcinogenic potential.	Not applicable.
Safety Pharmacology	
Safety pharmacology studies were conducted in vitro and in vivo (in monkeys) to assess imetelstat effects on the CNS, cardiovascular and respiratory systems.	Imetelstat is very unlikely to delay ventricular repolarization and have a proarrhythmic risk in humans based on the data from two studies that evaluated imetelstat effects in vitro on the hERG ion channel. These findings are consistent with

Key Safety findings (from nonclinical studies)	Relevance to human usage
Data from two studies that evaluated imetelstat effects in vitro on the human ether-à-go-go-related gene (hERG) ion channel (007-TOX-2007; PRE-14-002; Module 2.6.2, Section 4.1) were consistent in demonstrating that imetelstat does not inhibit hERG currents at concentrations up to 750 µg/mL, which results in a safety margin for imetelstat of > 140-fold based on the free plasma concentration at C_{max} of 5.37 µg/mL for MDS patients dosed at 7.1 mg/kg (reflecting C_{max} of 89.5 µg /mL for MDS, human plasma protein binding of 94%, and corresponding unbound imetelstat of 6%). These results are consistent with the general absence of QT effects for ODNs as a pharmacologic class which was supported by a recent systematic review of ECG evaluations with approved oligonucleotides (Noormohamed, 2023). In an in vivo safety pharmacology study, cynomolgus monkeys were administered single doses of imetelstat up to 14.1 mg/kg IV over a 6- or 24-hour period (GS04-072; Module 2.6.2, Section 4.2), resulting in imetelstat exposure levels (based on C_{max}) in excess of those predicted in MDS patients administered imetelstat in the clinic (i.e., > 2.6 times higher), with no treatment-related clinical signs observed, including no evidence of CNS effects. In addition, no significant changes in mean arterial pressure, heart rate, respiratory rate, body temperature, electrocardiographic activity, or blood gas parameters were noted up to the highest dose tested (14.1 mg/kg). Consistent with these findings, there were no test article-related changes observed in electrocardiography, blood pressure, and respiratory rate in the 9-month chronic pivotal toxicity study in monkeys with once-weekly administration of dose levels up to 14.1 mg/kg/week via 2-hour IV infusion (002-TOX-2008; Module 2.6.6, Section 3.9).	those from the safety pharmacology study in monkeys, as well as findings from the clinical studies in which no significant imetelstat-related pro-arrhythmic effects have been observed (Module 2.7.4, Section 4.1.1). The potential proarrhythmic effect of imetelstat has been evaluated with QT/QTc and PK assessments in a ventricular repolarization substudy (n = 45 total subjects; randomised 2:1 imetelstat:placebo) under Study MDS3001 at the request of the Food and Drug Administration (FDA) (Module 2.7.2, Section 3.5.2) and will be provided to the EMA post-approval. However, based on the current knowledge of imetelstat from nonclinical safety pharmacology assessments and clinical cardiac safety data, and supported by a recent systematic review of ECG evaluations with approved oligonucleotides (Noormohamed, 2023) and an extensive review of 29 oligonucleotide therapeutics that found no clinical proarrhythmic risk based on data from International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S7B/E14 studies (Qu, 2024), imetelstat is not likely to prolong the QT interval. Overall, imetelstat is considered to have a very low likelihood of presenting any safety risk for the CNS, cardiovascular and respiratory systems. In the clinical development programme imetelstat was not found to cause significant cardiac, nervous system or respiratory toxicity (Table tae02a; Table tae02b; Table tae02c).
Mechanisms for drug interactions	
Pharmacokinetic drug interactions Imetelstat did not induce CYP activity in human hepatocytes (303-1160; Module 2.7.2, Section 2.1.4.2). Imetelstat did not inhibit CYP activity in human hepatocytes, with IC_{50} values > 100 µM for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 (FK12087; FK11110; Module 2.7.2, Section 2.1.4.1.1; Module 2.7.2, Section 2.1.4.1.2). In	Several clinical studies have shown that oligonucleotides have a very low drug-drug interaction risk (Adjei, 2003; Geary, 2006; Mani, 2002; Yu, 2009). As oligonucleotides are likely metabolised into smaller fragments by nucleases in tissues with component fragments excreted in urine, they are not metabolised by classical hepatic enzymes (Geary, 2009). Therefore, oligonucleotides are not substrates of CYP enzymes (Geary, 2009; Yu, 2009) and they

Key Safety findings (from nonclinical studies)	Relevance to human usage
vitro inhibition of CYP isoforms by imetelstat in human hepatic microsomes (303-1159; 18019; Module 2.7.2, Section 2.1.4.1.3; Module 2.7.2 Section 2.1.4.1.4) occurred at IC_{50} values between 0.7 and 26 µM. The non-specificity of the inhibition suggests that it is not due to competitive inhibition of the CYPs and may, instead, be an artifact of the polyanionic nature of imetelstat, as described for other ODNs (Buckley, 2009; Kazmi, 2015; Kazmi, 2018). In a follow-up study, imetelstat did not affect the PK of [^{14}C]-Taxol, a known CYP2C8 substrate, in the rat following IV co-administration (WIL-493006; Module 2.6.4, Section 7.3). Imetelstat directly inhibited UGT1A1 enzyme activity in human liver microsomes, with an IC_{50} value of 1.3 µM (XT135034; Module 2.7.2, Section 2.1.4.1.5). Notably, this study was also conducted in human liver microsomes prior to emergence of data/consensus demonstrating artifactual test-system effects for other oligonucleotides (for CYPs and UGT enzymes, (Kazmi, 2018)). In vitro data demonstrated that imetelstat does not inhibit the P-glycoprotein (P-gp) transporter in Caco-2 cells at concentrations up to > 30 µM (or > 27x $C_{max,u}$) (18019; Module 2.7.2, Section 2.1.4.3.1). Imetelstat was also evaluated as an inhibitor of breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporting polypeptide 1 (OATP1)B1 and OATP1B3 transporters, organic anion transporter 1 (OAT1), OAT3, organic cation transporter 1 (OCT1), OCT2, and multidrug and toxin extrusion transporter 1 (MATE1), and MATE2-K. Imetelstat did not inhibit BSEP, OCT1, OCT2, MATE1, or MATE2-K at concentrations up to 70 µM (64x $C_{max,u}$) (XT228134; Module 2.7.2, Section 2.1.4.3.3). Imetelstat exhibited in vitro inhibitory potential for OAT3 with a relatively high IC_{50} value of 49.6 µM (45x $C_{max,u}$), and the R value falls below the guidance threshold for further evaluation for drug-drug interaction (DDI) potential (XT228134; Module 2.7.2, Section 2.1.4.3.3). Imetelstat was found to inhibit the hepatic uptake transporters OATP1B1 and OATP1B3 with IC_{50} values of 5.87 and 1.20 µM, respectively (XT138038; Module 2.7.2, Section 2.1.4.3.2), the renal transporter OAT1 with IC_{50} of 8.75 µM (XT228134; Module 2.7.2, Section 2.1.4.3.3), and the efflux transporter BCRP with IC_{50} of 27.5 µM (XT228134;	are not expected to interact with small molecules that are predominately cleared through oxidative metabolic pathways (Geary, 2009). Additionally, the PK of oligonucleotides is not expected to be affected by modulation of drug transporters. Overall, there is a low risk of victim-based drug-drug interactions for imetelstat. In in vitro studies to evaluate the risk of perpetrator-based DDI potential for imetelstat, results for the OATP1B1, OATP1B3, OAT1, and BCRP transporters and the UGT1A1 enzyme exceeded the thresholds outlined in the Guidance documents, indicating that further evaluation of the perpetrator-based drug-drug interaction risk for imetelstat was required. An integrated assessment of clinical PK characteristics and safety data supports the conclusion that the risk of clinically relevant drug-drug interactions through inhibition of these pathways is unlikely (Module 2.7.2, Section 3.4.2.2). Consistent with other oligonucleotides, imetelstat has limited risk of clinically relevant perpetrator-based drug-drug interactions based on an integrated assessment of R value calculations, PK characteristics, concomitant medications, and clinical data. The imetelstat SmPC informs healthcare professionals that no interaction studies have been performed in humans. In vitro imetelstat is an inhibitor of BRCP, OAT1, OATP1B1 and OATP1B3 at concentrations similar to those reached on the day of imetelstat administration. The risk for an interaction, causing increased plasma concentrations of a co-administered substrate, declines with the rapidly declining plasma concentrations of imetelstat and is likely not relevant on the following days of the dose interval.

Key Safety findings (from nonclinical studies)	Relevance to human usage
Module 2.7.2, Section 2.1.4.3.3). The calculated R values for OATP1B1, OATP1B3, OAT1, and BCRP exceeded the guidance threshold, requiring further evaluation of the DDI risk. **Pharmacodynamic drug interactions** Imetelstat is intended to be used as monotherapy treatment for patients with MDS and therefore no formal pharmacodynamic (PD) drug interaction studies with imetelstat were performed.	
Other toxicity-related information or data	
Local tolerance Local tolerance to imetelstat administration at the injection site was evaluated in general toxicity studies in mice (GS04-070; 003-TOX-2008), rats (GS03-030) and monkeys (GS03-044; GS03-046; GS04-071; 002-TOX-2008). Injection site findings were largely limited to tail vein injection sites in mice and included vascular irritation, discolouration and microscopic observations of necrosis/inflammation and vascular/perivascular fibrosis (Module 2.6.6, Section 7).	The injection site pathology observed in mice was likely attributable to extravasation of imetelstat from the very small tail veins which commonly occurs with IV bolus injections in rodent studies. In contrast, imetelstat is administered to patients via slow (2-hour i.e., 250 mL/h) IV infusion and local injection site reactions are not a common occurrence in patients; therefore, these findings are not considered clinically relevant.
Phototoxicity Imetelstat was not cytotoxic or phototoxic in the 3T3 Neutral Red Uptake Phototoxicity Test at concentrations up to 1000 µg/mL (MB 10-19402.30; Module 2.6.6, Section 8.3).	No subjects treated with imetelstat in Phase 2/3 study MDS3001 experienced photosensitivity (Table tae02a; Table tae02b). Two (0.5%) subjects treated with imetelstat experienced photodermatosis TEAEs in Group C; neither TEAE was serious, of ≥ Grade 3 severity nor considered related to treatment (Table tae02c; Table tae02i; Table tae02l). Imetelstat is not recognised to cause photosensitivity.

Conclusions from the nonclinical development programme

The pharmacologic, PK and toxicologic profiles of imetelstat have been well characterised and the nonclinical data support the safe and intended clinical use of imetelstat for the treatment of adult patients with transfusion-dependent anaemia due to lower risk MDS.

Nonclinical findings that could have relevance for use in humans include cytopenias (most notably thrombocytopenia), complement activation, and coagulation abnormalities. Clinical data have confirmed that thrombocytopenia and neutropenia are recognised risks of imetelstat (Section SVII.1.1). The cytopenias are easily monitored in patients, can be managed with dose modifications and supportive care as needed, and the majority have been reversible and without clinical consequences. Coagulation abnormalities have been observed with imetelstat but similar to the 9-month toxicity study in monkeys, the degree and potential adverse sequelae of coagulation abnormalities and complement activation can be mitigated by administering imetelstat over a 2-hour IV infusion. These effects (coagulation abnormalities and complement activation) have not been seen to any clinically relevant extent in humans based on cumulative clinical experience with imetelstat, including the pivotal MDS3001 study.

Additional imetelstat toxicities included class-related effects on the liver and kidney but importantly, there were no degenerative changes or alterations in clinical pathology parameters indicative of hepatic dysfunction or injury, nor were there any remarkable changes in parameters of kidney function, which is consistent with the findings in humans (Section SVII.1.2).

In embryo-foetal developmental toxicity studies, imetelstat was not teratogenic. Although administration of imetelstat to pregnant mice and rabbits resulted in embryo-lethal effects at a dose of 28.2 mg/kg, such effects were observed at maternal exposures that exceeded human exposures at the recommended clinical dose. These data, together with the genotoxicity studies that show that imetelstat does not pose a risk for mutagenicity or clastogenicity, suggest that imetelstat is unlikely to cause teratogenicity. However, imetelstat may cause embryonic or foetal loss when administered to a pregnant woman.

Based on data from two in vitro hERG ion channel studies, imetelstat is very unlikely to delay ventricular repolarization and have a proarrhythmic risk in humans, with consistent findings from the safety pharmacology study in monkeys and from the clinical development programme (Section SIV.1).

Overall, imetelstat is considered to have a very low likelihood of presenting any safety risk for the CNS, cardiovascular and respiratory systems.

While in vitro studies suggest potential for drug-drug interactions for imetelstat via OATP1B1, OATP1B3, OAT1, BCRP, and UGT1A1, imetelstat has limited risk of clinically relevant drug-drug interactions based on an integrated assessment of PK characteristics and clinical data, as summarised below:

- Imetelstat is dosed infrequently (q4w) and is rapidly cleared from plasma (t½ of 4.9 h). Imetelstat concentrations fall below the critical R value thresholds for inhibition by 3 to 12 h post-dose.
- There are no clinically relevant elevations in the OATP1B1/OATP1B3 and UGT1A1 substrate bilirubin in imetelstat subjects compared to placebo in Study MDS3001.
- There is no indication of altered safety profiles when imetelstat is administered with concomitant substrates of OATP1B1/OATP1B3 (statins) or UGT1A1 (deferasirox). Concomitant OAT1 substrates used with imetelstat are limited to antibiotics, which are used only as needed to treat infections, suggesting limited potential for OAT1-mediated DDIs in the MDS patient population.

Overall, there is limited risk of clinically relevant drug-drug interactions for imetelstat, consistent with other oligonucleotides.

The local tolerance findings in rodent studies were considered attributable to extravasation of imetelstat from the very small tail veins with IV bolus injections and not clinically relevant to patients who are administered imetelstat via a slow (2-hour) IV infusion. Local injection site reactions are not considered an important risk of imetelstat. Imetelstat is not recognised to induce phototoxicity.

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

Consistent with the SmPC Guideline 2009, study drug doses are expressed as milligrams of imetelstat (the active moiety) in the following sections that summarise data from clinical studies, while in the clinical study reports (CSRs) and summary sections included in the MAA, study drug doses are expressed as milligrams of imetelstat sodium (the active substance), a salt of imetelstat. To convert a quantity of imetelstat salt to the equivalent quantity of imetelstat, a factor of 0.9416 based on relative molar mass of the free acid form (4610 g/mol) to the sodium salt (4896 g/mol; 4610/4896 = 0.9416) is applied (i.e., 1 mg imetelstat sodium = 0.9416 mg imetelstat).

The imetelstat clinical development programme includes studies in haematological and solid tumour malignancies, as monotherapy or in combination with other drugs.

The key clinical studies to support the use of imetelstat as monotherapy for the treatment of adult patients with transfusion-dependent anaemia due to very low, low or intermediate risk 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 are listed below. These include the pivotal Phase 2/3 study (Study MDS3001), with a focus on the randomised, double-blind, placebo-controlled Phase 3 portion to support efficacy and safety, and four additional studies in haematology indications, including MDS, myelofibrosis (MF), essential thrombocytopenia (ET) or polycythemia vera (PV) and multiple myeloma (MM), to support safety.

- **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
- **CP14B013:** A Phase II Trial to Determine the Effect of Imetelstat (GRN163L) on Patients with Previously Treated Multiple Myeloma
- **CP14B015:** A Phase II Trial to Evaluate the Activity of Imetelstat (GRN163L) in Patients with Essential Thrombocythemia or Polycythemia Vera who Require Cytoreduction and Have Failed or Are Intolerant to Previous Therapy, or who Refuse Standard Therapy
- **CP14B019:** A Pilot Open-Label Study of the Efficacy and Safety of Imetelstat (GRN163L) in Myelofibrosis and other Myeloid Malignancies
- **MYF2001:** A Randomized, Single-Blind, Multicenter Phase 2 Study to Evaluate the Activity of 2 Dose Levels of Imetelstat in Subjects with Intermediate-2 or High-Risk Myelofibrosis (MF) Relapsed/Refractory to Janus Kinase (JAK) Inhibitor

To evaluate the overall safety profile of imetelstat monotherapy, analyses were performed for three safety groupings (Table 2). Group A represents the placebo-controlled safety data in MDS subjects available from Phase 3 portion of the MDS3001 Study. Group B represents all the subjects with low to intermediate-1 risk MDS who are transfusion-dependent and have failed to respond or have lost response or are ineligible for ESA and includes safety data from both parts of the MDS3001 (Phase 2 single arm and Phase 3 randomised). Group C represents all subjects with haematologic malignancies treated with imetelstat monotherapy.

All subjects in Groups A and B treated with imetelstat received a starting dose of 7.1 mg/kg (equivalent to 7.5 mg/kg imetelstat sodium) IV every 4 weeks (Q4W).

In Group C, doses in the pooled studies ranged from 4.4 mg/kg to 8.9 mg/kg (equivalent to 4.7 mg/kg to 9.4 mg/kg imetelstat sodium) every 4 weeks, Days 1 and 8 every 4 weeks and weekly. Of the 391 subjects treated with imetelstat in Group C, 48 subjects were treated with < 7.1 mg/kg Q4W imetelstat (MYF2001 4.4 mg/kg arm only), 204 subjects were treated with 7.1 mg/kg Q4W imetelstat (CP14B019 arm E and G; MDS3001 Phase 2 and 3; CP14B015 and CP14B013 7.1 mg/kg arm), and 139 subjects were treated with > 7.1 mg/kg Q4W imetelstat (CP14B019 arms A, B, D, and F; CP14B015, CP14B013 and MYF2001 8.9 mg/kg arm).

Table 2: Pooled Data Grouping

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	Hematologic 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)[1]
Total number of subjects		391 imetelstat 59 placebo 450 total	

ET = essential thrombocytopenia; IV = intravenous(ly); MDS = myelodysplastic syndromes; MF = myelofibrosis; MM = multiple myeloma; MPN = myeloproliferative neoplasms; PV = polycythemia vera
[1] Four subjects who received imetelstat in combination with lenalidomide are not included in the safety analyses.
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group B includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group C includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled), and Phase 2 open-label studies MYF2001, CP14B013, CP14B015, and CP14B019.
Clinical cut-off date: 13 Oct 2022 for MDS3001.

Clinical trial exposure data are presented for all subjects treated with imetelstat and placebo in MDS3001 Phase 3 (Group A), and for all subjects treated with imetelstat in MDS3001 Phase 2/3 (Group B) and Haematologic Malignancy Studies (Group C), by duration of exposure (Table 3), age group and gender (Table 4), race (Table 5) and ethnicity (Table 6).

Table 3: Duration of Exposure in MDS3001 Phase 3 (Group A), MDS3001 Phase 2/3 (Group B) and Haematologic Malignancy Studies (Group C)

Treatment duration (months), n (%)	Group A		Group B	Group C
	Imetelstat (N=118)	Placebo (N=59)	Imetelstat (N=175)	Imetelstat (N=391)
< 3	18 (15.3%)	8 (13.6%)	27 (15.4%)	81 (20.7%)
3-6	25 (21.2%)	19 (32.2%)	40 (22.9%)	95 (24.3%)
6-9	20 (16.9%)	9 (15.3%)	29 (16.6%)	52 (13.3%)
9-12	8 (6.8%)	7 (11.9%)	12 (6.9%)	33 (8.4%)
12-15	10 (8.5%)	4 (6.8%)	11 (6.3%)	25 (6.4%)
15-18	14 (11.9%)	6 (10.2%)	15 (8.6%)	27 (6.9%)
18-21	7 (5.9%)	1 (1.7%)	8 (4.6%)	16 (4.1%)
21-24	10 (8.5%)	1 (1.7%)	13 (7.4%)	22 (5.6%)

Treatment duration (months), n (%)	Group A		Group B	Group C
	Imetelstat (N=118)	Placebo (N=59)	Imetelstat (N=175)	Imetelstat (N=391)
24-27	3 (2.5%)	4 (6.8%)	6 (3.4%)	9 (2.3%)
27-30	0	0	1 (0.6%)	6 (1.5%)
30-33	3 (2.5%)	0	6 (3.4%)	9 (2.3%)
33-36	0	0	3 (1.7%)	8 (2.0%)
36-39	0	0	1 (0.6%)	2 (0.5%)
39-42	0	0	2 (1.1%)	3 (0.8%)
42-45	0	0	0	1 (0.3%)
45-48	0	0	0	0
48-51	0	0	0	0
51-54	0	0	0	0
54-57	0	0	0	0
57-60	0	0	1 (0.6%)	1 (0.3%)
60-63	0	0	0	1 (0.3%)

IV = intravenous(ly)
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group B includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group C includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled), and Phase 2 open-label studies MYF2001, CP14B013, CP14B015, and CP14B019.
Source data: Table tex04a; Table tex04b; Table tex04c
Clinical cut-off date: 13 Oct 2022 for MDS3001.

Table 4: Exposure by Age Group and Sex in MDS3001 Phase 3 (Group A), MDS3001 Phase 2/3 (Group B) and Haematologic Malignancy Studies (Group C)

	Group A		Group B	Group C
	Imetelstat (N=118)	Placebo (N=59)	Imetelstat (N=175)	Imetelstat (N=391)
Age Group, n (%)				
n[1]	118	59	175	391
< 65 years	27 (22.9%)	9 (15.3%)	41 (23.4%)	128 (32.7%)
≥ 65 – 75 years	56 (47.5%)	27 (45.8%)	81 (46.3%)	171 (43.7%)
≥ 75 years	35 (29.7%)	23 (39.0%)	53 (30.3%)	92 (23.5%)
Sex, n (%)				
n[1]	118	59	175	391
Male	71 (60.2%)	39 (66.1%)	103 (58.9%)	237 (60.6%)
Female	47 (39.8%)	20 (33.9%)	72 (41.1%)	154 (39.4%)

[1] The number of subjects in each group with non-missing parameter value.
IV = intravenous(ly)
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group B includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group C includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled), and Phase 2 open-label studies MYF2001, CP14B013, CP14B015, and CP14B019.
Source data: Table tdm01a; Table tdm01b; Table tdm01c
Clinical cut-off date: 13 Oct 2022 for MDS3001.

Table 5: Exposure by Race in MDS3001 Phase 3 (Group A), MDS3001 Phase 2/3 (Group B) and Haematologic Malignancy Studies (Group C)

	Group A		Group B	Group C
	Imetelstat (N=118)	**Placebo (N=59)**	**Imetelstat (N=175)**	**Imetelstat (N=391)**
Race, n (%)				
n[1]	118	59	174	390
White	95 (80.5%)	47 (79.7%)	141 (81.0%)	326 (83.6%)
Asian	8 (6.8%)	2 (3.4%)	10 (5.7%)	15 (3.8%)
Black or African American	1 (0.8%)	2 (3.4%)	2 (1.1%)	12 (3.1%)
Other[2]	14 (11.9%)	8 (13.6%)	21 (12.1%)	37 (9.5%)

[1] The number of subjects in each group with non-missing parameter value.
[2] Other races include races recorded as other, unknown, or not reported.
IV = intravenous(ly)
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group B includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group C includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled), and Phase 2 open-label studies MYF2001, CP14B013, CP14B015, and CP14B019.
Source data: Table tdm01a; Table tdm01b; Table tdm01c
Clinical cut-off date: 13 Oct 2022 for MDS3001.

Table 6: Exposure by Ethnicity in MDS3001 Phase 3 (Group A), MDS3001 Phase 2/3 (Group B) and Haematologic Malignancy Studies (Group C)

	Group A		Group B	Group C
	Imetelstat (N=118)	**Placebo (N=59)**	**Imetelstat (N=175)**	**Imetelstat (N=391)**
Ethnicity, n (%)				
n[1]	118	59	174	390
Hispanic or Latino	6 (5.1%)	5 (8.5%)	7 (4.0%)	18 (4.6%)
Not Hispanic or Latino	100 (84.7%)	47 (79.7%)	148 (85.1%)	316 (81.0%)
Not Reported	11 (9.3%)	6 (10.2%)	17 (9.8%)	44 (11.3%)
Unknown	1 (0.8%)	1 (1.7%)	2 (1.1%)	12 (3.1%)

[1] The number of subjects in each group with non-missing parameter value.
IV = intravenous(ly)
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group B includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group C includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled), and Phase 2 open-label studies MYF2001, CP14B013, CP14B015, and CP14B019.
Source data: Table tdm01a; Table tdm01b; Table tdm01c
Clinical cut-off date: 13 Oct 2022 for MDS3001.

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Exclusion criteria from pivotal Phase 2/3 study MDS3001 are detailed below.

