EU-RISK MANAGEMENT PLAN (RMP) FOR AZACITIDINE

VERSION 16.0, 26 May 2021

EU-RISK MANAGEMENT PLAN FOR AZACITIDINE

RMP Version to be Assessed as Part of this Application	16.0
Data Lock Point for this Current European Union–Risk Management Plan (EU-RMP)	Clinical studies: 15 Jul 2019 Postmarketing data: 18 May 2019
Date of Final Sign Off	26 May 2021
Rationale for Submitting an Updated RMP	Inclusion of an oral formulation of azacitidine with a new indication.

Table 1: Summary of Significant Changes in this RMP

Part	Module/Annex	Significant Changes in Each Module
Part I	--	Updated to include oral azacitidine formulation.
Part II Safety Specification	**Module SI** Epidemiology of the Indication and Target Population(s)	Updated to include indication for oral azacitidine formulation.
	Module SII Nonclinical Part of the Safety Specification	Updated to reflect relevance of nonclinical findings to human usage for oral azacitidine of nonclinical findings.
	Module SIII Clinical Trial Exposure	Updated to include clinical study exposure for oral azacitidine formulation.
	Module SIV Populations Not Studied in Clinical Trials	Updated to include clinical study information for oral azacitidine formulation.
	Module SV Postauthorisation Experience	Updated to reflect revised data lock point.
	Module SVI Additional EU Requirements for the Safety Specification	No change.
	Module SVII Identified and Potential Risks	Updated to include clinical study data and safety concerns for oral azacitidine formulation.
	Module SVIII Summary of the Safety Concerns	Updated with safety concerns for oral azacitidine formulation.
Part III Pharmacovigilance Plan	--	Updated with routine pharmacovigilance measures for oral azacitidine formulation.
Part IV Plan for Postauthorisation Efficacy Studies	--	No change.

Table 1: Summary of Significant Changes in this RMP (Continued)

Part	Module/Annex	Significant Changes in Each Module
Part V Risk Minimisation Measures	--	Updated with routine risk minimisation measures for oral azacitidine formulation.
Part VI Summary of RMP	--	Summary provided for oral azacitidine formulation.
Part VII Annexes	**ANNEX 1** Eudravigilance Interface	Updated to reflect changes in the RMP.
	ANNEX 2 Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme	No change.
	ANNEX 3 Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan	No change.
	ANNEX 4 Specific Adverse Drug Reaction Follow-up Forms	Updated with the most recent follow-up forms for thrombocytopenia/bleeding and infections.
	ANNEX 5 Protocols for Proposed and Ongoing Studies in RMP Part IV	No change.
	ANNEX 6 Details of Proposed Additional Risk Minimisation Activities (if Applicable)	No change.
	ANNEX 7 Other Supporting Data (Including Referenced Material)	Updated to reflect changes in the RMP.
	ANNEX 8 Summary of Changes to the RMP Over Time	Updated to included details of approved EU-RMP v15.1.

Other RMP Versions under Evaluation:

RMP Version Number	Submitted On	Procedure Number
None	-	-

Details of the Currently Approved RMP:

Version Number	15.1
Approved with Procedure	EMEA/H/C/005300/0000
Date of Approval (Opinion Date)	02 Aug 2019

QPPV NAME AND CONTACT PERSON FOR THIS EU-RISK MANAGEMENT PLAN

Qualified Person for Pharmacovigilance (QPPV) and Contact Person for this RMP	Priv. Doz. Dr. Stefan Kaehler
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E-mail Address or Telephone Number of Contact Person	[redacted]