Exclusion criteria to ensure standardisation of the trial population that are common to most clinical trials are not presented, including:

- Subject has known allergies, hypersensitivity, or intolerance to imetelstat or its excipients
- Subject has received an experimental or investigational drug or used an invasive investigational medical device within 30 days prior to Cycle 1 Day 1 (C1D1) (Part 1) or Randomisation (Part 2) or is currently enrolled in an investigational study
- Major surgery within 4 weeks prior to C1D1 (Part 1) or Randomisation (Part 2) (excluding the placement of vascular access and other minor surgical procedures)
- Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the imetelstat metabolism, or put the study outcomes at undue risk; Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

Exclusion criteria related to ongoing or recent conditions or treatments that may interfere with the study results are likewise not presented, including:

- Prior treatment with imetelstat
- Have received corticosteroids > 30 mg/day prednisone or equivalent, or growth factor treatment within 4 weeks prior to C1D1 (Part 1) or Randomisation (Part 2);
- Prior treatment with a hypomethylating agent (e.g., azacitidine, decitabine);
- Prior treatment with lenalidomide, thalidomide, or other thalidomide analogues;
- Has received an ESA or any anti-MDS therapy, chemotherapy, immunomodulatory, or immunosuppressive therapy within 4 weeks prior to C1D1 (Part 1) or Randomisation (Part 2) (8 weeks for long-acting ESAs);
- Prior history of haematopoietic stem cell transplant;
- Subject was previously assessed as having IPSS intermediate-2 or high risk MDS;
- Subject with del(5q) karyotype;
- Subject with MDS/myeloproliferative neoplasm overlap syndrome.

The remaining exclusion criteria from Study MDS3001 are presented below and may be grouped together.

Females who are pregnant or are currently breastfeeding or planning to become pregnant while enrolled in this study or within 1 month after the end of dosing.

Subject is a man who plans to father a child while enrolled in this study or within 3 months after the end of dosing.

Reason for exclusion:

In embryo-foetal developmental toxicity studies, imetelstat was not teratogenic (Section Part II: Module SII). Although administration of imetelstat to pregnant mice and rabbits resulted in embryo-lethal effects at a dose of 28.2 mg/kg, such effects were observed at maternal exposures that exceeded human exposures at the recommended clinical dose. These data, together with the genotoxicity studies that show that imetelstat does not pose a risk for mutagenicity or clastogenicity, suggest that imetelstat is unlikely to cause teratogenicity but may cause embryonic or foetal loss when administered to a pregnant woman. Females who were pregnant, likely to become pregnant or lactating were excluded from the clinical development programme for safety reasons, similar to the majority of investigative clinical trials.

In MDS3001, use of highly effective method of birth control, male partner sterilisation, or true abstinence applied to females of childbearing potential during treatment and for 1 month after the end of dosing to minimise the risk of pregnancy. A woman of childbearing potential was required to have a negative serum (β-human chorionic gonadotropin) or urine pregnancy test at screening and on Day 1 of every cycle and at end of study (30 days post last dose). Furthermore, a man who was sexually active with a woman of childbearing potential and who had not had a vasectomy was required to use a barrier method of birth control during treatment and for 3 months after the end of dosing. All men were not permitted to donate sperm during the study.

There was no exposure to imetelstat during pregnancy or lactation in the clinical development programme.

Is it considered to be included as missing information? No. Embryo-foetal toxicity is an important potential risk (Section SVII.1.2).

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

Reason for exclusion:

Anaemia is recognised to be the most common disease characteristic of MDS, occurring in 80-85% of low-risk patients, 40% of whom eventually become RBC transfusion-dependent, but anaemia is also prevalent in the elderly population (Delgado, 2021; Foran, 2012). Data from the noninstitutionalised US population assessed in the third National Health and Nutrition Examination Survey (1988-1994) found that an estimated 11% of men and 10.2% of women aged 65 years and older had anaemia (Guralnik, 2004). Among patients with anaemia, approximately one third had evidence of nutrient deficiency, one third had anaemia of chronic inflammation or chronic renal disease, and one third had unexplained anaemia, while 1 in 6 patients with unexplained anaemia had findings compatible with MDS in the peripheral blood (Guralnik, 2004). Severe anaemia is detrimental as it increases the negative effects of co-morbidities, such as heart and lung failure (Section Part II: Module SI).

Including patients with anaemia attributed to other factors would have meant other therapeutic approaches for treating the anaemia would have been required and this may have impacted the efficacy and safety evaluation of imetelstat in the study.

Is it considered to be included as missing information? No

Rationale: Anaemia is expected in this patient population due to ineffective haematopoiesis. Anaemia and transfusion dependency represent the major issues for low-risk MDS patients with an estimated 50% of MDS patients presenting with anaemia with an Hgb level < 100 g/L (Castelli, 2018a). Apoptosis of blood cell progenitors is the main mechanism inducing anaemia in low-risk myelodysplasia, while in higher risk, myelodysplasia is the block of maturation (Castelli, 2018a). The observational European MDS Registry that includes newly diagnosed patients with IPSS low and intermediate-1 (lower-) risk MDS from 15 European countries reported that at diagnosis, 29% were transfusion dependent, 87% of patients had anaemia according to WHO criteria (< 120 g/L), and 63% had Hgb values below 100 g/L or were transfusion dependent (Castelli, 2018a). Therefore current available treatments to manage patients with LR-MDS focus mainly on treating cytopenias (predominantly anaemia) and optimising QoL (Fenaux, 2021; Section Part II: Module SI).

In Phase 3 MDS3001 (Group A), imetelstat treatment led to a significant and sustained increase in Hgb levels (based on central laboratory results) compared with placebo treatment, with the median Hgb rise from pretreatment in the longest transfusion independence (TI) period for 8-week RBC TI responders of 3.6 g/dL in the imetelstat group compared with 0.8 g/dL in the placebo group (Module 2.7.3, Section 3.2.2.3.1). The median Hgb peak in the longest RBC TI interval was 11.3 g/dL in the imetelstat group compared with 8.9 g/dL in the placebo group (Module 2.7.3, Table 9). Increases in Hgb provide direct evidence of clinical benefit to patients leading to symptom improvement. Additionally, in all subjects in the imetelstat group, there was a trend toward an increase in mean haemoglobin from baseline through Cycle 11 (Weeks 41 to 44), which is further indicative of the effectiveness of imetelstat (Module 2.7.4, Section 3.1.1.1.1).

While anaemia TEAEs were reported in a higher proportion of subjects in the imetelstat group compared with the placebo group (20.3% versus 10.2%; Table tae03a), laboratory results showed that worsening Hgb levels on treatment occurred at the same rate in the imetelstat and placebo groups, including the rate of Grade ≥ 3 worsening Hgb on treatment (Table tlab02a). Since all subjects were transfusion dependent at study enrollment and no parameters were given at which subjects were required to be transfused, transient decreases in Hgb were observed primarily early on in the study treatment period. The median onset to Grade 3 decreased Hgb was 2.0 weeks in both the imetelstat and placebo groups (range: 0.1 to 37.0 and 0.1 to 20.0 weeks, respectively) (Table tlab04a). When comparing the rate of transfusions pre- and post-treatment anaemia it is likely that adverse events (AEs) reported in the first few weeks were due to delaying of RBC transfusions while awaiting a possible treatment effect rather than an on-target effect of imetelstat. Furthermore, the late anaemia events reported often followed loss of a TI response. Lastly based on the objective and reliable Hgb laboratory data from MDS3001, no difference between the imetelstat and placebo groups was observed.

In Group B, the results in Phase 2 were consistent with and supportive of the results in Phase 3 (Module 2.7.4, Section 3.1.1.2).

In Group C, there was a trend toward an increase in mean Hgb from baseline through Cycle 13, most notably in the 7.1 mg/kg group, which is indicative of the efficacy of imetelstat (Module 2.7.4, Section 3.1.1.3.1). Haemoglobin was stable from baseline through about C8 and then increased and stabilised in the > 7.1 mg/kg group, while conversely decreasing and stabilising in the < 7.1 mg/kg group through approximately C14, consistent with diminished imetelstat efficacy at the lower dose. Results in Group C varied from Groups A and B due to differences in underlying disease (e.g., MDS vs MF).

The proposed indication for imetelstat is for the treatment of adult patients with transfusion-dependent anaemia due to lower risk MDS. It is not expected that patients with anaemia attributed to factors other than MDS will be treated with imetelstat in clinical practice as this off-label use is not supported by efficacy or safety data.

Diagnosed or treated for malignancy other than MDS, except:

Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before C1D1 (Part 1) or Randomisation (Part 2)

Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

Adequately treated cervical carcinoma in situ without evidence of disease

Reason for exclusion: Patients who were diagnosed or treated for malignancy other than MDS with the exceptions specified above were excluded from clinical trial participation as their inclusion could have impacted the efficacy or safety assessment of imetelstat in the study. Furthermore, any medications to treat the malignancy and associated adverse reactions may have impacted the study outcome.

Is it considered to be included as missing information? No

Rationale: While studies to evaluate the efficacy and safety of imetelstat in malignancies other than MDS including MM as per Group C (Section Part II: Module SIII) have been conducted, in addition to other solid tumour studies not included in the submission, the data are currently insufficient to support the efficacy and safety of imetelstat for oncology indications other than transfusion-dependent anaemia in MDS. However, there are no expected additional risks for use of imetelstat in patients with additional malignancies. Indeed, an analysis of the SEER database found that 14% of MDS patients in the US had other primary tumours diagnosed prior to receipt of an MDS diagnosis; the prostate (19.9%), breast (16.5%), non-Hodgkin lymphoma (8.4%), urinary/bladder (6.0%), and lung and bronchus (5.6%) were the most common sites reported (Ma, 2007). This suggests that in clinical practice patients with MDS could have another malignancy, but it is not expected that imetelstat would increase their risks or adversely affect their malignancy.

Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of C1D1 (Part 1) or Randomisation (Part 2), or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification

Reason for exclusion: Patients with clinically significant cardiovascular disease or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association (NYHA) Functional Classification were excluded from clinical trial participation, which is a typical exclusion criterion for oncology clinical development studies.

Is it considered to be included as missing information? No

Rationale: Despite the clinically significant cardiovascular disease exclusion, approximately a third of all subjects in Phase 3 MDS3001 had a medical history of a cardiac disorder (Table 7). The most frequent cardiac disorder medical history Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) from the Cardiac Disorders system organ class (SOC) in imetelstat and placebo treated subjects in Phase 3 MDS3001 (occurring in ≥ 2

subjects in both treatment groups) were atrial fibrillation (9.3% vs 8.5%), myocardial ischaemia (7.6% vs 3.4%), myocardial infarction (4.2% vs 3.4%), coronary artery disease (1.7% vs 0), cardiac failure (1.7% vs 6.8%), and arrhythmia (1.7% vs 3.4%), respectively. This is not unexpected as MDS is associated with an increased risk of cardiovascular disease largely attributed to an increased risk of myocardial infarction (Adrianzen Herrera, 2020). 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). Heart disease, mainly congestive heart failure, has been reported to affect 18% and 25% of younger and older LR-MDS patients, respectively (Castelli, 2018; Section Part II: Module SI).

There is no evidence that imetelstat is cardiotoxic from nonclinical studies. Tissue distribution studies using [^{35}S]-imetelstat showed the heart is not a target organ (Module 2.6.4, Section 4).

Imetelstat is very unlikely to delay ventricular repolarization and have proarrhythmic risk in humans. In vitro studies evaluating the effects of imetelstat on the hERG ion channel showed that imetelstat at concentrations up to 750 µg/mL did not have any inhibitory effect on hERG current, which results in a safety margin for imetelstat of > 140-fold based on the free/unbound maximum observed concentration in plasma ($C_{max,u}$) in subjects with MDS (Section Part II: Module SII; Module 2.7.2, Section 3.5.2).

No treatment-related clinical signs, including no changes in mean arterial pressure, heart rate, respiratory rate, body temperature, electrocardiographic activity, or blood gas parameters, as well as no evidence of CNS effects, were observed in cynomolgus monkeys administered single IV doses of imetelstat up to 14.1 mg/kg over a 6- or 24-hour period, resulting in imetelstat exposure levels in excess of those seen in patients administered imetelstat in the clinic (Section Part II: Module SII). Consistent with these findings, there were no imetelstat-related changes observed in electrocardiography, blood pressure, and respiratory rate in the 9-month chronic pivotal toxicity study in monkeys with once-weekly administration of dose levels up to 14.1 mg/kg/week via 2-hour IV infusion.

At the request of the FDA, a ventricular repolarization substudy to assess the effect of imetelstat on corrected QT (QTc) interval in an additional 45 subjects in MDS3001 (Module 2.7.2, Section 3.5.2) has been conducted and will be provided to the EMA post-approval. However, based on the current knowledge of imetelstat from nonclinical safety pharmacology assessments and clinical cardiac safety data, and supported by a recent systematic review of ECG evaluations with approved oligonucleotides (Noormohamed, 2023) and an extensive review of 29 oligonucleotide therapeutics that found no clinical proarrhythmic risk based on data from ICH S7B/E14 studies (Qu, 2024), imetelstat is not likely to prolong the QT interval. There is no anticipated increased risk for use of imetelstat in patients with clinically significant cardiovascular disease or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the NYHA Functional Classification.

Based on a numerical imbalance in the MDS3001 study for imetelstat and placebo and a possible causal association, healthcare professionals are advised in the imetelstat SmPC that atrial fibrillation (combined term of atrial fibrillation and atrial flutter) is an adverse reaction of imetelstat with similar guidance in the PL for patients.

Known history of human immunodeficiency virus (HIV) or any uncontrolled active systemic infection requiring IV antibiotics

Reason for exclusion: Patients who are immunocompromised such as those with HIV, active systemic hepatitis or requiring IV antibiotics for an uncontrolled active systemic infection were excluded as imetelstat is recognised to cause neutropenia and administration of a neutropenia-causing agent to an infectious process can potentially lead to a worsening of the existing infection.

Is it considered to be included as missing information? No

Rationale: It is not expected that imetelstat will be initiated in patients with an infection requiring treatment due to the potential to worsen the infection. As discussed in Section SVII.3.1, severe infections are an important identified risk of imetelstat. The imetelstat SmPC and package leaflet (PL) contain a warning for neutropenia and the risk of infection. There is guidance for healthcare professionals in the SmPC on how to manage neutropenia by monitoring patients and through dose modifications and the administration of granulocyte-colony stimulating factors and anti-infective therapies as clinically indicated. Healthcare professionals are advised in the imetelstat SmPC that sepsis and urinary tract infections are adverse reactions of imetelstat with similar guidance in the PL for patients.

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

Reason for exclusion: Patients with acute or chronic liver disease including cirrhosis were excluded as imetelstat can cause transient elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin. Furthermore, patients were required to have ALT, AST, and alkaline phosphatase (ALP) ≤ 2.5 times the upper limit of normal (x ULN) and 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) for inclusion in the study.

Is it considered to be included as missing information? No

Rationale: Imetelstat is expected to be metabolised predominantly in the tissue through nuclease-mediated cleavage of nucleotide residues from the parent oligonucleotide with hepatic microsomal enzymes not playing a significant role, consistent other oligonucleotides (Geary, 2009; Yu, 2009). Urinary excretion is expected to be the source of excretion for any catabolised component fragments of imetelstat as demonstrated in preclinical absorption, distribution, metabolism, and excretion (ADME) studies whereas hepatic elimination is known to contribute minimally to the excretion of imetelstat (Module 2.6.4, Section 6).

As presented in Section SIV.3, in Phase 3 study MDS3001 (Group A), most subjects in the imetelstat group had normal hepatic function (68 [58.6%] subjects) or mild (31 [26.7%] subjects) hepatic impairment at baseline (Table 7). Fewer subjects had moderate hepatic impairment (17 [14.7%] subjects), and thus interpretation of results in this subgroup should be made with caution. There was no trend of worse toxicity in increasingly hepatically impaired subjects.

In the imetelstat group, events reported more frequently in subjects with normal hepatic function or mildly impaired hepatic function at baseline compared to subjects with moderate hepatic impairment included SAEs (39.7% and 32.3% vs 5.9%, respectively), bleeding events

(26.5% and 19.4% vs 5.9%, respectively), and infections (41.2% and 54.8% vs 29.4%, respectively) (Module 2.7.4, Section 5.1.1). Higher incidences of infections were reported in the moderately hepatic impaired (50.0%) and normal hepatic function (46.7%) subgroups than in the mildly hepatic impaired subgroup (34.8%). The highest incidence of thrombocytopenia was reported in subjects with mild hepatic impairment (87.1%) compared to subjects with normal hepatic function (73.5%) or moderate hepatic impairment (58.8%).

Consistent with the imetelstat-treated subjects in Group A and the Group B pool, no clinically significant differences in the Group C pool of imetelstat-treated subjects were observed based on mild to moderate hepatic impairment (Module 2.7.4, Section 5.1.3). The effect of hepatic impairment on imetelstat PK was assessed in the popPK analysis using NCI Organ Dysfunction Working Group (NCI-ODWG) hepatic function category, with categories assessed as normal function, mild impairment, and combined moderate or severe impairment based on the distribution of data (Module 2.7.2, Section 3.3.5). There was no evidence for trends or differences in random effects on imetelstat clearance (CL) across hepatic function categories, supporting a lack of a significant effect of hepatic function category on imetelstat CL. Therefore, no dose adjustments for mild and moderate hepatic impairment are warranted for imetelstat. Limited information is available in subjects with severe hepatic impairment to derive dosing recommendations.

Use of imetelstat in patients with hepatic impairment or with known acute or chronic liver disease including cirrhosis is not expected to affect CL of imetelstat because, like other oligonucleotides, imetelstat is likely degraded by tissue nucleases and not hepatic cytochrome P450 (CYP) enzymes. The imetelstat SmPC informs healthcare professionals of the recommended dosing for patients with hepatic impairment. No dose adjustment is required for patients with mildly to moderately abnormal liver function tests (total bilirubin ≤ ULN and AST > ULN, or total bilirubin > 1x to 1.5x ULN (Grade 1) and any AST) or (total bilirubin > 1.5x to 3x ULN (Grade 2) and any AST). There is insufficient data in patients with severely abnormal liver function tests (total bilirubin > 3x ULN (Grade 3) and any AST) to support a dose recommendation.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

Overall, the incidence of TEAEs in study MDS3001 remained consistent over the course of treatment with no apparent increase in frequency over time; the most common TEAEs, including neutropenia, thrombocytopenia, occurred more frequently during the early months of treatment and decreased during later months suggesting a lack of cumulative toxicity.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 7: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

<table>
<tr><th>Type of Special Population</th><th>Exposure</th></tr>
<tr><td>Pregnant women</td><td rowspan="2">Not included in the clinical development programme.</td></tr>
<tr><td>Breastfeeding women</td></tr>
<tr><td>Paediatrics</td><td>Not included in the clinical development programme.</td></tr>
<tr><td>Patients with relevant comorbidities:
• Patients with hepatic impairment</td><td>In MDS3001, patients were required to have ALT, AST, and ALP ≤ 2.5 x ULN and 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) for inclusion in the study. Patients with acute or chronic liver disease including cirrhosis were excluded from clinical trial participation (Section SIV.1).
Hepatic impairment at baseline for subjects in Groups A, B and C is presented in the table below. Patients with severe hepatic impairment were not included in the clinical development programme.
Hepatic Impairment at Baseline in MDS3001 Phase 3 (Group A), MDS3001 Phase 2/3 (Group B) and Haematologic Malignancy Studies (Group C)
<table>
<tr><th rowspan="2"></th><th colspan="2">Group A</th><th>Group B</th><th>Group C</th></tr>
<tr><th>Imetelstat (N=118)</th><th>Placebo (N=59)</th><th>Imetelstat (N=175)</th><th>Imetelstat (N=391)</th></tr>
<tr><td colspan="5">Hepatic impairment, n (%)</td></tr>
<tr><td>[1]n</td><td>116</td><td>59</td><td>173</td><td>389</td></tr>
<tr><td>Normal</td><td>68 (58.6%)</td><td>39 (66.1%)</td><td>101 (58.4%)</td><td>239 (61.4%)</td></tr>
<tr><td>Mild</td><td>31 (26.7%)</td><td>14 (23.7%)</td><td>54 (31.2%)</td><td>120 (30.8%)</td></tr>
<tr><td>Moderate</td><td>17 (14.7%)</td><td>6 (10.2%)</td><td>18 (10.4%)</td><td>30 (7.7%)</td></tr>
</table>
AST = aspartate aminotransferase; IV = intravenous(ly)
[1]The number of subjects in each group with non-missing parameter value.
Hepatic impairment based on National Cancer Institute (NCI) classification according to total bilirubin and AST.
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group B includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group C includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled), and Phase 2 open-label studies MYF2001, CP14B013, CP14B015, and CP14B019.
Source data: Table tdm02a; Table tdm02b; Table tdm02c
Clinical cut-off date: 13 Oct 2022 for MDS3001.</td></tr>
<tr><td>• Patients with renal impairment</td><td>In MDS3001, patients were required to have serum creatinine ≤ 2.0 x ULN for inclusion in the study.
Renal impairment at baseline for subjects in Groups A, B and C is presented in the table below. Patients with severe renal impairment were not included in the clinical development programme.</td></tr>
</table>

<table>
<tr><th>Type of Special Population</th><th>Exposure</th></tr>
<tr><td></td><td>Renal Impairment at Baseline in MDS3001 Phase 3 (Group A), MDS3001 Phase 2/3 (Group B) and Haematologic Malignancy Studies (Group C)
<table>
<tr><th></th><th colspan="2">Group A</th><th>Group B</th><th>Group C</th></tr>
<tr><th></th><th>Imetelstat (N=118)</th><th>Placebo (N=59)</th><th>Imetelstat (N=175)</th><th>Imetelstat (N=391)</th></tr>
<tr><td colspan="5">Renal impairment, n (%)</td></tr>
<tr><td>n[1]</td><td>113</td><td>56</td><td>168</td><td>297</td></tr>
<tr><td>Normal</td><td>15 (13.3%)</td><td>6 (10.7%)</td><td>26 (15.5%)</td><td>52 (17.5%)</td></tr>
<tr><td>Mild</td><td>46 (40.7%)</td><td>18 (32.1%)</td><td>69 (41.1%)</td><td>111 (37.4%)</td></tr>
<tr><td>Moderate</td><td>52 (46.0%)</td><td>32 (57.1%)</td><td>73 (43.5%)</td><td>134 (45.1%)</td></tr>
</table>
IV = intravenous(ly)
[1]The number of subjects in each group with non-missing parameter value.
Renal impairment based on creatinine clearance.
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group B includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group C includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled), and Phase 2 open-label studies MYF2001, CP14B013, CP14B015, and CP14B019.
Source data: Table tdm02a; Table tdm02b; Table tdm02c
Clinical cut-off date: 13 Oct 2022 for MDS3001.</td></tr>
<tr><td>• Patients with cardiovascular impairment</td><td>In MDS3001, patients with clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of C1D1 (Part 1) or Randomisation (Part 2), or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the NYHA Functional Classification were excluded from clinical trial participation (Section SIV.1).
However, approximately a third of all subjects included in Phase 3 MDS3001 had a medical history of a cardiac disorder. The most frequent medical history cardiac disorders are presented in the table below.

The Most Frequent Medical History Cardiac Disorders in MDS3001 Phase 3 (Group A), MDS3001 Phase 2/3 (Group B) and Haematologic Malignancy Studies (Group C)
<table>
<tr><th></th><th colspan="2">Group A</th><th>Group B</th><th>Group C</th></tr>
<tr><th></th><th>Imetelstat (N=118)</th><th>Placebo (N=59)</th><th>Imetelstat (N=175)</th><th>Imetelstat (N=391)</th></tr>
<tr><td colspan="5">Cardiac disorders, n (%)</td></tr>
<tr><td>All Cardiac disorders</td><td>32 (27.1%)</td><td>28 (47.5%)</td><td>56 (32.0%)</td><td>89 (22.8%)</td></tr>
<tr><td>Atrial fibrillation</td><td>11 (9.3%)</td><td>5 (8.5%)</td><td>15 (8.6%)</td><td>24 (6.1%)</td></tr>
<tr><td>Myocardial ischaemia</td><td>9 (7.6%)</td><td>2 (3.4%)</td><td>10 (5.7%)</td><td>10 (2.6%)</td></tr>
<tr><td>Myocardial infarction</td><td>5 (4.2%)</td><td>2 (3.4%)</td><td>6 (3.4%)</td><td>9 (2.3%)</td></tr>
<tr><td>Coronary artery disease</td><td>2 (1.7%)</td><td>7 (11.9%)</td><td>8 (4.6%)</td><td>14 (3.6%)</td></tr>
</table></td></tr>
</table>

Type of Special Population	Exposure
	Cardiac failure: 2 (1.7%) / 4 (6.8%) / 4 (2.3%) / 2 (0.5%) Arrhythmia: 2 (1.7%) / 2 (3.4%) / 2 (1.1%) / 3 (0.8%) Angina pectoris: 1 (0.8%) / 3 (5.1%) / 7 (4.0%) / 10 (2.6%) Aortic valve incompetence: 1 (0.8%) / 2 (3.4%) / 1 (0.6%) / 1 (0.3%) Atrial flutter: 1 (0.8%) / 2 (3.4%) / 1 (0.6%) / 1 (0.3%) Cardiac failure congestive: 0 / 2 (3.4%) / 2 (1.1%) / 6 (1.5%) Mitral valve incompetence: 1 (0.8%) / 0 / 3 (1.7%) / 5 (1.3%) Palpitations: 0 / 0 / 3 (1.7%) / 7 (1.8%) IV = intravenous(ly) Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks. Group B includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks. Group C includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled), and Phase 2 open-label studies MYF2001, CP14B013, CP14B015, and CP14B019. Source data: Table tmh01a; Table tmh01b; Table tmh01c Clinical cut-off date: 13 Oct 2022 for MDS3001.
• Immunocompromised patients	Not included in the clinical development programme. Patients with a known history of HIV or any uncontrolled active systemic infection requiring IV antibiotics and patients who had received immunomodulatory, or immunosuppressive therapy within 4 weeks prior to C1D1 (Part 1) or Randomisation (Part 2) in MDS3001 were excluded from clinical trial participation (Section SIV.1).
• Patients with a disease severity different from inclusion criteria in clinical trials	The proposed indication of imetelstat is for the treatment of adult patients with transfusion-dependent anaemia due to lower risk MDS. All subjects included in MDS3001 were either International Prognostic Scoring System (IPSS) risk category low or intermediate-1 at baseline as presented in the table below. In Group C only subjects in MDS3001 were required to have an IPSS risk category of low or intermediate-1 at baseline. **IPSS Risk Category at Baseline in MDS3001 Phase 3 (Group A), MDS3001 Phase 2/3 (Group B) and Haematologic Malignancy Studies (Group C)** **Group A** — **Imetelstat (N=118)** / **Placebo (N=59)**; **Group B** — **Imetelstat (N=175)**; **Group C** — **Imetelstat (N=391)** **IPSS risk category, n (%)** n[1]: 118 / 59 / 175 / 175 Low: 80 (67.8%) / 39 (66.1%) / 116 (66.3%) / 116 (66.3%) Intermediate-1: 38 (32.2%) / 20 (33.9%) / 59 (33.7%) / 59 (33.7%) [1] The number of subjects in each group with non-missing parameter value. IPSS = International Prognostic Scoring System; IV = intravenous(ly)

<table>
<tr><th>Type of Special Population</th><th>Exposure</th></tr>
<tr><td></td><td>
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group B includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group C includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled), and Phase 2 open-label studies MYF2001, CP14B013, CP14B015, and CP14B019.
Source data: Table tdm02a; Table tdm02b; Table tdm02c
Clinical cut-off date: 13 Oct 2022 for MDS3001.

All subjects were required to have an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, 1 or 2. No subject had a ECOG > 2 as presented in the table below.

ECOG Performance Status at Baseline in MDS3001 Phase 3 (Group A), MDS3001 Phase 2/3 (Group B) and Haematologic Malignancy Studies (Group C)
<table>
<tr><th></th><th colspan="2">Group A</th><th>Group B</th><th>Group C</th></tr>
<tr><th></th><th>Imetelstat (N=118)</th><th>Placebo (N=59)</th><th>Imetelstat (N=175)</th><th>Imetelstat (N=391)</th></tr>
<tr><td colspan="5">ECOG performance status, n (%)</td></tr>
<tr><td>n[1]</td><td>118</td><td>59</td><td>175</td><td>391</td></tr>
<tr><td>0</td><td>42 (35.6%)</td><td>21 (35.6%)</td><td>63 (36.0%)</td><td>124 (31.7%)</td></tr>
<tr><td>1</td><td>70 (59.3%)</td><td>38 (64.4%)</td><td>101 (57.7%)</td><td>218 (55.8%)</td></tr>
<tr><td>0 or 1</td><td>112 (94.9%)</td><td>59 (100.0%)</td><td>164 (93.7%)</td><td>342 (87.5%)</td></tr>
<tr><td>2</td><td>6 (5.1%)</td><td>0</td><td>11 (6.3%)</td><td>49 (12.5%)</td></tr>
<tr><td>3, 4 or 5</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
</table>
[1] n = the number of subjects in each group with non-missing parameter value.
ECOG = Eastern Cooperative Oncology Group; IV = intravenous(ly)
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group B includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Group C includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled), and Phase 2 open-label studies MYF2001, CP14B013, CP14B015, and CP14B019.
Source data: Table tdm02a; Table tdm02b; Table tdm02c
Clinical cut-off date: 13 Oct 2022 for MDS3001.
</td></tr>
<tr><td>Population with relevant different ethnic origin</td><td>
Clinical trial exposure data by ethnicity are presented for subjects treated with imetelstat and placebo in MDS3001 Phase 3 (Group A), and for subjects treated with imetelstat in MDS3001 Phase 2/3 (Group B) and Haematologic Malignancy Studies (Group C) in Table 6 (Section Part II: Module SIII).
In all three groups, the majority of subjects were Not Hispanic or Latino; 84.7% (100 of 118) of imetelstat-treated subjects and 79.7% (47 of 59) of placebo-treated subjects in Group A, 85.1% (148 of 174) of imetelstat-treated subjects in Group B, and 81.0% (316 of 390) of imetelstat-treated subjects in Group C. This is in line with the expected ethnicity of patients with MDS where the minority of patients are Hispanic (Tinsley-Vance, 2021).
</td></tr>
</table>

Type of Special Population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme.
Subpopulations carrying relevant chromosomal abnormalities	In MDS3001, patients with del(5q) karyotype were excluded from clinical trial participation (Section SIV.1) to focus on the population with IPSS low, or intermediate-risk-1 MDS that was not associated with an isolated deletion 5Q cytogenetic abnormality and who did not receive prior treatment with lenalidomide or HMAs.

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation Exposure

On 6 June 2024, the FDA approved imetelstat (Rytelo) for adults with low- to intermediate-1 risk MDS with transfusion-dependent anaemia requiring four or more red blood cell units over 8 weeks who have not responded to or have lost response to or are ineligible for ESAs.

Since then, imetelstat was shipped for commercialisation in the US on 19 June 2024.

SV.1.1 Method Used to Calculate Exposure

Patient exposure has been estimated using vial demand data (for 47 mg and 188 mg vials) with the conversion to mg volume demand, an average patient weight of 75 kg, the dose of 7.1 mg/kg body weight, and the administration once every 4 weeks per patient.

SV.1.2 Exposure

An estimated 363 patients have been treated with imetelstat up to 06 September 2024.

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Imetelstat has no pharmacological properties that would promote its use for abuse or misuse for illegal purposes. No potential for drug dependence, misuse, or abuse have been noted for imetelstat in any of the clinical studies.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Infusion-related reactions

Infusion-related reactions (IRRs) are an identified risk not considered important for inclusion in the list of safety concerns in the RMP based on the severity of IRRs observed in the clinical studies.

During the early period of the clinical development programme, IRRs were commonly observed in Phase 1 and Phase 2 studies, the majority were of Grade 1 or 2 severity. The incidence of IRRs reduced substantially with the introduction of routine use of corticosteroid and antihistamine premedication prior to each infusion in all study protocols. In addition to pre-medication, subjects were observed during imetelstat infusions and for at least one hour after the infusion was completed.

IRRs were selected by the investigator by check box on the AE case report form (CRF) pages across studies.

In Phase 3 MDS3001 (Group A), IRRs occurred in 9 (7.6%) subjects in the imetelstat group and 2 (3.4%) subjects in the placebo group (Table 8). In the imetelstat group most events were Grade 1 or 2 severity; Grade 3 events were reported in 2 (1.7%) subjects and there were no Grade 4 or 5 events. The 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 (Table taesi03g). All events were considered related to study treatment (Table taesi01m). The most commonly reported IRR in the imetelstat group was headache reported in 5 (4.2%) subjects; all other IRRs were reported in 1 (0.8%) subject each (abdominal pain, arthralgia, asthenia, back pain, bone pain, diarrhoea, erythema, hypertensive crisis, malaise, non-cardiac chest pain, pruritus, and urticaria) (Table 8). One subject treated with imetelstat had a serious IRR event of Grade 3 hypertensive crisis. In the placebo group all events were Grade 1 and considered related to study treatment; there were no serious events.

Table 8: Infusion-related Reaction TEAEs Phase 3 Study MDS3001 (Group A)

Category Preferred Term	Imetelstat (N=118) n (%)			Placebo (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

Category Preferred Term	Imetelstat (N=118) n (%)			Placebo (N=59) n (%)		
	Any Grade	Grade 3/4	SAE	Any Grade	Grade 3/4	SAE
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

AE = adverse event; CRF = case report form; IRR = infusion-related reaction; IV = intravenous(ly); MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Notes: IRRs were selected by the investigator by check box on the AE CRF pages across studies.
TEAEs are defined as events that occur or worsen after the first dose of study drug. A subject can have ≥ 1 IRR TEAE.
Percentages calculated with the number of subjects in each treatment group as denominator.
MedDRA v25.0 was used for TEAE coding.
Source data: Table taesi02m; Table taesi04g
Clinical cut-off date: 13 Oct 2022 for MDS3001.

Five (4.2%) subjects in the imetelstat group had IRRs that led to study treatment interruption (Table taesi01m). One subject in the imetelstat group discontinued imetelstat due to an IRR event of Grade 2 pruritus. No subjects in the placebo group had a treatment delay or discontinuation due to an IRR. No subject in either treatment group had a dose reduction due to an IRR event. IRRs were managed by symptom relief medication (steroids, antihistamines, blood pressure medications and pain medications; MDS3001 CSR [Phase 3]/ Listing lsicm04_p2).

The data from the MDS3001 Final Analysis (cutoff date 13 October 2023) were in line with the Primary Analysis of the Phase 3 data described above (cutoff date 13 October 2022). IRR TEAEs (any grade) were reported in 9 (7.6%) subjects in the imetelstat group and 2 (3.4%) subjects in the placebo group (Table tsfaesi03_p2). The majority of IRR TEAEs were Grade 1/2 severity (Table tsfaesi03_p2). Similar to the Primary Analysis, there were no Grade 4 or 5 events in either group. No new IRR Grade 3 or 4 events or SAEs were reported in either group at the time of the Final Analysis (Table tsfaesi03_p2; Table tsfaesi08_p2).

The occurrence of IRRs was similar in the Phase 2 and Phase 3 imetelstat groups (Group B). In the Phase 2 imetelstat group (N=57), IRR (any grade) were reported in 6 (10.5%) subjects, and Grade 3/4 events were reported in 4 (7.0%) subjects (Table taesi02n). The median time to onset of the Grade 3/4 events was 520.5 days (range: 379 to 1197 days) in the 4 subjects with Grade 3/4 IRRs in the Phase 2 imetelstat group (Table taesi03h). The most commonly reported infusion-related reaction was back pain (3 [5.3%]), followed by chest pain and hypotension (2 [3.5%] each) (Table taesi02n). There were no Grade 4 or Grade 5 events and no serious events in the Phase 2 imetelstat group (Table taesi04h). Imetelstat was interrupted in 5 subjects due to an IRR in the Phase 2 imetelstat group and no subjects discontinued treatment due to an IRR (Table taesi01n). Infusion-related reactions were managed by

symptom relief medication (steroids, antihistamines, blood pressure medications and pain medications; MDS3001 CSR [Phase 2]/ Listing lsicm04_p1).

In the Group C pool (N=391), no new safety signals related to IRRs were identified. Similar to Groups A and B, IRRs (any grade) were reported in 56 (14.3%) subjects, and Grade 3/4 events were reported in 13 (3.3%) subjects (Table taesi02o). The median time to onset of the Grade 3/4 events was 337.0 days (range: 1 to 1197 days) in the 13 subjects with Grade 3/4 IRRs (Table taesi03i). The most commonly reported infusion-related reaction was infusion related reaction (13 [3.3%] subjects), followed by pyrexia (9 [2.3%]), and chills and dyspnoea (8 [2.0%] subjects each) (Table taesi02o). There were no Grade 4 or Grade 5 IRR events in the overall pooled Group C subject population (Listing lae02c; Table taesi01o).

In Group C, 7 (1.8%) subjects had a total of 10 IRR events that were SAEs, including 1 imetelstat-treated subject from Group A with Grade 3 hypertensive crisis (Table taesi04i). The other 9 IRR events occurring in 6 subjects included Grade 2/3 chills, dyspnoea, pulmonary congestion, pulmonary oedema, syncope, infusion related reaction (Listing lae02c). Three subjects in Group C discontinued treatment due to IRR TEAEs (Table taesi01o) including the Group A subject mentioned above (Grade 2 pruritus), 1 subject with a Grade 2 event of pruritis, and 1 subject with Grade 3 dyspnoea and Grade 2 arthritis (Listing lae02d).

IRRs are not an important risk of imetelstat as the majority of TEAEs were mild to moderate in severity. IRRs can be managed in clinical practice through use of prophylactic antihistamines and corticosteroids prior to treatment together with dose modifications and supportive care as needed for the management of symptoms. Imetelstat is a product subject to restricted medical prescription and is administered under supervision of experienced healthcare professionals. As part of this close management, early detection and treatment of IRR per institutional standards would be expected. Therefore, guidance in the SmPC, PL, and restricted medical prescription are considered sufficient to manage this risk in clinical practice.

The imetelstat SmPC recommends that all patients receiving an imetelstat infusion are premedicated with diphenhydramine (25 to 50 mg) and hydrocortisone (100 to 200 mg), or equivalent, at least 30 minutes before dosing with imetelstat. Premedication should be administered before any doses of imetelstat to prevent or reduce potential IRRs. Patients should be monitored for adverse reactions for at least one hour after the infusion has been completed. The SmPC includes a warning that IRRs have been reported during treatment with imetelstat and were generally mild or moderate in severity. 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. Symptoms of IRRs should be managed with supportive care, and interrupting the infusion, decreasing the infusion rate or discontinuing treatment based on the severity and frequency of occurrence as recommended should be considered. Patients are warned in the PL that IRRs may happen during or soon after they are given Rytelo and can be mild to severe. To help prevent these reactions, their doctor or nurse will give them medicines at least 30 minutes before receiving Rytelo and they will be monitored closely for at least one hour afterwards. Patients are advised to tell their doctor or nurse straight away if they get signs of an IRR including low or very high blood pressure; sudden shortness of breath; lack of energy; not feeling well; headache; feeling sick (nausea); vomiting; diarrhoea; unusual heavy sweating; itchy or red skin; swelling; fever; or pain in some parts of the body (such as chest, stomach, joint, back or bone pain). Infusion-related reactions are listed as an adverse reaction in the

SmPC and PL to alert healthcare professionals and patients, respectively, that IRRs have been observed in clinical trials and may occur in clinical practice.

Infusion-related reactions will continue to be monitored using routine pharmacovigilance activities.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- None

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Thrombocytopenia

Thrombocytopenia is an identified risk not considered important for inclusion in the list of safety concerns in the RMP as it has been characterised in the clinical development programme.

Thrombocytopenia is a known ODN class effect and an additional potential mechanism of imetelstat-induced, reversible thrombocytopenia is the on-target effect of imetelstat on haematopoietic progenitor cells (HPCs). Imetelstat selectively affects the proliferation of malignant HPCs and leukemic stem cells while having limited effects on normal HPCs. In a well-established system of ex vivo megakaryopoiesis, imetelstat has multiple effects on maturation of malignant megakaryocytes (MK, the immature platelet precursors) and depletes these malignant cells, while delaying normal MK maturation. This leads to the eventual reduction of the pool of mature MK manifesting as thrombocytopenia. This MK maturation is restored 3 days after drug withdrawal (Mosoyan, 2017).

In the nonclinical programme, a variable degree of thrombocytopenia was observed in repeat-dose toxicity studies in mice and monkeys (Section Part II: Module SII).

In pivotal Phase 3 study MDS3001 patients were required to have platelets $\geq 75 \times 10^9$/L independent of platelet transfusion support for inclusion in the study. As patients with severe thrombocytopenia are at higher risk of haemorrhage, these events were closely monitored.

In Phase 3 study MDS3001 (Group A), the incidence of thrombocytopenia TEAEs was higher in the imetelstat group compared with the placebo group; 75.4% (89 of 118 subjects) versus 10.2% (6 of 59 subjects), respectively (Table 9). Similarly, 73 (61.9%) subjects treated with imetelstat experienced Grade 3/4 thrombocytopenia TEAEs compared with 5 (8.5%) subjects treated with placebo. There were no serious adverse events (SAEs) of thrombocytopenia reported in either treatment group. A high proportion of the thrombocytopenia TEAEs were considered by the investigator to be related to imetelstat treatment (67.8% subjects); 5.1% subjects had treatment-related TEAEs in the placebo group. In the imetelstat group, thrombocytopenia led to cycle delay in 55 (46.6%) subjects, dose reduction in 27 (22.9%) subjects, and discontinuation of imetelstat in 4 (3.4%) subjects. Most events occurred in the earlier months of treatment and rates decreased over time for any

grade and Grade 3/4 thrombocytopenia (Table tae07a), suggesting a lack of cumulative toxicity.

Table 9: Thrombocytopenia TEAEs - Phase 3 Study MDS3001 (Group A)

Subjects with Thrombocytopenia, n (%)	Imetelstat (N=118)	Placebo (N=59)
Any TEAE	89 (75.4%)	6 (10.2%)
Grade 3 or 4 TEAE	73 (61.9%)	5 (8.5%)
Grade 5 (fatal) TEAE	0	0
Treatment-related TEAE	80 (67.8%)	3 (5.1%)
Treatment-related Grade 3 or 4 TEAE	64 (54.2%)	2 (3.4%)
Treatment-emergent SAE	0	0
Treatment-related SAE	0	0
TEAE that led to cycle delay	55 (46.6%)	1 (1.7%)
TEAE that led to dose reduction	27 (22.9%)	1 (1.7%)
TEAE that led treatment withdrawal	4 (3.4%)	0

IV = intravenous(ly); SAE = serious adverse event; TEAE = treatment-emergent adverse event
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Notes: TEAEs are defined as events that occur or worsen after the first dose of study drug.
Percentages calculated with the number of subjects in each treatment group as denominator.
MedDRA v25.0 was used for TEAE coding.
Source data: Table tae02a; Table tae02j; Table tae02g; Table tae02m; Table tae02y; Table tae02s; Table tae02p.
Clinical cut-off date: 13 Oct 2022 for MDS3001.

Platelet transfusions were given to 21 (17.8%) subjects in the imetelstat group and 1 (1.7%) subject in the placebo group. Platelet transfusions were generally given in response to low platelets, early in treatment, not in the setting of a bleeding event, and with a median of 1 course per subject in both treatment groups (MDS3001 CSR [Phase 3]/ Section 12.4.4.2.1.1).

An evaluation of haematology laboratory data found that most subjects in the imetelstat and placebo groups (83.9% and 81.4%, respectively) had no thrombocytopenia at baseline, and 13.6% and 18.6% of subjects, respectively, had Grade 1 thrombocytopenia (Table tlab02a; Table tlab06a). In the imetelstat group most subjects (113 [95.8%]) had worsening thrombocytopenia from baseline while on treatment, including 47 (39.8%) subjects who worsened by 3 grades and 19 (16.1%) subjects who worsened by 4 grades during the study (Table tlab06a). In the placebo group, 20 (33.9%) subjects had worsening thrombocytopenia from baseline while on treatment, including 1 (1.7%) subject who worsened by 3 grades and 1 (1.7%) subject who worsened by 4 grades (Table tlab06a).

The median time to onset of Grade 3/4 thrombocytopenia in the imetelstat group was 6 weeks (range: 1.7 to 88.3 weeks) and the median duration was 1.4 weeks (range: 0.1 to 12.6 weeks) (Table 10). Most (86.3%) Grade 3/4 thrombocytopenia events in the imetelstat group resolved to Grade ≤ 2 in under 4 weeks. There was a trend toward an early decrease in mean platelets with stabilisation at a lower level of platelets (around 100 x 10^9/L) over the course of treatment compared to baseline, which is consistent with on-target effects of imetelstat.

Table 10: Grade 3/4 Thrombocytopenia Based on Platelet Counts - Phase 3 Study MDS3001 (Group A)

Parameter	Imetelstat (N=118)	Placebo (N=59)
Median time to onset of decreased platelets (weeks) (min, max)	6.0 (1.7, 88.3)	15.14 (6.4, 40.6)
Median duration of Grade 3/4 thrombocytopenia event (weeks) (min, max)	1.43 (0.1, 12.6)	2.00 (0.3, 11.6)
Number of Grade 3/4 thrombocytopenia events	212	9
Resolution to ≤ Grade 2 in < 4 weeks, n (%)	183 (86.3%)	4 (44.4%)
Resolution to ≤ Grade 2 in ≥ 4 weeks, n (%)	17 (8.0%)	1 (11.1%)

IV = intravenous(ly)
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Percentages calculated with the number of subjects in each treatment group as denominator.
Source data: Table tlab04a; Table tlab04d; Table tlab05a
Clinical cut-off date: 13 Oct 2022 for MDS3001.

The data from the MDS3001 Final Analysis (cutoff date 13 October 2023) were in line with the Primary Analysis of the Phase 3 data described above (cutoff date 13 October 2022). Thrombocytopenia TEAEs (any grade) were reported in 89 (75.4%) subjects in the imetelstat group and 6 (10.2%) subjects in the placebo group (Table tsfae05_p2). The majority of thrombocytopenia TEAEs were Grade 3/4, and most were reported by the investigators as related to treatment (Table tsfae05_p2; Table tsfae04_p2). There were no SAEs of thrombocytopenia in either group (Table tsfae09_p2).

An evaluation of haematology laboratory data from the MDS3001 Final Analysis found that most subjects (114/118 [96.6%]) in the imetelstat group had worsening thrombocytopenia from baseline while on treatment, including 51 (43.2%) subjects who worsened by 3 grades and 26 (22.0%) subjects who worsened by 4 grades during the study (Table tsflb06_p2). In the placebo group, 21 of 59 (35.6%) subjects had worsening thrombocytopenia from baseline while on treatment, including 3 (5.1%) subjects who worsened by 3 grades and 2 (3.4%) subjects who worsened by 4 grades. The median time to onset of Grade 3 or Grade 4 decreased platelets was 6.00 weeks (range: 1.7 to 88.3 weeks) in the imetelstat group and 15.14 weeks (range: 6.4 to 40.6 weeks) in the placebo group (Table tsflb09a_p2). Most (86.1%) Grade 3/4 thrombocytopenia events in the imetelstat group resolved to Grade ≤ 2 in under 4 weeks (Table tsflb12_p2).

Similar trends were observed in the Phase 2 supportive study MDS3001 (Group B) (Module 2.7.4, Section 2.1.7.2.2). In Group B, thrombocytopenia based on laboratory assessments occurred in 94.3% of subjects treated with imetelstat (N=175); Grade 3/4 thrombocytopenia occurred in 62.9% of subjects in this group (Module 2.7.4, Table 103).

In the Group C pool (N=391), there were no unexpected or unusual findings related to thrombocytopenia in subjects treated with imetelstat (Table 11). The lower incidence of thrombocytopenia in Group C (55.0%) compared to imetelstat-treated subjects in Group A (75.4%; Table 9) and Group B (70.9%; Table tae02b) was due to lower rates of thrombocytopenia reported in MF and ET/PV subjects in Studies MYF2001, CB14B019, and CB14B015. The trends observed in subjects treated with imetelstat in Group A and Group B were also observed in Group C including that most thrombocytopenia TEAEs were Grade 3/4 and related to study treatment, and SAEs were infrequent (Table 11). Furthermore, the incidence of thrombocytopenia decreased over time for both any grade and Grade 3/4 events, and across all dose groups (Table tae07c).

A total of 61 (15.6%) subjects in Group C had a thrombocytopenia TEAE that led to dose reduction and 18 (4.6%) subjects had a thrombocytopenia TEAE that led to treatment withdrawal (Table 11). Cycle delay was not collected evenly across studies in Group C and is not reported.

Table 11: Thrombocytopenia TEAEs - Studies Phase 2 and 3 MDS3001, CP14B013, CP14B015, CP14B019, MYF2001 (Group C)

	Imetelstat			
Subjects with Thrombocytopenia, n (%)	**< 7.1 mg/kg[a] Q4W (N=48)**	**7.1 mg/kg[b] Q4W (N=204)**	**> 7.1 mg/kg[c] Q4W (N=139)**	**Total Pooled (N=391)**
Any TEAE	11 (22.9%)	135 (66.2%)	69 (49.6%)	215 (55.0%)
Grade 3 or 4 TEAE	11 (22.9%)	113 (55.4%)	59 (42.4%)	183 (46.8%)
Grade 5 (fatal) TEAE	0	0	0	0
Treatment-related TEAE	7 (14.6%)	118 (57.8%)	36 (25.9%)	161 (41.2%)
Treatment-related Grade 3 or 4 TEAE	7 (14.6%)	97 (47.5%)	28 (20.1%)	132 (33.8%)
Treatment-emergent SAE	1 (2.1%)	2 (1.0%)	1 (0.7%)	4 (1.0%)
Treatment-related SAE	1 (2.1%)	2 (1.0%)	1 (0.7%)	4 (1.0%)
TEAE that led to dose reduction	2 (4.2%)	44 (21.6%)	15 (10.8%)	61 (15.6%)
TEAE that led treatment withdrawal	0	11 (5.4%)	7 (5.0%)	18 (4.6%)

Q4W = once every 4 weeks; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Group C includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled), and Phase 2 open-label studies MYF2001, CP14B013, CP14B015, and CP14B019.
[a] MYF2001 4.4 mg/kg arm only.
[b] CP14B019 arm E and G; MDS3001 Phase 2 and 3 (Imetelstat); CP14B015 and CP14B013 7.1 mg/kg arm.
[c] CP14B019 arm A, B, D, and F; CP14B015, CP14B013 and MYF2001 8.9 mg/kg arm.
Notes: TEAEs are defined as events that occur or worsen after the first dose of study drug.
Percentages calculated with the number of subjects in each treatment group as denominator.
MedDRA v25.0 was used for TEAE coding.
Source data: Table tae02c; Table tae02l; Table tae02i; Table tae02o; Table tae02u; Table tae02r
Clinical cut-off date: 13 Oct 2022 for MDS3001.

Based on laboratory assessments, the median time to onset of Grade 3 or Grade 4 decreased platelets in Group C was 6.0 weeks (range: 0.6 to 168.7 weeks) (Table tlab04c). Most Grade 3/4 events (79.9%) resolved to Grade ≤ 2 in under 4 weeks (Table tlab05c). Most subjects (69.8%) had no thrombocytopenia at baseline, and 25.6% had Grade 1 thrombocytopenia (Table tlab06c). More subjects in the 7.1 mg/kg group had no thrombocytopenia at baseline (82.4%) than in the < 7.1 mg/kg and > 7.1 mg/kg groups (50.0% and 58.3%, respectively). There was a trend toward an early decrease in mean platelets with stabilisation at a lower level over the course of treatment which is consistent with on-target effects of imetelstat.

In summary, thrombocytopenia is a recognised and expected adverse reaction of imetelstat related to its on-target effect on malignant HPCs. Thrombocytopenia based on laboratory assessments occurred in 94.3% of subjects treated with imetelstat in the Phase 2 and Phase 3 MDS3001 study; Grade 3/4 thrombocytopenia occurred in 62.9% of subjects in this group. Grade 3/4 thrombocytopenia was generally reversible to Grade 2 or less through dose reduction, cycle delay and platelet transfusion within the 4-week dosing schedule. In the majority of subjects (> 85%) with Grade 3/4 thrombocytopenia in the Phase 3 study, events resolved to Grade ≤ 2 in under 4 weeks. Treatment discontinuation was only necessary in a very small number of cases. While dose modifications occurred as mandated per protocol in both the Phase 2 and Phase 3 study, > 90% overall dose intensity of the 7.1 mg/kg dose was

achieved over the treatment period for all subjects. There were no SAEs of thrombocytopenia reported in either imetelstat or placebo groups in Phase 3 MDS3001.

Healthcare professionals treating patients with MDS are experienced in the management of thrombocytopenia. Imetelstat is a product subject to restricted medical prescription and is administered under supervision of experienced healthcare professionals. As part of this close management, early detection and treatment of thrombocytopenia per institutional standards would be expected. Therefore, guidance in the SmPC, PL, and restricted medical prescription are considered sufficient to manage this risk in clinical practice.

The imetelstat SmPC provides guidance to monitor complete blood cell counts before administration of each dose of imetelstat, weekly following administration of the first two doses, and for any case of Grade 3 or Grade 4 thrombocytopenia or as clinically indicated. Dose modifications for thrombocytopenia include delaying treatment until platelets are $\geq 50 \times 10^9$/L and resuming at the same or reduced dose as recommended based on severity grade and occurrence. Treatment with imetelstat should be permanently discontinued if the patient cannot tolerate the lowest dose level of 4.4 mg/kg. The SmPC includes a warning that new or worsening Grade 3 or Grade 4 thrombocytopenia has been observed in the clinical studies and that these patients should be monitored for bleeding events as a precaution. The need for platelet transfusions should be assessed as clinically appropriate. Patients should be advised to report any signs or symptoms of bruising or bleeding immediately. The next dose should be delayed and resumed at the same or reduced dose as recommended. Thrombocytopenia, epistaxis, haematoma, gastrointestinal bleeding, and haematuria are included as adverse reactions in the SmPC and PL to alert healthcare professionals and patients, respectively, that these adverse reactions occurred in clinical trials and may occur in clinical practice.

The imetelstat PL provides guidance for the patient to talk to their doctor or nurse before they are given Rytelo if they have recently had reactions such as bruising more easily, bleeding more than expected, nosebleeds, blood in the urine or stool, or any other signs of bleeding as the bleeding or bruising can worsen if certain types of their blood cells begin to decrease after they have received Rytelo. Patients are advised that their doctor or nurse will monitor them for specific side effects and do blood tests to keep control of their blood cell counts before every dose of Rytelo and weekly after their first two doses. Medicines to make more blood cells may be given if the patient's blood cell counts are low. Low blood levels of platelets (thrombocytopenia) are a very common serious side effect and may include the following symptoms: bruising more easily or bleeding more than expected, a bruise or collection of blood (haematoma), prolonged bleeding from cuts, nosebleed, blood in the gut, urine or stool or black stool.

Thrombocytopenia will be further monitored using routine pharmacovigilance activities.

- Neutropenia

Neutropenia is an identified risk not considered important for inclusion in the list of safety concerns in the RMP as it has been characterised in the clinical development programme.

Neutropenia is an expected effect of imetelstat and an indicator of on-target activity, as imetelstat selectively affects the proliferation of malignant HPCs and leukemic stem cells while sparing normal HPCs. Neutropenia is also a prominent manifestation of the ineffective haematopoiesis associated with MDS.

In pivotal Phase 3 study MDS3001 patients were required to have absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L independent of growth factor support for inclusion in the study. As it is

recognised that patients with severe neutropenia have a high risk of developing infections following the onset of severe neutropenia, these events were closely monitored. Infection TEAEs were identified using the MedDRA SOC Infections and infestations.

In Phase 3 MDS3001 (Group A), neutropenia TEAEs were higher in imetelstat compared with placebo treated subjects; 73.7% (87 of 118 subjects) versus 6.8% (4 of 59 subjects), respectively (Table 12). Similarly, 80 (67.8%) subjects treated with imetelstat experienced Grade 3/4 neutropenia TEAEs compared with 2 (3.4%) subjects treated with placebo. There were no SAEs of neutropenia reported in either treatment group. Most of the neutropenia TEAEs were considered by the investigator to be related to imetelstat (64.4%); 5.1% subjects had treatment-related TEAEs in the placebo group.

In the imetelstat group, neutropenia led to dose reduction in 39 (33.1%) subjects, cycle delay in 60 (50.8%) subjects, and discontinuation of study treatment in 6 (5.1%) subjects (Table 12). Treatment discontinuation due to neutropenia occurred later in treatment (≥ 100 days) in all but 1 subject (MDS3001 CSR [Phase 3]/ Table 65). TEAEs of neutropenia occurred at highest incidence during the first 3 months of treatment and decreased in frequency over time, suggesting a lack of cumulative toxicity.

In the placebo group, 1 (1.7%) subject had a dose reduction due to neutropenia, and 1 (1.7%) subject had a cycle delay due to neutropenia (Table 12). No subjects in the placebo group discontinued study treatment due to neutropenia.

Forty-one (34.7%) subjects in the imetelstat group and 2 (3.3%) subjects in the placebo group had at least 1 dose of myeloid growth factors as of the cut-off date, with the majority of subjects receiving myeloid growth factors in Cycles 2 through 4.

Table 12: Neutropenia TEAEs Phase 3 Study MDS3001 (Group A)

Subjects with Neutropenia, n (%)	Imetelstat (N=118)	Placebo (N=59)
Any TEAE	87 (73.7%)	4 (6.8%)
Grade 3 or 4 TEAE	80 (67.8%)	2 (3.4%)
Grade 5 (fatal) TEAE	0	0
Treatment-related TEAE	76 (64.4%)	3 (5.1%)
Treatment-related Grade 3 or 4 TEAE	69 (58.5%)	2 (3.4%)
Treatment-emergent SAE	0	0
Treatment-related SAE	0	0
TEAE that led to cycle delay	60 (50.8%)	1 (1.7%)
TEAE that led to dose reduction	39 (33.1%)	1 (1.7%)
TEAE that led treatment withdrawal	6 (5.1%)	0

IV = intravenous(ly); MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Notes: TEAEs are defined as events that occur or worsen after the first dose of study drug.
Percentages calculated with the number of subjects in each treatment group as denominator.
MedDRA v25.0 was used for TEAE coding.
Source data: Table tae02a; Table tae02j; Table tae02g; Table tae02m; Table tae02y; Table tae02s; Table tae02p.
Clinical cut-off date: 13 Oct 2022 for MDS3001.

An evaluation of haematology laboratory data found that most subjects (108/118 [91.5%]) in the imetelstat group had worsening neutropenia from baseline while on treatment, including 49 (41.5%) subjects who worsened by 3 grades and 20 (16.9%) subjects who worsened by

4 grades during the study (Table tlab02a; Table tlab06a). In the placebo group, 28 of 59 (47.5%) subjects had worsening neutropenia from baseline while on treatment, including 2 (3.4%) subjects who worsened by 3 grades. No subjects worsened by 4 grades during the study.

The median time to onset of Grade 3 or Grade 4 decreased neutrophils was 4.43 weeks (range: 1.0 to 81.0 weeks) in the imetelstat group and 13.00 weeks (range: 3.0 to 23.0 weeks) in the placebo group (Table 13). The median duration for Grade 3/4 neutropenia was 1.86 weeks (range: 0 to 15.9 weeks) in the imetelstat group and 2.21 weeks (range: 1.0 to 4.6 weeks) in the placebo group. Most (81.0%) Grade 3/4 neutropenia events in the imetelstat group resolved to Grade ≤ 2 in under 4 weeks.

Febrile neutropenia was reported for 1 subject (0.8%) in the imetelstat group (Grade 3, reported as serious and related to imetelstat treatment, recovered in 10 days, resulting in a cycle delay) (Table tae02y; Listing lae02e). No subjects in the placebo group had febrile neutropenia (Table tae02a).

Table 13: Grade 3/4 Neutropenia Based on Neutrophil Counts - Phase 3 Study MDS3001 (Group A)

Parameter	Imetelstat (N=118)	Placebo (N=59)
Median time to onset of decreased neutrophils (weeks) (min, max)	4.43 (1.0, 81.0)	13.00 (3.0, 23.0)
Median duration of Grade 3/4 neutropenia event (weeks) (min, max)	1.86 (0, 15.9)	2.21 (1.0, 4.6)
Number of Grade 3/4 neutropenia events	279	6
Resolution to ≤ Grade 2 in < 4 weeks, n (%)	226 (81.0%)	3 (50.0%)
Resolution to ≤ Grade 2 in ≥ 4 weeks, n (%)	40 (14.3%)	2 (33.3%)

IV = intravenous(ly)
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Percentages calculated with the number of subjects in each treatment group as denominator.
Source data: Table tlab04a; Table tlab04d; Table tlab05a
Clinical cut-off date: 13 Oct 2022 for MDS3001.

The data from the MDS3001 Final Analysis (cutoff date 13 October 2023) were in line with the Primary Analysis of the Phase 3 data described above (cutoff date 13 October 2022). Neutropenia TEAEs (any grade) were reported in 89 (75.4%) subjects in the imetelstat group and 5 (8.5%) subjects in the placebo group (Table tsfae05_p2). The majority of neutropenia TEAEs were Grade 3/4, and most were reported by the investigators as related to treatment (Table tsfae05_p2; Table tsfae04_p2). There were no SAEs of neutropenia in either group (Table tsfae09_p2).

An evaluation of haematology laboratory data from the MDS3001 Final Analysis found that most subjects (109/118 [92.4%]) in the imetelstat group had worsening neutropenia from baseline while on treatment, including 56 (47.5%) subjects who worsened by 3 grades and 29 (24.6%) subjects who worsened by 4 grades during the study (Table tsflb06_p2). In the placebo group, 28 of 59 (47.5%) subjects had worsening neutropenia from baseline while on treatment, including 3 (5.1%) subjects who worsened by 3 grades and 1 (1.7%) subject who worsened by 4 grades. The median time to onset of Grade 3 or Grade 4 decreased neutrophils was 4.57 weeks (range: 1.0 to 81.0 weeks) in the imetelstat group and 13.00 weeks (range: 3.0 to 23.0 weeks) in the placebo group (Table tsflb09a_p2). Most (80.1%) Grade 3/4

neutropenia events in the imetelstat group resolved to Grade ≤ 2 in under 4 weeks (Table tsflb12_p2).

Consistent results for neutropenia were observed in the Phase 2 supportive study (Module 2.7.4, Section 2.1.7.3.2.1). In Group B, neutropenia based on laboratory assessments occurred in 92.0% of subjects treated with imetelstat (N=175); Grade 3/4 neutropenia occurred in 69.1% of subjects in this group (Module 2.7.4, Table 101).

In the Group C pool (N=391), there were no unexpected or unusual findings related to neutropenia in subjects treated with imetelstat (Table 14). The lower overall incidence of neutropenia in Group C (49.1%) compared to Groups A and B (73.7%; Table 12 and 71.4%; Table tae02b, respectively) was due to lower reported incidences of neutropenia in subjects from the MF studies, who share an equal proportion of the Group C pool (43.2%) with MDS subjects (44.8%).

The trends observed in subjects treated with imetelstat in Group A and Group B were also observed in Group C including that most neutropenia TEAEs were Grade 3/4 and related to study treatment, and SAEs were infrequent (1 SAE of Grade 4 neutropenia considered related to imetelstat that led to dose reduction [Listing lae02c]) (Table 14).

A total of 76 (19.4%) subjects in Group C had a neutropenia TEAE that led to dose reduction and 17 (4.3%) subjects had a neutropenia TEAE that led to treatment withdrawal (Table 14). Cycle delay was not collected evenly across studies in Group C and is not reported.

Table 14: Neutropenia TEAEs - Studies Phase 2 and 3 MDS3001, CP14B013, CP14B015, CP14B019, MYF2001 (Group C)

	Imetelstat			
Subjects with Neutropenia, n (%)	**< 7.1 mg/kg[a] Q4W (N=48)**	**7.1 mg/kg[b] Q4W (N=204)**	**> 7.1 mg/kg[c] Q4W (N=139)**	**Total Pooled (N=391)**
Any TEAE	5 (10.4%)	136 (66.7%)	51 (36.7%)	192 (49.1%)
Grade 3 or 4 TEAE	5 (10.4%)	124 (60.8%)	48 (34.5%)	177 (45.3%)
Grade 5 (fatal) TEAE	0	0	0	0
Treatment-related TEAE	5 (10.4%)	114 (55.9%)	30 (21.6%)	149 (38.1%)
Treatment-related Grade 3 or 4 TEAE	5 (10.4%)	105 (51.5%)	26 (18.7%)	136 (34.8%)
Treatment-emergent SAE	0	1 (0.5%)	0	1 (0.3%)
Treatment-related SAE	0	1 (0.5%)	0	1 (0.3%)
TEAE that led to dose reduction	0	64 (31.4%)	12 (8.6%)	76 (19.4%)
TEAE that led treatment withdrawal	2 (4.2%)	11 (5.4%)	4 (2.9%)	17 (4.3%)

Q4W = once every 4 weeks; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Group C includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled), and Phase 2 open-label studies MYF2001, CP14B013, CP14B015, and CP14B019.
[a] MYF2001 4.4 mg/kg arm only.
[b] CP14B019 arm E and G; MDS3001 Phase 2 and 3 (Imetelstat); CP14B015 and CP14B013 7.1 mg/kg arm.
[c] CP14B019 arm A, B, D, and F; CP14B015, CP14B013 and MYF2001 8.9 mg/kg arm.
Notes: TEAEs are defined as events that occur or worsen after the first dose of study drug.
Percentages calculated with the number of subjects in each treatment group as denominator.
MedDRA v25.0 was used for TEAE coding.
Source data: Table tae02c; Table tae02l; Table tae02i; Table tae02o; Table tae02u; Table tae02r
Clinical cut-off date: 13 Oct 2022 for MDS3001.

Based on laboratory assessments, the median time to onset of Grade 3 or Grade 4 decreased neutrophils was 5.0 weeks (range: 0.7 to 216.9 weeks) (Table tlab04c). Most Grade 3/4

events (82.4%) resolved to Grade ≤ 2 in under 4 weeks (Table tlab05c). Most subjects (89.0%) had no neutropenia at baseline, and 6.6% had Grade 1 neutropenia (Table tlab06c).

Febrile neutropenia was reported for 11 subjects in the overall Group C pool, including 4 subjects from the Group B pool and 7 additional subjects, including 1 subject in the < 7.1 mg/kg group, 1 subject in the 7.1 mg/kg group, and 5 subjects in the > 7.1 mg/kg group (Table tae02c; Listing lae02e). The extent of the initial decrease in neutrophils after start of treatment was largest in the > 7.1 mg/kg group with subsequent partial recovery to below normal range over the course of treatment.

In summary, neutropenia is a recognised and expected adverse reaction of imetelstat with Grade 3/4 neutropenia frequently observed throughout the clinical studies, particularly during the first few cycles of treatment. Neutropenia based on laboratory assessments occurred in 92.0% of subjects treated with imetelstat in the Phase 2 and Phase 3 MDS3001 study; Grade 3/4 neutropenia occurred in 69.1% of subjects in this group. Grade 3/4 neutropenia was generally reversible to Grade 2 or less through dose reduction, cycle delay or growth factor support within the 4-week dosing schedule. Treatment discontinuation was only necessary in a very small number of cases. While dose modifications occurred as mandated per protocol in both the Phase 2 and Phase 3 study, > 90% overall dose intensity of the 7.1 mg/kg dose was achieved over the treatment period for all subjects. Infections such as urinary tract infection were also observed, the majority were of Grade 1 or 2 severity and assessed as not related to treatment by the investigator. There were no SAEs of neutropenia reported in either imetelstat or placebo groups in Phase 3 MDS3001.

Imetelstat is a product subject to restricted medical prescription and is administered under supervision of experienced healthcare professionals. As part of this close management, early detection and treatment of neutropenia per institutional standards would be expected. Therefore, guidance in the SmPC, PL, and restricted medical prescription are considered sufficient to manage this risk in clinical practice. Healthcare professionals treating patients with MDS are experienced in the management of neutropenia and are aware of the risk of infections in patients with severe neutropenia. The risk of neutropenia can be minimised in clinical practice through monitoring, dose modifications, and provision of support care including granulocyte-colony stimulating factors and anti-infectives, as needed.

The imetelstat SmPC provides guidance to monitor complete blood cell counts 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 or as clinically indicated. Dose modifications for neutropenia include delaying treatment until absolute neutrophil counts are $\geq 1.0 \times 10^9$/L and resuming at the same or reduced dose as recommended based on severity grade and occurrence. Treatment with imetelstat should be permanently discontinued if the patient cannot tolerate the lowest dose level of 4.4 mg/kg. The SmPC includes a warning that neutropenia has been reported during treatment with imetelstat, including new or worsening Grade 3 or Grade 4 neutropenia and that these patients 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. Neutropenia, sepsis, and urinary tract infection are listed as adverse reactions in the SmPC and PL to alert healthcare professionals and patients, respectively, that neutropenia and infections have occurred in clinical trials and may occur in clinical practice.

The imetelstat PL provides guidance for the patient to talk to their doctor or nurse before they are given Rytelo if they have signs of an infection such as fever, chills, feeling unwell, or any other sign of infection as the infection can worsen if certain types of their blood cells begin to decrease after they have received Rytelo. Patients are advised that their doctor or nurse will monitor them for specific side effects and do blood tests to keep control of their blood cell counts before every dose of Rytelo and weekly after their first two doses. Medicines to help fight infection or make more blood cells may be given if the patient's blood cell counts are low. Low blood levels of neutrophils (neutropenia) are a very common serious side effect which may include the following symptoms: fever, cough, sore throat, chills, feeling unwell, or any other sign of infection. Furthermore, an infection in the bloodstream (sepsis) is a common serious side effect that may occur.

Neutropenia will be further monitored using routine pharmacovigilance activities.

Known risks that do not impact the risk-benefit profile:

- Immunogenicity

Immunogenicity is a risk not considered important for inclusion in the list of safety concerns in the RMP based on the anti-drug antibodies (ADA) observed and their impact on the PK, efficacy, or safety of imetelstat.

As with all ODNs, there is potential for immunogenicity. Immune responses to ODNs may include generation of anti-drug antibodies (ADA) which have potential to impact the product's pharmacokinetics (PK), pharmacodynamics (PD), efficacy, and safety. The detection of antibody formation against ODNs is highly dependent on the sensitivity and specificity of the assay.

Formation of ADA against imetelstat was assessed in the Phase 2/Phase 3 study MDS3001 in the LR MDS population and the Phase 2 study MYF2001 in the MF population using a validated bioanalytical method which included a three-tiered approach: 1) a screening assay which detected anti-imetelstat antibodies; 2) a confirmatory competition assay to assess the specificity of initial positive screening results; and 3) a titration assay for confirmed positive results to obtain semi-quantitative results for titres of detected ADA (Module 2.7.2, Section 4.1).

In Study MDS3001, 28 of 166 (16.9%) evaluable subjects developed ADA to imetelstat, with ADA onset occurring after imetelstat treatment (i.e., treatment-induced ADA response). There was no pre-existing immunogenicity to imetelstat. The median time to onset of ADA was approximately 38 weeks following the start of treatment, or after 8 treatment cycles, which is slightly later than the median duration of treatment (approximately 35 weeks). The peak titre ranged from 10 to 160 (median: 30).

In Study MYF2001, 22 of 107 (20.6%) evaluable subjects developed ADA to imetelstat, with all exhibiting a treatment-induced ADA response. One subject was ADA positive at baseline but negative at all other timepoints, so was categorised as ADA negative overall. The median time to onset of ADA was approximately 25 weeks following the start of treatment, or after 8 treatment cycles. The peak titre ranged from 10 to 2560 (median: 60).

Graphical evaluation of the imetelstat PK time course showed that ADA did not appear to affect imetelstat PK, as there were no clear differences in imetelstat concentrations for subjects at timepoints when they were ADA-positive compared to ADA negative in Studies MDS3001 and MYF2001. Further, formal covariate analysis by population PK (popPK)

modelling for both categorical (time invariant) and time-variant ADA status indicated that ADA was not a significant covariate on imetelstat clearance.

In Study MDS3001, ADA did not negatively impact the overall efficacy response rate for 8-week TI (64.3% for ADA-positive vs 34.8% for ADA negative), 24-week TI (46.4% vs 24.6%), hematologic improvement-erythroid (HI-E) (2018) (67.9% vs 41.3%), or HI-E (2006) (82.1% vs 60.9%). Although numerical differences suggested higher response rates for ADA-positive subjects, this may be due to longer time on treatment compared to ADA-negative subjects (78.4 weeks vs 33.2 weeks). ADA-positive subjects with high peak titre exhibited similar effects with no apparent negative impact on efficacy and an apparent increased efficacy response rates and longer time on treatment compared to those with low peak titre.

Imetelstat ADA did not result in detectable loss of efficacy in Study MDS3001 (Module 2.7.2, Section 4.1). The longest TI interval was not negatively affected in ADA positive subjects compared to ADA negative subjects (67.9 weeks vs 44.4 weeks) and was similar for subjects with high and low peak titre (68.4 weeks vs 65.1 weeks). Graphical evaluation showed no clear temporal relationship between the end of the TI interval and onset of ADA.

There was no apparent effect of ADA on imetelstat safety in Study MDS3001, as ADA positive and ADA negative subjects exhibited similar rates of drug-related TEAEs (92.9% vs 84.1%) and drug-related Grade ≥ 3 TEAEs (75.0% vs 74.6%). There were no drug-related serious TEAEs or TEAEs with outcome of death in ADA positive subjects. Further, there were no clear trends in rate of drug-related TEAEs between subjects with low peak titre and high peak titre.

Infusion-related TEAEs in Study MDS3001 were more frequent in ADA-positive compared to ADA-negative subjects (17.9% vs 7.3%), although the sample size was small. All infusion-related TEAEs in ADA-positive subjects were Grade 3 or lower, with the majority being Grade 1 or 2, and none were considered serious. Importantly, IRRs are minimised by administering pre-infusion medications and monitoring patients for at least one hour after the infusion, and managed with supportive care, and interrupting the infusion, decreasing the infusion rate or following other dose modifications based on the severity and frequency of occurrence.

Immunogenicity is not an important risk as ADA do not appear to impact the PK, efficacy, or safety of imetelstat and thus do not impact the benefit/risk profile of imetelstat. This is consistent with findings for approved oligonucleotides for which there have been no reports of clinically meaningful impacts of ADA (Bano, 2022).

The imetelstat SmPC informs healthcare professionals that during treatment with imetelstat at the recommended dose, ADA were detected in 17% of participants. No evidence of ADA impact on PK, safety, or efficacy was observed, however, data are still limited.

Immunogenicity will continue to be monitored using routine pharmacovigilance activities.

Other reasons for considering the risks not important:

- None

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk 1: Severe bleeding

Severe bleeding is an important identified risk of imetelstat. As a known clinical sequelae of thrombocytopenia, severe bleeding is a possible clinical outcome. As discussed below, the rates of severe bleeding observed were low with imetelstat and similar to placebo in Phase 3 study MDS3001. While the current data do not suggest an imbalance of severe bleeding events, there remains a risk given thrombocytopenia is a recognised and expected adverse reaction of imetelstat related to its on-target effect on malignant HPCs. The imetelstat SmPC includes a warning that new or worsening severe Grade 3 or Grade 4 thrombocytopenia has been observed in the clinical studies and to monitor these patients for bleeding events as a precaution. 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 thrombocytopenia or as clinically indicated. The need for platelet transfusions should be assessed as clinically appropriate. As a precaution, patients should be advised to report any signs or symptoms of bruising or bleeding immediately. The next dose should be delayed and resumed at the same or reduced dose as recommended. Furthermore, while severe bleeding events have not been observed with imetelstat, epistaxis, haematoma, gastrointestinal bleeding, and haematuria are listed as adverse reactions in the SmPC and PL to alert healthcare professionals and patients, respectively, that these adverse reactions have occurred in clinical trials and that bleeding events may occur in clinical practice.

The imetelstat PL provides guidance for the patient to talk to their doctor or nurse before they are given Rytelo if they have recently had reactions such as bruising more easily, bleeding more than expected, nosebleeds, blood in the urine or stool, or any other signs of bleeding as the bleeding or bruising can worsen if certain types of their blood cells begin to decrease after they have received Rytelo. Patients are advised that their doctor or nurse will monitor them for specific side effects and do blood tests to keep control of their blood cell counts before every dose of Rytelo and weekly after their first two doses. Medicines to make more blood cells may be given if the patient's blood cell counts are low. Low blood levels of platelets (thrombocytopenia) are a very common serious side effect which may include the following symptoms: bruising more easily or bleeding more than expected, a bruise or collection of blood (haematoma), prolonged bleeding from cuts, nosebleed, blood in the gut, urine or stool or black stool. The bleeding events that were observed in the clinical studies were manageable with standard treatments.

In nonclinical studies, a variable degree of haemorrhage was observed in repeat-dose toxicity studies in mice and monkeys (Section Part II: Module SII).

In Phase 3 study MDS3001, bleeding TEAEs (any grade) were reported in 25 (21.2%) subjects in the imetelstat group and 7 (11.9%) subjects in the placebo group, with Grade 3/4 events reported in 3 (2.5%) subjects and 1 (1.7%) subject, respectively (Section SVII.3.1). The most commonly reported bleeding event in the imetelstat group was epistaxis (7 [5.9%] subjects), followed by haematoma (6 [5.1%] subjects) (Table 15). Three subjects had events considered related to imetelstat by the investigator (gingival bleeding, epistaxis, and prothrombin time prolonged), all of which were Grade 1 (MDS3001 CSR [Phase 3]/ Listing lsfae03). Three subjects treated with imetelstat had Grade 3/4 bleeding TEAEs (haematuria, gastrointestinal haemorrhage, and oesophageal varices haemorrhage), all of which were SAEs and none were considered related to treatment (Listing lae02c; Table tae03g). In the placebo group, 1 subject had Grade 3/4 bleeding TEAEs (small

intestinal haemorrhage), that were SAEs and not considered related to treatment. There were no Grade 5 bleeding events in either treatment group (Table tae05a).

The median time to onset of the Grade 3/4 bleeding events in the 3 subjects treated with imetelstat was 32 days (range: 24 to 633 days) and the time to onset for the Grade 3/4 bleeding event in the 1 subject treated with placebo was 209 days (Table taesi03d). In the imetelstat group, 1 subject discontinued treatment due to an SAE of unrelated Grade 4 gastrointestinal haemorrhage (mentioned above) (Table tae02p), 2 subjects had study cycle delays due to epistaxis (Table tae02y); no subjects had bleeding events that led to study treatment reduction (Table tae02s). In the placebo group, the Grade 3/4 small intestinal haemorrhage led to cycle delay (Table tae02y); there were no bleeding events that led to study treatment discontinuations or dose reductions (Table tae02p; Table tae02s).

Overall, the rates of SAEs and severe bleeding observed were low with imetelstat and similar to placebo in Phase 3 study MDS3001, and there were no severe bleeding events that occurred in context of ±7-days of Grade 3/4 thrombocytopenia (Table 16). Most bleeding events were minor Grade 1/2 events, and most were reported as not related to study drug. These results were consistent over time, as demonstrated by the additional 1-year of data provided in the Final Analysis of MDS3001 Phase 3 study (Section SVII.3.1).

Risk-benefit impact:

The benefit of imetelstat as a treatment for adult patients with transfusion-dependent anaemia due to lower risk MDS, a life-threatening condition with an unmet clinical need, is considered to outweigh the risk of severe bleeding which can be managed in clinical practice through healthcare professional awareness of the possible risk and through patient monitoring and provision of supportive care.

Severe bleeding will be further characterised in Study MDS3001 Extension Phase (Part III).

Important Identified Risk 2: Severe infections

Severe infections are an important identified risk of imetelstat. As a known clinical sequelae of neutropenia, severe infections are a possible clinical outcome. As discussed below, the rates of severe infections observed were low with imetelstat and placebo in Phase 3 study MDS3001. While the current data do not suggest an imbalance of severe infections, there remains a risk given neutropenia is an expected adverse reaction of imetelstat. The imetelstat SmPC includes a warning that new or worsening severe Grade 3 or Grade 4 neutropenia has been observed in the clinical studies and to monitor these patients for infections including sepsis as a precaution. 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 or as clinically indicated. 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 infection immediately. The next dose should be delayed and resumed at the same or reduced dose as recommended. Sepsis and urinary tract infection are included as adverse reactions in the SmPC and PL to alert healthcare professionals and patients, respectively, that infections occurred in clinical trials and may occur in clinical practice.

The imetelstat PL provides guidance for the patient to talk to their doctor or nurse before they are given Rytelo if they have signs of an infection such as fever, chills, feeling unwell, or any other sign of infection as the infection can worsen if certain types of their blood cells begin to

decrease after they have received Rytelo. Patients are advised that their doctor or nurse will monitor them for specific side effects and do blood tests to keep control of their blood cell counts before every dose of Rytelo and weekly after their first two doses. Medicines to help fight infection or make more blood cells may be given if the patient's blood cell counts are low. Low blood levels of neutrophils (neutropenia) are a very common serious side effect which may include the following symptoms: fever, cough, sore throat, chills, feeling unwell, or any other sign of infection. Furthermore, an infection in the bloodstream (sepsis) is a common serious side effect that may occur. The infections that were observed in the clinical studies were manageable with standard treatments.

In Phase 3 study MDS3001, infection TEAEs (any grade) were reported in 50 (42.4%) subjects in the imetelstat group and 20 (33.9%) subjects in the placebo group, with Grade 3/4 events reported in 12 (10.2%) subjects and 8 (13.6%) subjects, respectively (Section SVII.3.1). The most commonly reported infection in the imetelstat group was COVID-19 (18 [15.3%] subjects), followed by urinary tract infection (7 [5.9%] subjects) and pneumonia (4 [3.4%] subjects) (Table 18). Four subjects had Grade 4 infections (COVID-19 pneumonia, Enterococcal sepsis, and 2 sepsis; 1 of which was considered related to study treatment by the investigator) (Listing lae2e). One subject had a Grade 5 infection of sepsis considered not related to study treatment after almost two years on treatment with imetelstat (Table tae05a; Table tae05d). In the placebo group, the most commonly reported infection was COVID-19 (4 [6.8%] subjects) (Table 18). One subject had a Grade 4 infection of listeriosis, considered not related to study treatment and there were no Grade 5 infections in the placebo group (Listing lae02e; Table tae02j; Table tae05a).

It is of note that treatment was ongoing in Study MDS3001 at the time the COVID-19 pandemic started in March 2020 resulting in the monitoring of COVID-related impacts to study participants as recommended by worldwide health authorities. In the imetelstat group, 22 (18.6%) subjects had TEAEs related to COVID-19 (Module 2.7.4, Section 2.1.7.3.1.3). Most of these events were Grade 1 or Grade 2. One subject had Grade 3 COVID-19 pneumonia, and 1 subject had Grade 4 COVID-19 pneumonia; both events were reported as SAEs. No events were considered related to imetelstat. In the placebo group, 8 (13.6%) subjects had TEAEs related to COVID-19, including 3 subjects with SAEs of Grade 3 COVID-19 pneumonia. There were no other Grade ≥ 3 events. No subjects in either treatment group discontinued study treatment due to COVID-19-related TEAEs. Two subjects, one in each treatment group, had Grade 5 (fatal) non-TEAEs related to COVID-19 (COVID-19 pneumonia and multiple organ dysfunction syndrome). Both these deaths occurred in follow up, > 30 days after the last dose of study treatment.

The median time to onset of first Grade 3/4 infection in the imetelstat group and placebo group was 142.0 days (range: 20 to 644 days) and 61.5 days (range: 15 to 638 days), respectively (Table taesi03j). In the imetelstat group, infections led to cycle delay in 17 (14.4%) subjects, most commonly COVID-19 (9 [7.6%] subjects) (Table tae02y). One subject had a dose reduction due to an SAE of Grade 3 neutropenic sepsis (Table tae02s; Listing lae02e). One subject discontinued study treatment due to 2 infection events (nonserious Grade 3 renal abscess and serious Grade 4 sepsis; both related to treatment) (Table tae02p; Listing lae02e). In the placebo group, 7 (11.9%) subjects had cycle delays due to infections, most commonly COVID-19 (2 [3.4%] subjects) (Table tae02y); no subjects had a dose reduction or discontinued study treatment due to an infection (Table tae02s; Table tae02p).

Overall the rates of SAEs and severe infections observed with imetelstat were low and similar to placebo in the Phase 3 study MDS3001, and the incidence was also similar between groups

for severe infections that occurred in context of ±7-days of Grade 3/4 neutropenia (Table 19). Most events were minor Grade 1/2 infections, and most were reported as not related to study drug. These results were consistent over time, as demonstrated by the additional 1-year of data provided in the Final Analysis of MDS3001 Phase 3 study (Section SVII.3.1).

Risk-benefit impact:

The benefit of imetelstat as a treatment for adult patients with transfusion-dependent anaemia due to lower risk MDS, a life-threatening condition with an unmet clinical need, is considered to outweigh the risk of severe infections which can be managed in clinical practice through healthcare professional awareness of the risk and through patient monitoring and provision of supportive care.

Severe infections will be further characterised in Study MDS3001 Extension Phase (Part III).

Important Potential Risk 1: Severe hepatotoxicity

Severe hepatotoxicity is an important potential risk. The transient hepatic enzyme elevations that occur in some patients may be a manifestation of immune stimulation although the mechanism is not known. Hepatic effects are also expected in patients with MDS due to iron overload related toxicity. The imetelstat SmPC recommends liver function tests before administration of each dose and includes dose modifications for Grade 3 or 4 elevated liver function tests including delaying treatment until adverse reactions are Grade 1 or at baseline Grade and restarting at one dose level lower. Treatment with imetelstat should be permanently discontinued if the patient cannot tolerate the lowest dose level of 4.4 mg/kg. Aspartate aminotransferase increased, alanine aminotransferase increased and blood alkaline phosphatase increased are listed in the SmPC as adverse reactions based on laboratory measurements to alert healthcare professionals that these adverse reactions have been observed in clinical trials and may occur in clinical practice. Likewise, patients are advised in the PL that their doctor or nurse will monitor them for specific side effects and do blood tests (liver function tests) before every administration of Rytelo. They are informed that increased levels of liver enzymes shown in blood tests are very common side effects of imetelstat. Hepatic enzyme elevations were managed in clinical trials with cycle delays and reducing the dose.

In nonclinical studies, imetelstat-related histomorphologic changes in the liver were relatively benign under all treatment conditions in mice, rats, and monkeys. Importantly, there were no degenerative changes or alterations in clinical pathology parameters indicative of hepatic dysfunction or injury nor were there any remarkable changes in parameters of kidney function (Section Part II: Module SII).

In Phase 3 study MDS3001, hepatic adverse events (any grade) were reported in 28.8% subjects treated with imetelstat and in 16.9% placebo-treated subjects (Section SVII.3.1). Though imetelstat treated subjects had a higher rate of hepatic events overall compared with placebo, the difference was primarily driven by the high incidence of increased transaminases (ALT and AST) and ALP increased. Excluding these events reflecting laboratory abnormalities, the incidence rate of hepatic TEAEs was similar between groups with 16.9% with imetelstat versus 15.3% with placebo at Primary Analysis and 16.9% with imetelstat versus 16.9% with placebo at Final Analysis. Incidence was also similar between imetelstat and placebo groups for hyperbilirubinaemia and bilirubin conjugated increased (9.3% versus 10.2%) and gamma-glutamyltransferase increased (3.4% versus 3.4%).

The majority of hepatic adverse events were non-serious, Grade 1 or Grade 2 in severity, and resolved within 2 weeks. The median time to onset of the Grade 3/4 hepatic TEAEs was 198 days (range: 1 to 633 days) in the imetelstat group and 113 days (range: 85 to 330 days) in the placebo group (Table taesi03a). Seventeen (14.4%) subjects had hepatic TEAEs considered related to imetelstat by the investigator, 3 (2.5%) of which were Grade 3/4 (Table taesi01a). In the placebo group, 4 (6.8%) subjects had hepatic TEAEs considered related to imetelstat, 2 (3.4%) of which were Grade 3/4 (Table taesi01a). No subjects discontinued study treatment due to a hepatic TEAE in either treatment group (Table taesi01a).

Based on laboratory assessments, the maximum worsening from baseline for liver function abnormalities in imetelstat and placebo treated subjects in Study MDS3001 is presented in Table 21. Few subjects had worsening to Grade ≥ 3 selected hepatic enzyme parameters based on laboratory assessment. All cases of Grade 3/4 laboratory hepatic enzyme elevations in the imetelstat and placebo groups resolved to Grade ≤ 2, most in less than 4 weeks (Table tlab05d). The median duration of all hepatic enzyme elevations was < 2 weeks in the imetelstat group and < 5 weeks in the placebo group (Table tlab04m). No subjects met Hy's law criteria.

These results were consistent over time, as demonstrated by the additional 1-year of data provided in the Final Analysis of MDS3001 Phase 3 study (Section SVII.3.1).

Risk-benefit impact:

The benefit of imetelstat as a treatment for adult patients with transfusion-dependent anaemia due to lower risk MDS, a life-threatening condition with an unmet clinical need, is considered to outweigh the potential risk of severe hepatotoxicity for which a causal relationship has not been determined with imetelstat at this time and can be managed in clinical practice through healthcare professional awareness of the possible risk, monitoring and dose modifications based on severity grade and occurrence.

Severe hepatotoxicity will be further characterised in Study MDS3001 Extension Phase (Part III).

Important Potential Risk 2: Embryo-foetal toxicity

Embryo-foetal toxicity is an important potential risk of imetelstat.

In embryo-foetal developmental toxicity studies, imetelstat was not teratogenic (Section Part II: Module SII). While embryo-lethal effects were observed after administration of 28.2 mg/kg imetelstat to pregnant mice and rabbits, such effects were observed at maternal exposures that exceeded human exposures at the recommended clinical dose. These data, together with the genotoxicity studies that show that imetelstat does not pose a risk for mutagenicity or clastogenicity, suggest that imetelstat is unlikely to cause teratogenicity, but may cause embryonic or foetal loss when administered to a pregnant woman.

Similar to the majority of investigative clinical trials, females who were pregnant or who were planning to become pregnant while enrolled in the study or within 1 month after the end of dosing were excluded from participation in study MDS3001 (Section SIV.1). Likewise, men who were planning to father a child while enrolled in the study or within 3 months after the end of dosing were excluded. These exclusion criteria, together with the additional study requirements relating to pregnancy prevention (Section SVII.3.2), meant there was no exposure to imetelstat during pregnancy in the clinical development programme.

In clinical practice, use of imetelstat in women of childbearing potential is expected to be limited given that the median age at diagnosis of MDS is over 70 years old and less than 10% of patients are younger than 50 years old (Neukirchen, 2011; Fenaux, 2021), but use in this population may occur. In study MDS3001 subjects of childbearing potential were included but numbers were limited; 23% subjects treated with imetelstat (N=118) were < 65 years (range: 44, 87 years) and 15% placebo subjects were < 65 years (N=59) (range: 39, 85 years) (Table 4), which reflects the patient population.

Risk-benefit impact:

The benefit of imetelstat as a treatment for adult patients with transfusion-dependent anaemia due to lower risk MDS, a life-threatening condition with an unmet clinical need, is considered to outweigh the potential risk of using imetelstat in pregnancy which has yet to be confirmed in humans and can be managed in clinical practice by adhering to the guidance in the SmPC and PL that warns about the potential risk to a foetus and recommends pregnancy testing prior to use and use of effective contraception.

Missing information 1: Long-term safety

To support the safety of imetelstat for the treatment of adult patients with transfusion-dependent anaemia due to lower risk MDS, the clinical development programme includes pivotal Phase 2/3 study (MDS3001), and four additional studies in haematology indications, including MDS, MF, ET or PV and MM (MYF2001, CP14B013, CP14B015, CP14B019) (Section Part II: Module SIII). Analyses were performed for three safety groupings, Group A, Group B, and Group C (Table 2). Duration of exposure for these study populations is presented in Table 3 (Section Part II: Module SIII) with median duration of exposure presented in Section SVII.3.2. Based on the available data, it is acknowledged that long-term safety data for imetelstat are limited. However, analysis of TEAEs in these subjects showed that the incidence of TEAEs was consistent over the course of treatment with no apparent increase in frequency over time and no indication of late onset or cumulative toxicities (Module 2.7.4, Section 2.1.2.3.1). These results were consistent over time, as demonstrated by the additional 1 year of data in the MDS3001 Phase 3 Final Analysis (cutoff date 13 October 2023) which were in line with the Primary Analysis of the Phase 3 data (cutoff date 13 October 2022). No new safety signals were identified.

Risk-benefit impact:

The benefit of imetelstat as a treatment for adult patients with transfusion-dependent anaemia due to lower risk MDS, a life-threatening condition with an unmet clinical need, is considered to outweigh long-term safety, an area of missing information where data are limited but where the safety profile is expected to be the same as observed thus far in the clinical development programme.

Long-term safety will be further characterised in Study MDS3001 Extension Phase (Part III).

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Severe bleeding

Potential mechanisms:

The mechanism by which imetelstat may cause severe bleeding is unknown but it could be related to thrombocytopenia. Thrombocytopenia is a known ODN class effect and an additional potential mechanism of imetelstat-induced, reversible thrombocytopenia is the on-target effect of imetelstat on haematopoietic progenitor cells (HPCs). Imetelstat selectively affects the proliferation of malignant HPCs and leukemic stem cells while having limited effects on normal HPCs. In a well-established system of ex vivo megakaryopoiesis, imetelstat has multiple effects on maturation of malignant megakaryocytes (MK, the immature platelet precursors) and depletes these malignant cells, while only delaying normal MK maturation. This leads to the eventual reduction of the pool of mature MK manifesting as thrombocytopenia. This MK maturation is restored 3 days after drug withdrawal (Mosoyan, 2017).

Another potential mechanism for the bleeding observed not associated with thrombocytopenia may relate to prolongation of aPTT. In the nonclinical programme, haemorrhage was observed in multiple tissues in mice and monkeys at high imetelstat doses/exposures, consistent with the known ODN class effect of inhibition of the intrinsic coagulation pathway, reflected by prolongation of aPTT (Section Part II: Module SII). In the early clinical development programme, serial aPTT was measured following infusion in Phase 1 studies based on nonclinical toxicology findings that showed aPTT prolongations and bleeding, and transient Grade 1 and 2 aPTT prolongations were observed in subjects treated with imetelstat. The aPTT prolongations did not have significant clinical sequelae. While aPTT and prothrombin time were not routinely measured in the Phase 2 studies, no bleeding events associated with coagulation abnormalities were reported in these studies.

In Phase 3 MDS3001, most subjects treated with imetelstat were within normal range at baseline for aPTT and prothrombin INR (92.8% and 76.6%, respectively) and remained within normal range during treatment (75.3% and 84.0%, respectively) (Table tlab06g; Table tlab02g). A maximum CTCAE grade of Grade 3 for aPTT or prothrombin INR was only reported for 1 subject each. Similarly in the placebo group, most subjects were within normal range at baseline for aPTT and prothrombin INR (90.0% and 73.9%, respectively) and remained within normal range during treatment (82.0% and 71.7%, respectively). Grade 3 aPTT and Grade 3 prothrombin time were reported for 2 subjects and 1 subject, respectively. Similar trends in aPTT levels over time were observed in the Phase 3 imetelstat and placebo groups, with an early increase followed by relative stabilisation above baseline with some peaks over the course of the study (Module 2.7.4, Section 3.1.2). Similar trends were observed across dose groups in Group C for aPTT and prothrombin time levels over time.

Evidence source and strength of evidence:

The mechanism by which imetelstat may cause severe bleeding is unknown but it could be related to thrombocytopenia. Thrombocytopenia is a recognised and expected effect of imetelstat based on its mechanism of action. In study MDS3001, bleeding events occurred in 21.2% of subjects treated with imetelstat and in 11.9% of placebo-treated subjects. The

bleeding events that were observed in this study were mainly of mild or moderate severity with very few severe or serious events in subjects treated with imetelstat, and these were not considered related to treatment. Bleeding events in other studies were also generally of mild or moderate severity with very few severe or serious events and the majority were unrelated to imetelstat treatment.

Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice.

Characterisation of the risk:

In the nonclinical programme, haemorrhage was observed in multiple tissues in mice and monkeys, at high imetelstat doses/exposures (Section Part II: Module SII), consistent with the known ODN class effect of inhibition of the intrinsic coagulation pathway, reflected by prolongation of aPTT, considered the likely main cause of the haemorrhages.

In pivotal Phase 3 study MDS3001 patients were required to have platelets $\geq 75 \times 10^9$/L independent of platelet transfusion support for inclusion in the study. As patients with severe thrombocytopenia are at higher risk of haemorrhage, these events were closely monitored. Bleeding TEAEs were identified using the MedDRA Standardised MedDRA query (SMQ) Haemorrhages.

In Phase 3 study MDS3001 (Group A), bleeding TEAEs (any grade) were reported in 25 (21.2%) subjects in the imetelstat, with Grade 3/4 events reported in 3 (2.5%) subjects (Table 15). The most commonly reported bleeding event in the imetelstat group was epistaxis (7 [5.9%] subjects), followed by haematoma (6 [5.1%] subjects). Three subjects had events considered related to imetelstat (gingival bleeding, epistaxis, and prothrombin time prolonged), all of which were Grade 1 (MDS3001 CSR [Phase 3]/ Listing lsfae03). One subject had a Grade 3 event (haematuria; SAE, associated with a bladder papilloma and Grade 2 thrombocytopenia), and 2 subjects had Grade 4 events, both SAEs (1 subject with gastrointestinal haemorrhage on Study Day 25 following hospitalization for an unrelated left femoral fracture who had concurrent Grade 1 thrombocytopenia, and 1 subject with oesophageal varices haemorrhage on Study Day 633) (Listing lae02c). All of these Grade 3/4 bleeding events were considered not related to imetelstat by the investigator (Table tae03g; Table tae05a).

In the placebo group, bleeding TEAEs (any grade) were reported in 7 (11.9%) subjects, and Grade 3/4 events were reported in 1 (1.7%) subject (Table 15). The most commonly reported bleeding event was contusion (3 [5.1%] subjects) (Listing lae02d). One subject had 2 events of Grade 1 contusion considered related to treatment. There were no other treatment-related events. One subject had 2 events of Grade 3 small intestinal haemorrhage (SAE, not related), and the time to the first event was 209 days after first dose (Table taesi03d).

The median time to onset of the Grade 3/4 bleeding events in 3 subjects treated with imetelstat was 32 days (range: 24 to 633 days) and the time to onset for the Grade 3/4 bleeding event in the 1 subject treated with placebo was 209 days (Table taesi03d). All these Grade 3/4 bleeding events were serious and there were no Grade 5 bleeding TEAEs (Table tae05a). In the imetelstat group, 1 subject discontinued treatment due to an SAE of unrelated Grade 4 gastrointestinal haemorrhage (mentioned above) (Table tae02p), 2 subjects had study cycle delays due to epistaxis (Table tae02y); no subjects had bleeding events that led to study treatment reduction (Table tae02s). In the placebo group, the Grade 3/4 small intestinal haemorrhage led to cycle delay (Table tae02y); there were no bleeding events that led to study treatment discontinuations or dose reductions (Table tae02p; Table tae02s).

Table 15: Bleeding TEAEs - Phase 3 Study MDS3001 (Group A)

	Imetelstat (N=118) n (%)			Placebo (N=59) n (%)		
Preferred Term	**Any Grade**	**Grade 3/4**	**SAE**	**Any Grade**	**Grade 3/4**	**SAE**
Subjects with ≥ 1 bleeding TEAE	25 (21.2%)	3 (2.5%)	3 (2.5%)	7 (11.9%)	1 (1.7%)	1 (1.7%)
Epistaxis	7 (5.9%)	0	0	0	0	0
Haematoma	6 (5.1%)	0	0	0	0	0
Ecchymosis	2 (1.7%)	0	0	1 (1.7%)	0	0
Gastrointestinal haemorrhage	2 (1.7%)	1 (0.8%)	1 (0.8%)	0	0	0
Haematuria	2 (1.7%)	1 (0.8%)	1 (0.8%)	0	0	0
Haemorrhoidal haemorrhage	2 (1.7%)	0	0	0	0	0
Contusion	1 (0.8%)	0	0	3 (5.1%)	0	0
Gingival bleeding	1 (0.8%)	0	0	0	0	0
International normalised ratio increased	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
Puncture site haemorrhage	1 (0.8%)	0	0	0	0	0
Melaena	0	0	0	1 (1.7%)	0	0
Retinal haemorrhage	0	0	0	1 (1.7%)	0	0
Small intestinal haemorrhage	0	0	0	1 (1.7%)	1 (1.7%)	1 (1.7%)

IV = intravenous(ly); MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Notes: TEAEs are defined as events that occur or worsen after the first dose of study drug.
Percentages calculated with the number of subjects in each treatment group as denominator.
MedDRA v25.0 was used for TEAE coding.
Source data: Table taesi02g; Table taesi04d
Clinical cut-off date: 13 Oct 2022 for MDS3001.

To evaluate whether bleeding events were associated with severe thrombocytopenia, the temporal association between decreased Grade 3/4 platelet counts based upon laboratory results and concurrent bleeding AEs was evaluated and found that of the 77 (65.3%) subjects with Grade 3/4 decreased platelets while on imetelstat treatment, 9 (7.6%) subjects had a Grade 1/2 bleeding event within 7 days of the laboratory result (Table 16). However, none of the subjects in the imetelstat group had Grade 3/4 or serious bleeding events associated with Grade 3/4 decreased platelets. In the placebo group, 5 (8.5%) subjects had Grade 3/4 decreased platelets while on study treatment, and none had a bleeding event within 7 days of the laboratory result.

Table 16: Subjects with Grade 3/4 Decrease in Platelets and Bleeding TEAEs Within 7 Days - Phase 3 Study MDS3001 (Group A)

	Imetelstat (N=118) n (%)	Placebo (N=59) n (%)
Number of subjects with Grade 3/4 platelets on treatment, n (%)	77 (65.3%)	5 (8.5%)
Grade 3/4 platelets with any bleeding events within +/- 7 days	9 (7.6%)	0
With Grade 1/2 bleeding events	9 (7.6%)	0
With Grade 3/4 bleeding events	0	0
With serious bleeding events	0	0

IV = intravenous(ly); MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Notes: TEAEs are defined as events that occur or worsen after the first dose of study drug.
Percentages calculated with the number of subjects in each treatment group as denominator.
MedDRA v25.0 was used for TEAE coding.
Source data: Table tlab07a
Clinical cut-off date: 13 Oct 2022 for MDS3001.

The data from the MDS3001 Final Analysis (cutoff date 13 October 2023) were in line with the Primary Analysis of the Phase 3 data described above (cutoff date 13 October 2022). Bleeding TEAEs (any grade) were reported in 22 (22.9%) subjects in the imetelstat group and 7 (11.9%) subjects in the placebo group (Table tsfaesi02_p2). The majority of bleeding events in the imetelstat group were Grade 1/2 and most were reported as not related to study drug by the investigator (Table tsfaesi02_p2; Table tsfae04_p2). The additional 2 subjects in the imetelstat group at Final Analysis had non-serious Grade 1 events of epistaxis reported as not related to imetelstat for 1 event and probably related for the other event. The incidence of SAEs of bleeding events was low and similar between imetelstat and placebo groups (4 [3.4%] subjects versus 1 [1.7%] subject, respectively), and also for Grade 3/4 events (3 [2.5%] subjects versus 1 [1.7%] subject, respectively) (Table tsfaesi07_p2; Table tsfaesi02_p2). In addition, there were no Grade 3/4 bleeding events in context of concurrent (±7 days) Grade 3/4 thrombocytopenia and no fatal bleeding events in either group (Table tsflb41_p2; Table tsfaesi07_p2).

Similar trends were observed in the Phase 2 supportive study MDS3001 (Group B) (Module 2.7.4, Section 2.1.7.2.2.2).

In the Group C pool (N=391), bleeding TEAEs of any grade were reported in 127 (32.5%) subjects treated with imetelstat, and Grade 3/4 bleeding TEAEs were reported in 23 (5.9%) subjects (Table taesi02i). As in Groups A and B, the most commonly reported bleeding event was epistaxis (10.7%). Thirty-six subjects (9.2%) had bleeding events considered related to imetelstat, most of which were Grade 1 or 2, and a majority were epistaxis or contusion (Table taesi01i; Listing lae02d).

The most commonly reported Grade 3/4 bleeding events were epistaxis (1.0%), oesophageal varices haemorrhage (0.8%), and haematoma, haematuria, and blood loss anaemia (0.5%) (Table taesi02i). Most of the Grade 3/4 events were SAEs (Table taesi04f). The median time to onset of Grade 3/4 bleeding events in the overall Group C pool was 233.0 days (range: 24 to 1018 days) (Table taesi03f).

There were 2 Grade 5 bleeding events of haemorrhage in the Group C pool (Table tae05c; Listing lae02c) including a subject who had a related serious Grade 5 bleeding TEAE of haemorrhage that led to treatment discontinuation in the > 7.1 mg/kg group (from the MYF2001 8.9 mg/kg arm), and a subject who had an unrelated serious Grade 5 bleeding event of oesophageal varices haemorrhage in the 7.1 mg/kg group (from the CP14B015 7.1 mg/kg arm).

In the Group C pool, 2 subjects discontinued treatment due to Grade 3/4 bleeding events: 1 subject in the 7.1 mg/kg group (from MDS3001 Phase 3 imetelstat arm) due to an SAE of unrelated Grade 4 gastrointestinal haemorrhage, and 1 subject in the > 7.1 mg/kg group (from MYF2001 8.9 mg/kg arm) due to SAE of related Grade 3 aneurysm ruptured (right groin) (Listing lae02e). No subject in the Group C pool had a dose reduction due to a bleeding event (Table tae02u). Cycle delay was not collected evenly across studies in Group C and is not reported.

Among the 198 (50.6%) subjects with Grade 3/4 decreased platelets while on study treatment within ±7 days of the laboratory result, 32 (8.2%) subjects had a Grade 1/2 bleeding event, 4 (1.0%) subjects had a Grade 3/4 bleeding event, and 7 (1.8%) subjects had a serious bleeding event (Table 17).

Table 17: Subjects with Grade 3/4 Decrease in Platelets and Bleeding TEAEs Within 7 Days - Studies Phase 2 and 3 MDS3001, CP14B013, CP14B015, CP14B019, MYF2001 (Group C)

	Imetelstat			
	< 7.1 mg/kg[a] Q4W (N=48)	**7.1 mg/kg[b] Q4W (N=204)**	**> 7.1 mg/kg[c] Q4W (N=139)**	**Total Pooled (N=391)**
Number of subjects with Grade 3/4 platelets on treatment, n (%)	14 (29.2%)	120 (58.8%)	64 (46.0%)	198 (50.6%)
Grade 3/4 platelets with any bleeding events within +/- 7 days	2 (4.2%)	18 (8.8%)	16 (11.5%)	36 (9.2%)
With Grade 1/2 bleeding events	2 (4.2%)	16 (7.8%)	14 (10.1%)	32 (8.2%)
With Grade 3/4 bleeding events	0	2 (1.0%)	2 (1.4%)	4 (1.0%)
With serious bleeding events	0	2 (1.0%)	5 (3.6%)	7 (1.8%)

Q4W = once every 4 weeks; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event
Group C includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled), and Phase 2 open-label studies MYF2001, CP14B013, CP14B015, and CP14B019.
[a] MYF2001 4.4 mg/kg arm only.
[b] CP14B019 arm E and G; MDS3001 Phase 2 and 3 (Imetelstat); CP14B015 and CP14B013 7.1 mg/kg arm.
[c] CP14B019 arm A, B, D, and F; CP14B015, CP14B013 and MYF2001 8.9 mg/kg arm.
Notes: TEAEs are defined as events that occur or worsen after the first dose of study drug.
Percentages calculated with the number of subjects in each treatment group as denominator.
MedDRA v25.0 was used for TEAE coding.
Source data: Table tlab07c
Clinical cut-off date: 13 Oct 2022 for MDS3001.

Risk factors and risk groups:

Thrombocytopenia is associated with a risk of bleeding. While the correlation of severity of thrombocytopenia and bleeding risk is uncertain, spontaneous bleeding can occur with a

platelet count under 10 x 10^9/L and surgical bleeding with counts below 50 x 10^9/L (Jinna, 2022).

Preventability:

Imetelstat is a product subject to restricted medical prescription and is administered under supervision of experienced healthcare professionals. As part of this close management, early detection and treatment of severe bleeding per institutional standards would be expected, should it occur. Therefore, routine risk minimisation measures that comprise guidance in the SmPC, PL, and restricted medical prescription are considered sufficient to manage this risk in clinical practice.

Healthcare professionals treating patients with MDS are aware of the risk of bleeding in patients with severe thrombocytopenia. The imetelstat SmPC includes a warning that new or worsening Grade 3 or Grade 4 thrombocytopenia has been observed in the clinical studies and that these patients should be monitored for bleeding events as a precaution. 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 thrombocytopenia or as clinically indicated. Dose modifications for thrombocytopenia include delaying treatment until platelets are ≥ 50 x 10^9/L and resuming at the same or reduced dose as recommended based on severity grade and occurrence. Treatment with imetelstat should be permanently discontinued if the patient cannot tolerate the lowest dose level of 4.4 mg/kg. The need for platelet transfusions should be assessed as clinically appropriate. Patients should be advised to report any signs or symptoms of bruising or bleeding immediately. The next dose should be delayed and resumed at the same or reduced dose as recommended. Furthermore, while severe bleeding events have not been observed with imetelstat, epistaxis, haematoma, gastrointestinal bleeding, and haematuria are listed as adverse reactions in the SmPC and PL to alert healthcare professionals and patients, respectively, that these adverse reactions have occurred in clinical trials and that bleeding events may occur in clinical practice.

The imetelstat PL provides guidance for the patient to talk to their doctor or nurse before they are given Rytelo if they have recently had reactions such as bruising more easily, bleeding more than expected, nosebleeds, blood in the urine or stool, or any other signs of bleeding which may worsen if their platelet counts decrease after they have received Rytelo. Patients are advised that their doctor or nurse will monitor them for specific side effects and do blood tests to keep control of their blood cell counts before every administration of Rytelo and weekly after their first two administrations of Rytelo. Low blood levels of platelets (thrombocytopenia) are a very common serious side effect which may include the following symptoms: bruising more easily or bleeding more than expected, a bruise or collection of blood (haematoma), prolonged bleeding from cuts, nosebleed, blood in the gut, urine or stool or black stool.

Impact on the risk-benefit balance of the product:

Transfusion-dependent anaemia due to lower risk MDS is a serious and life-threatening condition with limited treatment options and no established standard of care (Section Part II: Module SI).

Bleeding events were closely monitored in the clinical studies as thrombocytopenia is a recognised and expected adverse reaction of imetelstat related to its on-target effect on malignant HPCs, and the risk of bleeding in patients with severe thrombocytopenia is recognised. The bleeding events that were observed in the clinical studies were mainly of

Grade 1 or 2 severity with very few ≥ Grade 3 TEAEs or SAEs. None of the Grade 3/4 bleeding events were considered related to imetelstat treatment.

The benefit of imetelstat as a treatment for adult patients with transfusion-dependent anaemia due to lower risk MDS is considered to outweigh the risk of severe bleeding which can be managed in clinical practice through healthcare professional awareness of the risk and through patient monitoring and provision of supportive care.

Severe bleeding will be further characterised in Study MDS3001 Extension Phase (Part III).

Public health impact:

Healthcare professionals treating patients with MDS are aware of the risk of bleeding in patients who experience severe thrombocytopenia. Since MDS is a rare condition (Section Part II: Module SI) and severe bleeding, should it occur, can be managed in clinical practice through healthcare professional awareness of the risk and through patient monitoring and provision of supportive care, the potential impact on public health is expected to be low.

Important Identified Risk: Severe infections

Potential mechanisms:

Infections are a potential outcome of neutropenia. Neutropenia is an expected effect of imetelstat and an indicator of on-target activity, as imetelstat selectively affects the proliferation of malignant HPCs and leukemic stem cells while sparing normal HPCs. Neutropenia is also a prominent manifestation of the ineffective haematopoiesis associated with MDS.

Evidence source and strength of evidence:

Infections are a potential outcome of neutropenia. Neutropenia is a recognised and expected effect of imetelstat based on its mechanism of action.

In study MDS3001, infections occurred in 42.4% subjects treated with imetelstat and in 33.9% placebo-treated subjects. The infections were mainly of mild or moderate severity and not related to treatment; severe infections occurred in 10.2% subjects treated with imetelstat and in 13.6% subjects treated with placebo. Infections in other studies were also generally of mild or moderate severity with few severe or serious events and the majority were unrelated to imetelstat treatment. Infections were managed in clinical trials with dose modifications, cycle delays and supportive care.

Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice.

Characterisation of the risk:

In pivotal Phase 3 study MDS3001 patients were required to have absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L independent of growth factor support for inclusion in the study. As it is recognised that patients with severe neutropenia have a high risk of developing infections following the onset of severe neutropenia, these events were closely monitored. Infection TEAEs were identified using the MedDRA SOC Infections and infestations.

In the imetelstat group in Phase 3 MDS3001, treatment-emergent infections (any grade) were reported in 42.4% (50 of 118) subjects, and 12 (10.2%) subjects had Grade 3/4 infections (Table 18). The most commonly reported infection in the imetelstat group was COVID-19 (18 [15.3%] subjects), followed by urinary tract infection (7 [5.9%] subjects) and pneumonia

(4 [3.4%] subjects). Four (3.4%) subjects had Grade 4 infections (1 subject each with COVID-19 pneumonia and Enterococcal sepsis, and 2 subjects with sepsis, 1 of which was considered related to study treatment) (Listing lae2e). One subject had a Grade 5 infection of sepsis considered not related to study treatment after almost two years on treatment with imetelstat (Table tae05a; Table tae05d). The subject had no prior Grade 3/4 neutropenia until 11 days prior to the onset of sepsis when the neutrophil value was Grade 4. The investigator assessed the sepsis as related to the underlying MDS and other conditions including cardiac disease and pulmonary infection. Serious infections were reported in 14 (11.9%) subjects, the most common of which was pneumonia (3 [2.5%] subjects) (Table tae02g).

The median time to onset of first Grade 3/4 infection in the imetelstat group was 142.0 days (range: 20 to 644 days) (Table taesi03j). Six (5.1%) subjects had infections considered related to study treatment, including sinusitis, pneumonia bacterial, pneumonia, renal abscess, sepsis, urinary tract infection, and neutropenic sepsis (Table tae02j).

In the placebo group, 20 (33.9%) subjects had infections, including 8 (13.6%) subjects with Grade 3/4 infections (Table 18). The most commonly reported infection was COVID-19 (4 [6.8%] subjects). One subject had a Grade 4 infection of listeriosis, considered not related to study treatment (Listing lae02e). There were no infections considered related to study treatment in the placebo group (Table tae02j), and no Grade 5 infections (Table tae05a). Serious infections were reported in 8 (13.6%) subjects, the most common of which was COVID-19 pneumonia (3 [5.1%] subjects) (Table tae02g). The median time to onset of first Grade 3/4 infection in the placebo group was 61.5 days (range: 15 to 638 days) (Table taesi03j).

Sepsis events were reported in 5 subjects in the imetelstat group, including SAEs of Grade 5 sepsis (not related; described above), Grade 4 sepsis (related; led to discontinuation of imetelstat), Grade 4 enterococcal sepsis (not related), Grade 3 Escherichia sepsis (not related), and Grade 3 neutropenic sepsis (related, led to dose reduction) (Table taesi02s; Listing lae02e). There were no sepsis events reported in the placebo group.

Table 18: Infection TEAEs Reported in ≥ 5% of Either Group or Reported Serious in Any Subject - Phase 3 Study MDS3001 (Group A)

	Imetelstat (N=118) n (%)			Placebo (N=59) n (%)		
Preferred Term	**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

	Imetelstat (N=118) n (%)			Placebo (N=59) n (%)		
Preferred Term	**Any Grade**	**Grade 3/4**	**SAE**	**Any Grade**	**Grade 3/4**	**SAE**
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%)

IV = intravenous(ly); MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Notes: TEAEs are defined as events that occur or worsen after the first dose of study drug.
Percentages calculated with the number of subjects in each treatment group as denominator.
MedDRA v25.0 was used for TEAE coding.
Source data: Table taesi02s; Table taesi02g
Clinical cut-off date: 13 Oct 2022 for MDS3001.

In the imetelstat group, infections led to cycle delay in 17 (14.4%) subjects, most commonly COVID-19 (9 [7.6%] subjects) (Table tae02y). One subject had a dose reduction due to an SAE of Grade 3 neutropenic sepsis (Table tae02s; Listing lae02e). One subject discontinued study treatment due to 2 infection events (nonserious Grade 3 renal abscess and serious Grade 4 sepsis; both related to treatment) (Table tae02p; Listing lae02e). In the placebo group, 7 (11.9%) subjects had cycle delays due to infections, most commonly COVID-19 (2 [3.4%] subjects) (Table tae02y); no subjects had a dose reduction or discontinued study treatment due to an infection (Table tae02s; Table tae02p).

An evaluation of the temporal association between decreased Grade 3/4 neutrophil counts based upon laboratory results and concurrent infection AEs found that of the 85 (72.0%)subjects with Grade 3/4 decreased neutrophils while on imetelstat treatment, 9 (7.6%) subjects had an infection within 7 days of the laboratory result (Table 19). Three subjects with sepsis events had Grade 3/4 infections associated with Grade 3/4 neutropenia, all of which were reported as SAEs (Listing llab05a). In the placebo group, among the 4 (6.8%) subjects with Grade 3/4 decreased neutrophils while on study treatment, 1 (1.7%) subject had a Grade 4 infection within 7 days of the laboratory result (Table 19; Listing llab05a).

Table 19: Subjects with Grade 3/4 Decrease in Neutrophils with Infection TEAEs Within 7 Days Phase 3 Study MDS3001 (Group A)

	Imetelstat (N=118) n (%)	Placebo (N=59) n (%)
Number of subjects with Grade 3/4 neutrophils on treatment, n (%)	85 (72.0%)	4 (6.8%)
Grade 3/4 neutrophils with any infection events within +/- 7 days	9 (7.6%)	1 (1.7%)
With Grade 1/2 infection events	6 (5.1%)	0
With Grade 3/4 infection events	3 (2.5%)	1 (1.7%)
With serious infection events	3 (2.5%)	1 (1.7%)

IV = intravenous(ly); MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Notes: TEAEs are defined as events that occur or worsen after the first dose of study drug.
Percentages calculated with the number of subjects in each treatment group as denominator.
MedDRA v25.0 was used for TEAE coding.
Source data: Table tlab07a
Clinical cut-off date: 13 Oct 2022 for MDS3001.

The data from the MDS3001 Final Analysis (cutoff date 13 October 2023) were in line with the Primary Analysis of the Phase 3 data described above (cutoff date 13 October 2022). Infection TEAEs (any grade) were reported in 56 (47.5%) subjects in the imetelstat group and 20 (33.9%) subjects in the placebo group (Table tsfae05_p2). The majority of infections were Grade 1/2, and most were reported by the investigator as not related to treatment (Table tsfae05_p2; Table tsfae04_p2). The additional 6 subjects in the imetelstat group at Final Analysis had non-serious Grade 1/2 events of infections (PTs: COVID-19, Urinary tract infection, Respiratory tract infection viral, Nasopharyngitis, Viral infection, and Wound infection [1 subject each]), all reported by the investigator as not related to imetelstat. The incidence of SAEs of infections was similar between the imetelstat and placebo groups (14 [11.9%] subjects versus 8 [13.6%] subjects, respectively), as was the incidence of Grade 3/4 infections (12 [10.2%] subjects and 7 [11.9%] subjects, respectively (Table tsfae09_p2; Table tsfae05_p2). One subject had Grade 5 pneumonia in the placebo group, reported by the investigator as possibly related to treatment. There was no additional fatality in the imetelstat group at Final Analysis. Consistent with the Primary Analysis, the incidence was similar between groups for Grade 3/4 infections in context of concurrent (±7 days) Grade 3/4 neutropenia (3 [2.5%] subjects versus 1 [1.7%] subject, respectively) (Table tsflb41_p2).

Similar trends were observed in the Phase 2 supportive study MDS3001 (Module 2.7.4, Section 2.1.7.3.2.2).

In the Group C pool (N=391), infection TEAEs of any grade were reported in 186 (47.6%) subjects treated with imetelstat and 53 (13.6%) subjects had Grade 3/4 infections including Grade 3/4 related to treatment in 16 (4.1%) subjects (Table taesi02u; Table taesi01u). The most commonly reported infection was urinary tract infection (33 [8.4%] subjects), followed by upper respiratory tract infection (31 [7.9%] subjects), pneumonia (26 [6.6%] subjects), and nasopharyngitis (19 [4.9%] subjects) (Table taesi02u). The median time to first Grade 3/4 infection was 97.0 days (range: 1 to 862 days) (Table taesi03l). Thirty-four (8.7%) subjects had infections considered related to study treatment, including pneumonia, urinary tract infection, sinusitis, upper respiratory tract infection, Herpes zoster, and nasopharyngitis reported in more than 1 subject each (Table tae02l). Serious infections were reported in 53 (13.6%) subjects, the most common of which was pneumonia (17 [4.3%] subjects) (Table tae02i).

Six subjects discontinued imetelstat due to infection AEs, including 1 subject in the < 7.1 mg/kg group with a fatal TEAE of sepsis, and 4 subjects with 5 events in the 7.1 mg/kg group (Grade 4 sepsis and Grade 3 renal abscess in 1 subject, and Grade 4 septic shock, Grade 3 pneumonia, and Grade 3 osteomyelitis in 1 subject each), and 1 subject in the > 7.1 mg/kg group with Grade 4 skin infection (Table tae02r; Listing lae02c; Listing lae2e). Two subjects had dose reductions due to an infection event: 1 subject with Grade 3/4 neutropenia sepsis in the 7.1 mg/kg group and 1 subject in the > 7.1 mg/kg group with Grade 3/4 lower respiratory tract infection viral (Table tae02u).

An evaluation of the temporal association between decreased Grade 3/4 neutrophil counts based upon laboratory results and concurrent infection AEs found that of the 197 (50.4%) subjects with Grade 3/4 decreased neutrophils while on imetelstat treatment, 31 (7.9%) subjects had an infection within 7 days of the laboratory result (Table 20). There were 12 (3.1%) subjects who had a Grade 3/4 infection and 8 (2.0%) subjects who had a serious infection within 7 days of decreased Grade 3/4 neutrophil counts.

Table 20: Subjects with Grade 3/4 Decrease in Neutrophils with Infection TEAEs Within 7 Days - Studies Phase 2 and 3 MDS3001, CP14B013, CP14B015, CP14B019, MYF2001 (Group C)

	Imetelstat			
	< 7.1 mg/kg[a] Q4W (N=48)	**7.1 mg/kg[b] Q4W (N=204)**	**> 7.1 mg/kg[c] Q4W (N=139)**	**Total Pooled (N=391)**
Number of subjects with Grade 3/4 neutrophils on treatment, n (%)	6 (12.5%)	135 (66.2%)	56 (40.3%)	197 (50.4%)
Grade 3/4 neutrophils with any infection events within +/- 7 days	1 (2.1%)	21 (10.3%)	9 (6.5%)	31 (7.9%)
With Grade 1/2 infection events	1 (2.1%)	17 (8.3%)	5 (3.6%)	23 (5.9%)
With Grade 3/4 infection events	1 (2.1%)	6 (2.9%)	5 (3.6%)	12 (3.1%)
With serious infection events	1 (2.1%)	4 (2.0%)	3 (2.2%)	8 (2.0%)

Q4W = once every 4 weeks; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event
Group C includes Study MDS3001 Phase 2 (single arm, open-label) and Phase 3 (randomised, placebo-controlled), and Phase 2 open-label studies MYF2001, CP14B013, CP14B015, and CP14B019.
[a] MYF2001 4.4 mg/kg arm only.
[b] CP14B019 arm E and G; MDS3001 Phase 2 and 3 (Imetelstat); CP14B015 and CP14B013 7.1 mg/kg arm.
[c] CP14B019 arm A, B, D, and F; CP14B015, CP14B013 and MYF2001 8.9 mg/kg arm.
Notes: TEAEs are defined as events that occur or worsen after the first dose of study drug.
Percentages calculated with the number of subjects in each treatment group as denominator.
MedDRA v25.0 was used for TEAE coding.
Source data: Table tlab07c
Clinical cut-off date: 13 Oct 2022 for MDS3001.

Risk factors and risk groups:

Neutropenia is the main predisposing factor for infection in MDS, but several other immune defects have been reported, including impaired neutrophil function, B-, T- and NK-cell defects and the possible consequences of iron overload due to red blood cell transfusions (Toma, 2012).

Preventability:

Imetelstat is a product subject to restricted medical prescription and is administered under supervision of experienced healthcare professionals. As part of this close management, early detection and treatment of infections per institutional standards would be expected. Therefore, routine risk minimisation measures that comprise guidance in the SmPC, PL, and restricted medical prescription are considered sufficient to manage this risk in clinical practice.

Healthcare professionals treating patients with MDS are aware of the risk of infections in patients with severe neutropenia. The imetelstat SmPC includes a warning that new or worsening Grade 3 or Grade 4 neutropenia has been observed in the clinical studies and that these patients should be monitored for infections including sepsis as a precaution. 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 or as clinically indicated. Dose modifications for neutropenia include delaying treatment until absolute neutrophil counts are $\geq 1.0 \times 10^9$/L and resuming at the same or reduced dose as recommended based on severity grade and occurrence. Treatment with imetelstat should be permanently discontinued if the patient cannot tolerate the lowest dose level of 4.4 mg/kg. 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 infection immediately. The next cycle should be delayed and resumed at the same or reduced dose as recommended. Sepsis and urinary tract infection are included as adverse reactions in the SmPC and PL to alert healthcare professionals and patients, respectively, that infections occurred in clinical trials and may occur in clinical practice.

The imetelstat PL provides guidance for the patient to talk to their doctor or nurse before they are given Rytelo if they have signs of an infection such as fever, chills, feeling unwell, or any other sign of infection, which may worsen if their neutrophil or white blood cell counts decrease after they have received Rytelo. Patients are advised that their doctor or nurse will monitor them for specific side effects and do blood tests to keep control of their blood cell counts before every administration of Rytelo and weekly after their first two administrations of Rytelo. Low blood levels of neutrophils (neutropenia) are a very common serious side effect which may include the following symptoms: fever, cough, sore throat, chills, feeling unwell, or any other sign of infection. Furthermore, an infection in the bloodstream (sepsis) is a common serious side effect that may occur.

Impact on the risk-benefit balance of the product:

Transfusion-dependent anaemia due to lower risk MDS is a serious and life-threatening condition with limited treatment options and no established standard of care (Section Part II: Module SI).

The infections observed in the clinical studies were mainly of Grade 1 or 2 severity and not related to imetelstat treatment. The most commonly reported infection was COVID-19, followed by urinary tract infection, and pneumonia. SAEs of febrile neutropenia (0.8%) and sepsis (1.7%) occurred infrequently. The rate of Grade 3/4 infection was similar between imetelstat and placebo groups in Phase 3 MDS3001 and the infections were manageable with dose modifications, cycle delays and supportive care. Treatment discontinuation was only necessary in a very small number of cases.

The benefit of imetelstat as a treatment for adult patients with transfusion-dependent anaemia due to lower risk MDS is considered to outweigh the risk of severe infections which can be managed in clinical practice through healthcare professional awareness of the possible risk and through patient monitoring and provision of supportive care.

Severe infections will be further characterised in Study MDS3001 Extension Phase (Part III).

Public health impact:

Healthcare professionals treating patients with MDS are aware of the risk of infections in patients with severe neutropenia. Since MDS is a rare condition (Section Part II: Module SI) and as severe infections, should they occur, can be managed in clinical practice through healthcare professional awareness of the risk and through patient monitoring and provision of supportive care, the potential impact on public health is expected to be low.

Important Potential Risk: Severe hepatotoxicity

Potential mechanisms:

Imetelstat is recognised to cause transient hepatic enzyme elevations but a possible causal association has not been established between imetelstat and severe hepatotoxicity. While the mechanism is not known, the transient hepatic enzyme elevations may be a manifestation of immune stimulation.

Imetelstat is expected to be metabolised into smaller fragments predominantly in the tissue through nuclease-mediated cleavage of nucleotide residues from the parent oligonucleotide, consistent with other oligonucleotides (Crooke, 2000; Gaus, 1997; Geary, 2001; Geary, 2009; Griffey, 1997; Yu, 2007); hepatic microsomal enzymes do not play a significant role. Hepatic elimination is known to contribute minimally to the excretion of imetelstat (Module 2.6.4, Section 6). Urinary excretion is the primary source of excretion for the catabolised component fragments of imetelstat as demonstrated in nonclinical ADME studies. Furthermore, hepatic CYP enzymes are not expected to metabolise imetelstat.

In nonclinical studies, along with the kidney, the liver was the second organ with the highest tissue concentrations of [^{35}S]-imetelstat (reflecting either intact/unchanged drug or its fragments) in rodents (Module 2.6.4, Section 4). However, dissimilar to the kidney, where ODNs like imetelstat remain largely confined to the proximal tubules, ODNs in the liver are distributed to all cell types, with the highest levels seen in Kupffer cells which concentrate the ODN in the lysosomes, giving rise to basophilic granules observed under microscopic evaluations.

The cellular infiltrates and possible acute phase response of the liver is postulated to be a manifestation of immune stimulation. Importantly, the imetelstat-related histomorphologic changes in the liver were relatively benign under all treatment conditions in the chronic pivotal studies (Module 2.4, Section 4.2). For both monkeys and mice, chronic administration of dose levels up to 15 and 40 mg/kg/week did not produce any degenerative changes or alterations in clinical or anatomic pathology parameters indicative of hepatic dysfunction or hepatocellular injury (i.e., no substantial elevations in serum transaminases, bilirubin, or ALP). This is consistent with the clinical experience in patients in which no cases of Hy's law have been reported with imetelstat treatment.

It is also of note that hepatic effects are expected in patients with MDS due to iron overload related toxicity, as discussed below.

Evidence source and strength of evidence:

A possible causal association between imetelstat and severe hepatotoxicity has not been established. The transient hepatic enzyme elevations that occur in some patients may be a manifestation of immune stimulation although the mechanism is not known. Hepatic effects are also expected in patients with MDS due to iron overload related toxicity.

In study MDS3001, hepatic adverse events (any grade) were reported in 28.8% subjects treated with imetelstat and in 16.9% placebo-treated subjects. The majority of hepatic adverse events were non-serious, Grade 1 or Grade 2 in severity, and resolved within 2 weeks. No subjects met Hy's law criteria. Hepatic enzyme elevations were managed in clinical trials with cycle delays and reducing the dose.

Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice.

Characterisation of the risk:

In the nonclinical programme, imetelstat-related histomorphologic changes in the liver were relatively benign under all treatment conditions in mice, rats, and monkeys (Section Part II: Module SII). The cellular infiltrates and possible acute phase response of the liver is postulated to be a manifestation of immune stimulation. Importantly there were no degenerative changes or alterations in clinical or anatomic pathology parameters indicative of hepatic dysfunction or hepatocellular injury (i.e., no substantial elevations in serum transaminases, bilirubin and ALP). This is consistent with the clinical experience in which no cases of Hy's law have been reported with imetelstat treatment.

In pivotal Phase 3 study MDS3001 subjects were required to have AST, ALT, and ALP ≤ 2.5 x ULN; 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 red blood cell [RBC] transfusion) for inclusion in the study (Section SIV.1). In this study, liver function abnormalities based on laboratory data including ALT Grade ≥ 3 (> 5.0 x ULN), AST Grade ≥ 3 (> 5.0 x ULN), bilirubin Grade ≥ 3 (> 3.0 x ULN), ALP Grade ≥ 3 (> 5.0 x ULN), ALT or AST Grade ≥ 2 (> 3.0 x ULN) with bilirubin Grade ≥ 2 (> 2.0 x ULN) and all hepatic adverse events were identified as an adverse event of interest (AEI).

During the clinical development programme, hepatotoxicity AEs were identified by searching with the MedDRA Version 20.0 SMQ (Broad) Hepatic Disorders.

As discussed above, hepatic effects are expected in patients with MDS due to iron overload related toxicity. In Phase 3 MDS3001 (Group A), approximately 43% and 35% of subjects in the imetelstat and placebo groups, respectively, had a medical history of conditions associated with iron overload (hyperferritenaemia, haemosiderosis, haemachromotosis, and iron overload), and approximately 14% and 10% of subjects in the 2 groups, respectively, had a history of hepatobiliary disorders (Table tmh01a; MDS3001 CSR [Phase 3]/ Listing lsimh01_p2). In addition, 64% and 63% of subjects, respectively, were on iron chelating agents at the time of entering the study or while on treatment (Table tcm01a).

Hepatic TEAEs (any grade) were reported in 28.8% of subjects in the imetelstat group and 16.9% of subjects in the placebo group in Phase 3 MDS3001 (Table 21). Though imetelstat treated subjects had a higher rate of hepatic events overall compared with placebo, the difference was primarily driven by the high incidence of increased transaminases and ALP increased. Excluding these events reflecting laboratory abnormalities, the incidence rate of hepatic TEAEs was similar between groups with 16.9% with imetelstat versus 15.3% with placebo at Primary Analysis and 16.9% with imetelstat versus 16.9% with placebo at Final Analysis. Incidence was also similar between imetelstat and placebo groups for hyperbilirubinaemia and bilirubin conjugated increased (9.3% versus 10.2%) and gamma-glutamyltransferase increased (3.4% versus 3.4%).

The most commonly reported hepatic TEAEs in both treatment groups were ALT increased (11.9% in the imetelstat group and 6.8% in the placebo group), AST increased (9.3% and 6.8%), and hyperbilirubinaemia (9.3% and 10.2%), respectively. Grade 3/4 hepatic events and SAEs were similar between the groups. Grade 3/4 hepatic events occurred in 6.8% of subjects in the imetelstat group and 5.1% of subjects in the placebo group, with the most common Grade 3/4 hepatic event, ALT increased, occurring in 3 (2.5%) subjects in the imetelstat group and in 2 (3.4%) subjects in the placebo group. Other Grade 3/4 events occurred in 1 subject each in either group. There were no Grade 5 events in either treatment group (Table taesi01a).

There was only 1 hepatic SAE in the imetelstat group (oesophageal varices haemorrhage), and this SAE was not considered related to imetelstat by the investigator (Table taesi04a; Listing lae02b); there were no SAEs in the placebo group.

Table 21: Hepatic TEAEs Phase 3 Study MDS3001 (Group A)

Category Preferred Term	Imetelstat (N=118) n (%)			Placebo (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
Hyperbilirubinaemia	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
Hypoalbuminaemia	0	0	0	1 (1.7%)	0	0

IV = intravenous(ly); MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Notes: TEAEs are defined as events that occur or worsen after the first dose of study drug.
Percentages calculated with the number of subjects in each treatment group as denominator.
MedDRA v25.0 was used for TEAE coding.

Source data: Table taesi02a; Table taesi04a
Clinical cut-off date: 13 Oct 2022 for MDS3001.

The median time to onset of the Grade 3/4 hepatic TEAEs was 198 days (range: 1 to 633 days) in the imetelstat group and 113 days (range: 85 to 330 days) in the placebo group (Table taesi03a). Seventeen (14.4%) subjects had hepatic TEAEs considered related to imetelstat by the investigator, 3 (2.5%) of which were Grade 3/4 (Table taesi01a). In the placebo group, 4 (6.8%) subjects had hepatic TEAEs considered related to imetelstat, 2 (3.4%) of which were Grade 3/4 (Table taesi01a). One subject in the imetelstat group had a dose reduction due to Grade 2 events of ALT increased and AST increased (not related to imetelstat) (Table tae02s; Listing lae02b). Two subjects had dose reductions in the placebo group due to hepatic TEAEs (Grade 2/3 events of ALT increased, AST increased and GGT increased) all of which were considered related to study treatment (Table tae02s; Listing lae02b). No subjects discontinued study treatment due to a hepatic TEAE in either treatment group (Table taesi01a).

Based on laboratory assessments, the maximum worsening from baseline for liver function abnormalities in imetelstat and placebo treated subjects in Study MDS3001 is presented in Table 22. Worsening of ALP from baseline (to any grade) was observed at a higher rate in the imetelstat group compared to the placebo group (44.9% vs 11.9%, respectively). Similarly, worsening of AST from baseline (to any grade) was observed at a higher rate in the imetelstat group compared to placebo (48.3% vs 22% respectively). There was no difference in the rate of worsening bilirubin from baseline (to any grade) between the imetelstat and placebo group (both 39%), and the rates of worsening of ALT from baseline (to any grade) were similar in the imetelstat group and placebo group (39.3% vs 37.3%, respectively).

Table 22: Maximum Post-baseline CTCAE Grade, Worsened Since Baseline for Liver Function Abnormalities in Study MDS3001 (Group A)

Worst on treatment	Imetelstat (N=118) n (%)	Placebo (N=59) n (%)
Alanine Aminotransferase (ALT) (U/L)		
n	117	59
No worsening	71 (60.7%)	37 (62.7%)
1	36 (30.8%)	16 (27.1%)
2	6 (5.1%)	3 (5.1%)
3	4 (3.4%)	3 (5.1%)
4	0	0
Alkaline Phosphatase (ALP) (U/L)		
n	118	59
No worsening	65 (55.1%)	52 (88.1%)
1	48 (40.7%)	7 (11.9%)
2	5 (4.2%)	0
3	0	0
4	0	0
Aspartate Aminotransferase (AST) (U/L)		
n	118	59
No worsening	61 (51.7%)	46 (78.0%)
1	50 (42.4%)	10 (16.9%)

Worst on treatment	Imetelstat (N=118) n (%)	Placebo (N=59) n (%)
2	6 (5.1%)	2 (3.4%)
3	1 (0.8%)	1 (1.7%)
4	0	0
Bilirubin (umol/L)		
n	118	59
No worsening	72 (61.0%)	36 (61.0%)
1	28 (23.7%)	15 (25.4%)
2	17 (14.4%)	7 (11.9%)
3	1 (0.8%)	1 (1.7%)
4	0	0

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous(ly)
Note: Worsened defined as CTCAE grade elevated after baseline. The grade 1-4 summaries categorize subjects according to the maximum grade lab among those labs that have worsened since baseline.
Note: Percentage is calculated from the subjects in each group with a non-missing baseline and post-baseline parameter value as the denominator.
Group A includes Study MDS3001 Phase 3 (randomised, placebo-controlled). Imetelstat dosing was 7.1 mg/kg IV every 4 weeks.
Source data: Table tlab02d
Clinical cut-off date: 13 Oct 2022 for MDS3001

The median time to worsening by at least 1 grade in the imetelstat and placebo groups, respectively, were 3.5 weeks and 8.1 weeks for ALT, 17.0 weeks and 20.0 weeks for ALP, 15.9 weeks and 12.0 weeks for AST, and 2.0 and 5.1 weeks for bilirubin (MDS3001 CSR [Phase 3]/ Table tsflb26a_p2).

Few subjects had worsening to Grade ≥ 3 selected hepatic enzyme parameters based on laboratory assessment. The median time to worsening to Grade ≥ 3 of ALT in the imetelstat (n=4) and placebo groups (n=3), respectively, was 29.6 weeks and 12.0 weeks (Table tlab04j). One subject in each group had worsening to Grade ≥ 3 for AST (27.6 and 5.6 weeks, respectively) and for bilirubin (28.0 and 16.0 weeks, respectively). No subjects had worsening to Grade ≥ 3 ALP.

All cases of Grade 3/4 laboratory hepatic enzyme elevations in the imetelstat and placebo groups resolved to Grade ≤ 2, most in less than 4 weeks (Table tlab05d). The median duration of all hepatic enzyme elevations was < 2 weeks in the imetelstat group and < 5 weeks in the placebo group (Table tlab04m).

A Hepatic Expert Committee (HEC) comprised of independent hepatology experts was formed to examine the safety of imetelstat from a liver toxicity perspective and to help with understanding of hepatologic events as they emerged. Two subjects, both in the imetelstat group, met the laboratory criteria for Hy's law, i.e., ALT or AST Grade ≥ 2 (> 3.0 x ULN) with concurrent (within 7 days) bilirubin Grade ≥ 2 (> 2.0 x ULN) (Listing llab02a); however, an alternative aetiology for these hepatic enzyme elevations was established. In one case the rapid resolution of liver enzyme and bilirubin elevations following the withdrawal of deferasirox and the positive rechallenge with deferasirox provided a more likely aetiology for the hepatotoxicity as described in the deferasirox label. In the second case, the hepatic enzyme elevations were more likely due to the multiple risk factors for hepatic enzyme elevations including a high red blood cell (RBC) transfusion burden, chronic

hemosiderosis secondary to RBC transfusions, presence of a gallbladder stone, ineffective erythropoiesis due to LR-MDS, and possibly deferasirox-induced liver injury. In summary, no cases meeting Hy's law criteria were observed, as confirmed by the HEC.

The data from the MDS3001 Final Analysis (cutoff date 13 October 2023) were in line with the Primary Analysis of the Phase 3 data described above (cutoff date 13 October 2022). Hepatic TEAEs (any grade) were reported in 33 (28.0%) subjects in the imetelstat group and 11 (18.6%) subjects in the placebo group (Table tsfaesi01_p2). The majority of hepatic TEAEs were Grade 1/2 and there were no Grade 5 events in either group (Table tsfaesi01_p2). Grade 3/4 hepatic TEAEs were reported in 11 (9.3%) subjects in the imetelstat group and 3 (5.1%) subjects in the placebo group (Table tsfaesi01_p2). No new hepatic SAEs were reported in either group at the time of the Final Analysis; 1 (0.8%) subject in the imetelstat group experienced oesophageal varices haemorrhage (Table tsfaesi06_p2) which was the same subject discussed above and reported in the Primary Analysis.

Based on laboratory assessments from the MDS3001 Final Analysis, worsening of ALP from baseline (to any grade) was observed at a higher rate in the imetelstat group compared to the placebo group (48.3% vs 11.9%, respectively) (Table tsflb16_p2). Similarly, worsening of AST from baseline (to any grade) was observed at a higher rate in the imetelstat group compared to placebo (52.5% vs 22.0% respectively). There was no difference in the rate of worsening bilirubin from baseline (to any grade) between the imetelstat and placebo group (39.8% vs 39.0% respectively), and the rates of worsening of ALT from baseline (to any grade) were similar in the imetelstat group and placebo group (42.7% vs 37.3%, respectively) (Table tsflb16_p2). The median time to worsening by at least 1 grade in the imetelstat and placebo groups, respectively, were 4.0 weeks and 8.1 weeks for ALT, 17.0 weeks and 20.0 weeks for ALP, 18.0 weeks and 12.0 weeks for AST, and 2.0 and 5.1 weeks for bilirubin based on laboratory assessments (Table tsflb26a_p2).

Results in Phase 2 for hepatic TEAE/hepatic enzyme abnormalities were generally consistent with and supportive of the findings in imetelstat-treated subjects in Phase 3 (Group B) (Module 2.7.4, Section 2.1.7.1.2).

In the Group C pool (N=391), a medical history of iron overload was reported in 59 (15.1%) subjects, hepatobiliary disorders were reported in 37 (9.5%) subjects, and 127 (32.5%) subjects were using iron chelating agents at the time of entering the study or while on treatment (Table tmh01c; Table tcm01c). The proportions of subjects with a history of iron overload and iron-chelator use were less than in the LR MDS pool, due to RBC transfusion dependence inclusion criterion in Study MDS3001.

Hepatic TEAEs (any grade) were reported in 140 (35.8%) subjects and 39 (10.0%) subjects experienced at least 1 TEAE with maximum severity of Grade 3 or 4 (Table taesi02c). The most commonly reported hepatic TEAEs were AST increased (68 [17.4%] subjects), ALT increased (64 [16.4%] subjects), blood ALP increased (52 [13.3%] subjects), and blood bilirubin increased (24 [6.1%] subjects). The most common Grade 3 or 4 hepatic events in this population were ALT increased (10 [2.6%] subjects), AST increased and GGT increased (8 [2.0%] subjects each). Sixty-five (16.6%) subjects had hepatic TEAEs considered related to imetelstat (Table taesi01c).

The incidence of hepatic events was highest in the > 7.1 mg/kg group for all grade events and maximum Grade 3/4 events (43.9% and 12.9%, respectively) compared to the 7.1 mg/kg group (35.3% and 8.8%, respectively) and < 7.1 mg/kg group (14.6% and 6.3%, respectively) (Table taesi02c).

TEAEs reported at higher incidence in the > 7.1 mg/kg group compared to the 7.1 mg/kg and < 7.1 mg/kg groups included blood ALP increased (25.9% vs 6.9% and 4.2%, respectively) and blood bilirubin increased (12.9% vs 2.9% and 0%, respectively) (Table taesi02c). As the > 7.1 mg/kg group is comprised primarily of MF patients with these hepatic laboratory abnormalities commonly associated with the underlying MF, this is not unexpected.

A total of 16 subjects had serious hepatic events (Table taesi04c), including 3 subjects from Group B (7.1 mg/kg group) and 13 subjects from the Studies MYF2001, CP14B019, and CP14B015 (3 subjects from 7.1 mg/kg group and 9 subjects from > 7.1 mg/kg group). One subject from the 7.1 mg/kg group of Study CP14B015 had an SAE of hepatic encephalopathy, a Grade 3 cirrhosis, and a Grade 5 hepatic event (oesophageal varices haemorrhage), as described below. This was also the only subject to discontinue study treatment due to a hepatic TEAE (Table taesi01c; Listing lae02b).

Six subjects in the Group C pool had dose reductions due to hepatic events, including 3 subjects in the 7.1 mg/kg group from Study MDS3001 and 3 subjects in the > 7.1 mg/kg group from Studies MYF2001 (1 subject with serious Grade 3 AST increased) and CP14B015 (1 subject with Grade 2 ALT increased and Grade 1 AST increased; and 1 subject with Grade 2 events of ALT and AST) (Listing lae02b).

The median time to onset of Grade 3/4 hepatic TEAEs was 218.5 days (range: 1 to 962 days) for the 40 subjects with Grade 3/4 hepatic TEAEs in the overall Group C population (Table taesi03c).

In the overall pooled Group C subject population, worsening toxicity grades during treatment were reported for ALT (151 [38.6%] subjects), AST (177 [45.3%] subjects), ALP (180 [46.0%] subjects), and bilirubin (141 [36.1%] subjects) and most were from normal to Grades 1/2 (Table tlab02f; Table tlab06f). Worsening by 3 grades was reported for ALT in 11 (2.8%) subjects, AST in 7 (1.8%) subjects, ALP in 2 (0.5%) subjects, and bilirubin in 6 (1.5%) subjects, and worsening by 4 grades was reported for AST and bilirubin in 1 (0.3%) subject each (Table tlab06f).

The median time to worsening of hepatic enzyme parameters to Grade ≥ 3 based on laboratory parameters on study was 16.7 weeks (range: 1.0 to 84.1 weeks) for ALT, 20.8 weeks (range: 0.9 to 66.9 weeks) for ALP, 26.7 weeks (range: 1.1 to 87.0 weeks) for AST, and 42.7 weeks (range: 8.7 to 109.7 weeks) for bilirubin (Table tlab04l).

In Group C, all cases of Grade 3/4 laboratory hepatic enzyme elevations in the 7.1 mg/kg dose group resolved to Grade ≤ 2, most in < 4 weeks with a median duration for all hepatic enzyme elevations of ≤ 1.5 weeks (Table tlab05f; Table tlab04o). One of 5 cases of Grade 3/4 hepatic enzyme elevations was unresolved in the < 7.1 mg/kg group, and 7 of 26 Grade 3/4 hepatic enzyme elevations were unresolved in the > 7.1 mg/kg group.

No subjects met Hy's law criteria. A total of 7 subjects in the Group C pool had events that met the laboratory criteria for Hy's law, i.e., ALT or AST Grade ≥ 2 (> 3.0 x ULN) with concurrent (within 7 days) bilirubin Grade ≥ 2 (> 2.0 x ULN) (Listing llab02a), including the 3 subjects in the 7.1 mg/kg group from Group B, plus 2 subjects from the < 7.1 mg/kg group and 3 subjects from the > 7.1 mg/kg group from CP14B019. Alternative aetiology for all hepatic enzyme elevations was established.

Risk factors and risk groups:

Hepatic effects are expected in patients with MDS due to iron overload related toxicity. Transfusion dependence leading to iron overload has a negative impact on organ function

(notably in the liver, heart, and endocrine system) as well as leukemic progression and infectious complications in some analyses (Angelucci, 2020).

The risk of drug-induced hepatotoxicity depends on the medicinal product. Other risk factors, besides the medicinal products themselves, include demographic and genetic factors (Ahmad, 2017). Data-mining analyses of 236 drugs known to be associated with drug-induced liver injury (DILI) in the World Health Organization (WHO) Safety Report Database, VigiBase™ found that elderly patients (65 years or older) were much more likely to develop cholestatic injury while acute liver injury was more common in children (Hunt, 2014). Although gender does not appear to increase the risk for DILI overall, the majority of large registry studies suggest a female preponderance of idiosyncratic DILI (Ahmad, 2017). African-American race was found to be an independent risk factor for chronic DILI and Asian race was an independent predictor of reduced time to liver-related death or liver transplantation (Ahmad, 2017). A study of acute liver injury in the UK General Practice Research Database (GPRD) found that when two or more hepatotoxic drugs were given concurrently the risk of DILI increased 6-fold (de Abajo, 2004).

Genetic analyses have identified multiple polymorphisms of human leukocyte antigen (HLA) genes and genes involved in drug metabolism and transport as risk factors for DILI; most genetic risk factors for DILI identified so far are drug and population specific (Ahmad, 2017).

Preventability:

Imetelstat is a product subject to restricted medical prescription and is administered under supervision of experienced healthcare professionals. As part of this close management, early detection and management of severe hepatotoxicity would be expected should it occur. Therefore, routine risk minimisation measures that comprise guidance in the SmPC, PL, and restricted medical prescription are considered sufficient to manage this risk in clinical practice.

Severe hepatotoxicity can be managed in clinical practice through routine laboratory monitoring and dose modifications. The imetelstat SmPC recommends liver function tests before administration of each dose and includes dose modifications for Grade 3 or 4 elevated liver function tests including delaying treatment until adverse reactions to Grade 1 or baseline and restarting at one dose level lower. Treatment with imetelstat should be permanently discontinued if the patient cannot tolerate the lowest dose level of 4.4 mg/kg. Aspartate aminotransferase increased, alanine aminotransferase increased and blood alkaline phosphatase increased are listed in the SmPC as adverse reactions based on laboratory measurements to alert healthcare professionals that these adverse reactions have been observed in clinical trials and may occur in clinical practice. Likewise, patients are advised in the PL that their doctor or nurse will monitor them for specific side effects and do blood tests (liver function tests) before every dose of Rytelo. They are informed that increased levels of liver enzymes shown in blood tests are very common side effects of imetelstat.

Impact on the risk-benefit balance of the product:

Transfusion-dependent anaemia due to lower risk MDS is a serious and life-threatening condition with limited treatment options and no established standard of care (Section Part II: Module SI).

The hepatic enzyme elevations observed in the clinical studies were closely monitored as hepatic effects are expected in patients with MDS due to iron overload related toxicity. The majority of hepatic TEAEs in the clinical studies were non-serious, Grade 1 or Grade 2 in severity, and resolved within 2 weeks. No subjects met Hy's law criteria.

The benefit of imetelstat as a treatment for adult patients with transfusion-dependent anaemia due to lower risk MDS is considered to outweigh the potential risk of severe hepatotoxicity which has yet to be confirmed and can be managed in clinical practice through healthcare professional awareness of the possible risk and dose modifications.

Severe hepatotoxicity will be further characterised in Study MDS3001 Extension Phase (Part III).

Public health impact:

Healthcare professionals treating patients with MDS are used to monitoring patients for hepatic enzyme elevations. Since MDS is a rare condition (Section Part II: Module SI) and as severe hepatotoxicity, should it occur, can be managed in clinical practice through healthcare professional awareness of the possible risk, monitoring and dose modifications, the potential impact on public health is expected to be low.

Important Potential Risk: Embryo-foetal toxicity

Potential mechanisms:

The mechanism by which imetelstat may cause embryonic or foetal loss when administered to a pregnant woman is unknown.

Evidence source and strength of evidence:

The mechanism by which imetelstat may cause embryonic or foetal loss is unknown.

There are no available human data on imetelstat use in pregnant women. Nonclinical studies found that imetelstat administered at high doses may cause foetal loss but there was no evidence that imetelstat is teratogenic.

Findings from studies in animals may be relevant for humans and in the absence of data in humans suggest a potential safety concern.

Characterisation of the risk:

Similar to the majority of investigative clinical trials, females who were pregnant or who were planning to become pregnant while enrolled in the study or within 1 month after the end of dosing were excluded from participation in study MDS3001 (Section SIV.1). Likewise, men who were planning to father a child while enrolled in the study or within 3 months after the end of dosing were excluded. These exclusion criteria, together with the additional study requirements relating to pregnancy prevention, meant there was no exposure to imetelstat during pregnancy in the clinical development programme (Section SIV.3).

As discussed in Section Part II: Module SI, the median age for MDS diagnosis is over 70 years old and less than 10% of patients are younger than 50 years old (Neukirchen, 2011; Fenaux, 2021). As such the number of women of childbearing potential in the target population is expected to be low.

In Phase 3 study MDS3001 (Group A), the median subject age of the imetelstat group was 71.5 years (range: 44 to 87 years) and in the placebo group was 73 years (range: 39 to 85 years) (Table tdm01a). There were more males than females in both the imetelstat group (60.2% and 39.8%) and placebo group (66.1% and 33.9%) in this study (Table tdm01a). In Group B the median age of imetelstat treated subjects was 71 years (range: 44 to 87 years) and 41.1% of subjects were female (Table tdm01b). In the overall pooled Group C population (N=391), the median age was 68.0 years (range: 21 to 93 years) and 39.4% of

subjects were female (Table tdm01c), the younger age reflects the wider indications included in this pool (Section Part II: Module SIII).

In embryo-foetal developmental toxicity studies, embryo-lethal effects were observed following administration of 28.2 mg/kg imetelstat to pregnant mice and rabbits that produced maternal exposures (based on AUC) that are approximately 3.4-times (mice) or 26.4-times (rabbits) the human exposure at the recommended clinical dose. 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 (Section Part II: Module SII). Non-significant increases in fused sternebrae were noted at 28.2 mg/kg in rabbits, a dose deemed to be maternally toxic based on decreases in mean gestation body weight. Importantly, imetelstat was not found to be teratogenic and these data, together with the genotoxicity studies show that imetelstat does not pose a risk for mutagenicity or clastogenicity, suggesting imetelstat is unlikely to cause teratogenicity, but may cause embryonic or foetal loss when administered to a pregnant woman.

Risk factors and risk groups:

Women of childbearing potential not using effective contraception during imetelstat treatment and for at least 1 week after the last dose.

Preventability:

The imetelstat SmPC warns healthcare professionals to advise pregnant women of the potential risk to a foetus. Based on findings in animals, imetelstat may cause embryo-foetal harm when administered to a pregnant woman. Administration of imetelstat to pregnant mice and rabbits during the period of organogenesis resulted in embryo-foetal mortality at maternal exposures (AUC) ≥ 3.4-times the human exposure at the recommended clinical dose. There are no or limited data on the use of imetelstat in pregnant women. Imetelstat is not recommended during pregnancy and in women of childbearing potential not using contraception. The pregnancy status of females of reproductive potential should be verified before starting treatment with imetelstat and 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.

The imetelstat PL provides guidance for the patient to talk to their doctor before starting Rytelo if they are pregnant, think they may be pregnant or are planning to have a baby. Imetelstat is not recommended during pregnancy and in women who are able to have children but are not using contraception. Women who could become pregnant are recommended to use effective contraception (birth control) during treatment with Rytelo and for at least 1 week after the last dose. The patient should talk with their doctor or nurse about the best contraception to use to avoid pregnancy. If the patient becomes pregnant or thinks that they are pregnant during treatment with Rytelo they should tell their doctor straight away. Their doctor or nurse will check that they are not pregnant with a test before they start treatment.

Impact on the risk-benefit balance of the product:

Transfusion-dependent anaemia due to lower risk MDS is a serious and life-threatening condition with limited treatment options and no established standard of care (Section Part II: Module SI).

The risk of imetelstat in pregnancy is unknown as there was no exposure during pregnancy in the clinical development programme. Embryo-foetal developmental toxicity studies in mice

and rabbits suggest that imetelstat is unlikely to cause teratogenicity but may cause embryonic or foetal loss when administered to a pregnant woman.

The benefit of imetelstat as a treatment for adult patients with transfusion-dependent anaemia due to lower risk MDS is considered to outweigh the potential risk of using imetelstat in pregnancy which has yet to be confirmed in humans and can be managed in clinical practice by adhering to the guidance in the SmPC and PL that warns against use during pregnancy and recommends pregnancy testing prior to use and use of effective contraception.

Public health impact:

Healthcare professionals treating patients with MDS are aware of the potential risk of using cancer treatments during pregnancy. Since the median age of the target population is over 70 years of age and MDS is a rare condition (Section Part II: Module SI), and as the risk of imetelstat in pregnancy can be managed in clinical practice through adhering to the SmPC and PL guidance that warns against use during pregnancy and recommends pregnancy testing prior to use and use of effective contraception, the potential impact on public health is expected to be low.

SVII.3.2 Presentation of the Missing Information

Missing information: Long-term safety

Evidence source:

In Phase 3 study MDS3001 (Group A), as of the clinical cut-off (13 October 2022), 64.4% of subjects in the imetelstat group and 66.1% of subjects in the placebo group were remaining on study in follow-up (Table tds02a). The median time on study was longer for the imetelstat group (19.48 months, range: 1.38 to 36.17 months) compared to the placebo group (17.61 months, range: 0.72 to 34.27 months) (Table tdur02a).

For the pooled imetelstat group (N=175) (Group B), the median time on study was 23.43 months (range: 1.38 to 79.11 months) and 52% subjects were remaining on study in follow-up as of the clinical cut-off (Table tdur02b; Table tds02b).

In the overall pooled Group C population (N=391), the median time on study for all subjects was 31.97 months (range: 0.16 to 79.11 months) and 23.3% subjects were still on study in follow-up as of the data cut-off date (Table tdur02c; Table tds02c).

In MDS3001 the overall incidence of TEAEs remained consistent over the course of treatment with no apparent increase in frequency over time; the most common TEAEs, including neutropenia, thrombocytopenia, occurred more frequently during the early months of treatment and decreased during later months suggesting a lack of cumulative toxicity (Module 2.7.4, Section 2.1.2.3.1). These results were consistent over time, as demonstrated by the additional 1 year of data in the MDS3001 Phase 3 Final Analysis (cutoff date 13 October 2023) which were in line with the Primary Analysis of the Phase 3 data (cutoff date 13 October 2022). No new safety signals were identified. However, it is acknowledged that long-term safety data for imetelstat are limited and Study MDS3001 Extension Phase will help to further characterise long-term safety.

Population in need of further characterisation:

Long-term safety will be further characterised in Study MDS3001 Extension Phase (Part III).

PART II: MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Table 23: Summary of 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

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for the safety concerns:

Not applicable.

Other forms of routine pharmacovigilance activities for the safety concerns:

Not applicable.

III.2 Additional Pharmacovigilance Activities

Study MDS3001 Extension Phase

Study short name and 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

Rationale and study objectives:

To evaluate the long-term safety[1] in transfusion dependent subjects with low- or immediate-1 risk MDS that is relapsed/refractory to ESA treatment receiving imetelstat.

Study design:

Subjects benefiting from imetelstat at the end of the main study (ie, 24 months after last subject randomised in the main study of Part 2) per investigator assessment may continue to receive imetelstat during the Extension Phase. Subjects in the Post-treatment Follow-up Phase of the main study will also continue in the Extension Phase for assessment of long-

[1] Only analyses that collect safety information are applicable for Study MDS3001 Extension Phase in the RMP.

term safety. Subjects in the QTc substudy may also enter the Extension Phase after the clinical cut-off for the primary analysis (the exposure-response analysis) for the QTc substudy is reached.

Subjects will be followed in the Extension Phase for at least 5 years from the first dose of imetelstat in Part 2 of the main study (including treatment and follow-up), or 3 years of post-treatment follow-up from the last dose of study treatment, whichever occurs later, or until death, withdrawal of consent, study termination, or until a subject is lost to follow-up. During the Extension Phase, the Independent Hepatic Expert Committee (HEC) will be available to review all hepatic adverse events and liver function test abnormalities at least on a quarterly basis, or more frequently if needed.

The Extension Phase does not apply to Part 1 (Phase 2) MDS3001 subjects.

Study population:

Key eligibility criteria include the following: ≥18 years of age; diagnosis of MDS according to World Health Organization criteria confirmed by bone marrow aspirate and biopsy within 12 weeks prior to C1D1 (Part 1) or Randomisation (Part 2); IPSS low or intermediate-1 risk non-del(5q) MDS that is relapsed/refractory to ESA treatment; RBC transfusion dependent; an ECOG Performance Status score of 0, 1 or 2; and no prior treatment with either a hypomethylating agent or lenalidomide.

Study MDS3001 Extension Phase was initiated in Q4 2023 and is due for completion in Q4 2026. As of 05 June 2024, there are 104 subjects enrolled in the study (24 were on treatment, and 80 in follow-up). Six subjects withdrew from the study after entering the extension phase due to death (4 subjects), adverse event (1 subject) and withdrawal by subject (1 subject). Ten additional subjects are eligible for enrolment in the Extension Phase.

Milestones:

Study initiation: Q4 2023

Study completion: Q4 2026

Final study report: Q4 2027

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 24: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

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[1] 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

[1]Only analyses that collect safety information are applicable for Study MDS3001 Extension Phase in the RMP.

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no planned or ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 25: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Severe bleeding (Important identified risk)	Routine risk communication: • Adverse reactions in SmPC section 4.8 • Side effects in PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Instruction for routine monitoring of complete blood cell counts prior to each dose, weekly following administration of the first 2 doses and for any cases of Grade 3 or 4 thrombocytopenia or as clinically indicated in SmPC sections 4.2 and 4.4 • Recommendation to delay treatment and resume at the same or reduced dose for Grade 3 or 4 thrombocytopenia in SmPC sections 4.2 and 4.4 • Recommendation to assess the need for platelet transfusions as clinically appropriate in SmPC section 4.4 • Warning to monitor patients with Grade 3 or Grade 4 thrombocytopenia for bleeding events in SmPC section 4.4 • Warning to advise patients to report any signs or symptoms of bruising or bleeding immediately as a precaution in SmPC section 4.4 • Warning for the patient to talk to their doctor or nurse before they are given Rytelo if they have recently had bleeding or bruising which may worsen if certain types of their blood cells begin to decrease after they have received Rytelo in PL section 2 • Guidance that the doctor or nurse will do blood tests to keep control of blood cell counts before each dose of Rytelo and every week during the first two doses in PL section 2 • Guidance that the doctor may delay giving the infusion and schedule it for another day, reduce the dose, or stop treatment with Rytelo depending on how the patient reacts to the medicine in PL section 3 Other routine risk minimisation measures beyond the Product Information: • Legal status: Restricted medical prescription
Severe infections (Important identified risk)	Routine risk communication: • Adverse reaction in SmPC section 4.8 • Side effect in PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety concern	Routine risk minimisation activities
	• Instruction for routine monitoring of complete blood cell counts prior to each dose, weekly following administration of the first 2 doses and for any cases of Grade 3 or 4 neutropenia or as clinically indicated in SmPC sections 4.2 and 4.4 • Recommendation to delay treatment and resume at the same or reduced dose for Grade 3 or 4 neutropenia in SmPC sections 4.2 and 4.4 • Warning to monitor patients with Grade 3 or Grade 4 neutropenia for infections including sepsis in SmPC section 4.4 • Recommendation to administer granulocyte-colony stimulating factors and anti-infective therapies as clinically appropriate in SmPC section 4.4 • Warning for the patient to talk to their doctor or nurse before they are given Rytelo if they have signs of an infection which may worsen if certain types of their blood cells begin to decrease after they have received Rytelo in PL section 2 • Guidance that the doctor or nurse will do blood tests to keep control of blood cell counts before each dose of Rytelo and every week during the first two doses in PL section 2 • Guidance that the doctor may delay giving the infusion and schedule it for another day, reduce the dose, or stop treatment with Rytelo depending on how the patient reacts to the medicine in PL section 3 Other routine risk minimisation measures beyond the Product Information: • Legal status: Restricted medical prescription
Severe hepatotoxicity (Important potential risk)	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • Instruction for routine monitoring of liver function tests before administration of each dose in SmPC section 4.2 • Recommendation to delay treatment until adverse reactions to Grade 1 or baseline and to restart at one dose level lower for Grade 3 or 4 elevated liver function tests in SmPC section 4.2 • Guidance that the doctor or nurse will do blood tests before each dose of Rytelo in PL section 2 • Guidance that the doctor may delay giving the infusion and schedule it for another day, reduce the dose, or stop treatment with Rytelo depending on how the patient reacts to the medicine in PL section 3 Other routine risk minimisation measures beyond the Product Information: • Legal status: Restricted medical prescription
Embryo-foetal toxicity (Important potential risk)	Routine risk communication: • Information on nonclinical findings in SmPC sections 4.4, 4.6 and 5.3 • Guidance that there are no data on the use of imetelstat in pregnant women in SmPC section 4.6

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • 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 • Warning that imetelstat is not recommended during pregnancy and in women of childbearing potential not using contraception and to verify the pregnancy status of females of reproductive potential before starting treatment with imetelstat in SmPC section 4.6 • Warning for women of childbearing potential to use effective contraception during treatment with imetelstat and for at least 1 week after the last dose in SmPC sections 4.4 and 4.6 • Warning for the patient to tell their doctor if they are pregnant, think they may be pregnant or are planning to have a baby before starting Rytelo in PL section 2 • Warning that Rytelo is not recommended during pregnancy and in women who are able to have children but are not using contraception in PL section 2 • Warning for women who could become pregnant to use effective contraception (birth control) during treatment with Rytelo and for at least 1 week after the last dose and for the patient to talk with their doctor or nurse about the best contraception to use to avoid pregnancy in PL section 2 • Warning for the patient to tell their doctor straight away if they become pregnant or think they are pregnant during treatment with Rytelo in PL section 2 • Guidance that the doctor or nurse will check that the patient is not pregnant with a test before they start treatment in PL section 2 Other routine risk minimisation measures beyond the Product Information: • Legal status: Restricted medical prescription
Long-term safety (Missing information)	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • None

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Section V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 26: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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* • *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*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Study MDS3001 Extension Phase*
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*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• *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*	• *Study MDS3001 Extension Phase*
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*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Study MDS3001 Extension Phase*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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* • *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*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *None*
Long-term safety (Missing information)	Routine risk minimisation measures: • *None* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Study MDS3001 Extension Phase*

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR RYTELO (IMETELSTAT)

This is a summary of the risk management plan (RMP) for Rytelo. The RMP details important risks of Rytelo, how these risks can be minimised, and how more information will be obtained about Rytelo's risks and uncertainties (missing information).

Rytelo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Rytelo should be used.

This summary of the RMP for Rytelo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Rytelo's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

Rytelo is authorised for the treatment of adult patients with transfusion-dependent anaemia due to lower risk myelodysplastic syndromes (MDS) (see SmPC for the full indication). It contains imetelstat as the active substance and it is given as an intravenous infusion.

Further information about the evaluation of Rytelo's benefits can be found in Rytelo's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage < link to the EPAR summary landing page >

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Rytelo, together with measures to minimise such risks and the proposed studies for learning more about Rytelo's risks, are outlined below.

- Measures to minimise the risks identified for medicinal products can be:
- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Rytelo is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Rytelo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Rytelo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Severe bleeding Severe infections
Important potential risks	Severe hepatotoxicity Embryo-foetal toxicity
Missing information	Long-term safety

II.B Summary of Important Risks

Important identified risk: Severe bleeding	
Evidence for linking the risk to the medicine	The mechanism by which imetelstat may cause severe bleeding is unknown but it could be related to thrombocytopenia. Thrombocytopenia is a recognised and expected effect of imetelstat based on its mechanism of action. In study MDS3001, bleeding events occurred in 21.2% of subjects treated with imetelstat and in 11.9% of placebo-treated subjects. The bleeding events that were observed in this study were mainly of mild or moderate severity with very few severe or serious events in subjects treated with imetelstat, and these were not considered related to treatment. Bleeding events in other studies were also generally of mild or moderate severity with very few severe or serious events and the majority were unrelated to imetelstat treatment. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice.
Risk factors and risk groups	Thrombocytopenia is associated with a risk of bleeding. While the correlation of severity of thrombocytopenia and bleeding risk is uncertain, spontaneous bleeding can occur with a platelet count

Important identified risk: Severe bleeding	
	under 10 x 10^9/L and surgical bleeding with counts below 50 x 10^9/L (Jinna, 2022).
Risk minimisation measures	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* • *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 imetelstat 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*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study MDS3001 Extension Phase See Section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Severe infections	
Evidence for linking the risk to the medicine	Infections are a potential outcome of neutropenia. Neutropenia is a recognised and expected effect of imetelstat based on its mechanism of action. In study MDS3001, infections occurred in 42.4% subjects treated with imetelstat and in 33.9% placebo-treated subjects. The infections were mainly of mild or moderate severity and not related to treatment; severe infections occurred in 10.2% subjects treated with imetelstat and in 13.6% subjects treated with placebo. Infections in other studies were also generally of mild or moderate severity with few severe or serious events and the majority were unrelated to imetelstat treatment. Infections were managed in clinical trials with dose modifications, cycle delays and supportive care. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice.

Important identified risk: Severe infections	
Risk factors and risk groups	Neutropenia is the main predisposing factor for infection in MDS, but several other immune defects have been reported, including impaired neutrophil function, B-, T- and NK-cell defects and the possible consequences of iron overload due to red blood cell transfusions (Toma, 2012).
Risk minimisation measures	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*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study MDS3001 Extension Phase See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Severe hepatotoxicity	
Evidence for linking the risk to the medicine	A possible causal association between imetelstat and severe hepatotoxicity has not been established. The transient hepatic enzyme elevations that occur in some patients may be a manifestation of immune stimulation although the mechanism is not known. Hepatic effects are also expected in patients with MDS due to iron overload related toxicity. In study MDS3001, hepatic adverse events (any grade) were reported in 28.8% subjects treated with imetelstat and in 16.9% placebo-treated subjects. The majority of hepatic adverse events were non-serious, Grade 1 or Grade 2 in severity, and resolved within 2 weeks. No subjects met Hy's law criteria. Hepatic enzyme elevations were managed in clinical trials with cycle delays and reducing the dose.

Important potential risk: Severe hepatotoxicity	
	Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice.
Risk factors and risk groups	Hepatic effects are expected in patients with MDS due to iron overload related toxicity. Transfusion dependence leading to iron overload has a negative impact on organ function (notably in the liver, heart, and endocrine system) as well as leukemic progression and infectious complications in some analyses (Angelucci, 2020). The risk of drug-induced hepatotoxicity depends on the medicinal product. Other risk factors, besides the medicinal products themselves, include demographic and genetic factors (Ahmad, 2017). Data-mining analyses of 236 drugs known to be associated with drug-induced liver injury (DILI) in the World Health Organization (WHO) Safety Report Database, VigiBase™ found that elderly patients (65 years or older) were much more likely to develop cholestatic injury while acute liver injury was more common in children (Hunt, 2014). Although gender does not appear to increase the risk for DILI overall, the majority of large registry studies suggest a female preponderance of idiosyncratic DILI (Ahmad, 2017). African-American race was found to be an independent risk factor for chronic DILI and Asian race was an independent predictor of reduced time to liver-related death or liver transplantation (Ahmad, 2017). A study of acute liver injury in the UK General Practice Research Database (GPRD) found that when two or more hepatotoxic drugs were given concurrently the risk of DILI increased 6-fold (de Abajo, 2004). Genetic analyses have identified multiple polymorphisms of human leukocyte antigen (HLA) genes and genes involved in drug metabolism and transport as risk factors for DILI; most genetic risk factors for DILI identified so far are drug and population specific (Ahmad, 2017).
Risk minimisation measures	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*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study MDS3001 Extension Phase See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	The mechanism by which imetelstat may cause embryonic or foetal loss is unknown. There are no available human data on imetelstat use in pregnant women. Nonclinical studies found that imetelstat administered at high doses may cause foetal loss but there was no evidence that imetelstat is teratogenic. Findings from studies in animals may be relevant for humans and in the absence of data in humans suggest a potential safety concern.
Risk factors and risk groups	Women of childbearing potential not using effective contraception during imetelstat treatment and for at least 1 week after the last dose.
Risk minimisation measures	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* • *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*

Missing information: Long-term safety	
Risk minimisation measures	Routine risk minimisation measures: • *None* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study MDS3001 Extension Phase See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Rytelo.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study MDS3001 Extension Phase

Purpose of the study:

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.

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PART VII ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

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