LIST OF ABBREVIATIONS FOR ALL PARTS/MODULES

ACE-27	Adult Comorbidity Evaluation-27
ADR	Adverse drug reaction
AE	Adverse event
AlloSCT	Allogeneic stem cell transplantation
AML	Acute myeloid leukaemia
AUC	Area under the concentration-time curve
BSA	Body surface area
CALGB	Cancer and Leukaemia Group B
CHF	Congestive heart failure
CI	Confidence interval
CLcr	Creatinine clearance
CMML	Chronic myelomonocytic leukaemia
CR	Complete remission
CRi	Complete remission with incomplete blood count recovery
CV	Cardiovascular
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
EEA	European Economic Area
ELN	European LeukemiaNet
EPAR	European Public Assessment Report
EU	European Union
EU-RMP	European Union-Risk Management Plan
FAB	French-American-British
G-CSF	Granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
HAEMACARE	Cancer Registry Based project on Haematologic malignancies
HMRN	Haematological Malignancy Research Network
HSCT	Haematopoietic stem cell transplantation
ICD-O	International Classification of Diseases for Oncology
ICH	International Council for Harmonisation
INT-1	Intermediate-1
INT-2	Intermediate-2

IP	Intraperitoneal(ly)
IPSS	International Prognostic Scoring System
IV	Intravenous(ly)
MDS	Myelodysplastic syndrome(s)
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
PK	Pharmacokinetic
PL	Package Leaflet
PT	Preferred term
QPPV	Qualified Person for Pharmacovigilance
RA	Refractory anaemia
RAEB	Refractory anaemia with excess blasts
RAEB-T	Refractory anaemia with excess blasts in transformation
RARECARE	Surveillance of Rare Cancers in Europe
RARS	Refractory anaemia with ringed sideroblasts
RMP	Risk Management Plan
RR	Relative risk
SAE	Serious adverse event
SC	Subcutaneous(ly)
SEER	Surveillance, Epidemiology and End Results
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA query
SOC	System Organ Class
tAML	Therapy-associated AML
tMDS	Therapy-associated MDS
US	United States
WHO	World Health Organization

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PART I: PRODUCT OVERVIEW

Table 2: Product Overview: Azacitidine

Active Substance(s) (International Nonproprietary Name or common name)	Azacitidine
Pharmacotherapeutic Group(s) (Anatomical Therapeutic Chemical classification Code)	Antineoplastic agents, pyrimidine analogues L01BC07
Marketing Authorisation Holder or Applicant	Bristol-Myers Squibb Pharma EEIG Plaza 254 Blanchardstown Corporate Park 2 Dublin 15, D15 T867 Ireland
Medicinal Products to which this RMP Refers	3
Invented Name(s) in the European Economic Area (EEA)	• Vidaza 25 mg/mL powder for suspension for injection • Azacitidine Celgene 25 mg/mL powder for suspension for injection • Onureg 200/300 mg film-coated tablets
Marketing Authorisation Procedure	Vidaza: centralised (EU/1/08/488/001) Azacitidine Celgene: centralised (EU/1/19/1382/001) Onureg: centralised Marketing Authorisation Application (MAA) under evaluation, product reference H0004761
Brief Description of Product Including Chemical Class, Summary of Mode of Action, Important Information About its Composition (eg, origin of active substance of biologicals, relevant adjuvants or residual vaccines)	Azacitidine [4-amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1*H*)-one] is an antineoplastic medicinal product that is believed to exert its antineoplastic effect by causing hypomethylation of deoxyribonucleic acid (DNA) and cytotoxicity on abnormal haematopoietic cells in the bone marrow.
Hyperlink to the Product Information	Summary of product characteristics (SmPC) for Vidaza SmPC for Azacitidine Celgene SmPC for Onureg
Indication(s) in the EEA	Throughout this document, Vidaza and Azacitidine Celgene will collectively be referred to as azacitidine for injection. Onureg will be referred to as oral azacitidine.

Table 2: Product Overview: Azacitidine (Continued)

Indication(s) in the EEA (Continued)	
Current	Azacitidine for injection Azacitidine is indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (HSCT) with: • intermediate-2 (INT-2) and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS). • chronic myelomonocytic leukaemia (CMML) with 10% to 29% marrow blasts without myeloproliferative disorder. • acute myeloid leukaemia (AML) with 20% to 30% blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification. • AML with > 30% marrow blasts according to the WHO classification. Oral azacitidine Onureg is indicated as maintenance therapy in adult patients with AML who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, HSCT.
Proposed	Not applicable
Dosage in the EEA	
Current	Azacitidine for injection 75 mg/m^2 of body surface area (BSA) injected subcutaneously (SC), daily for 7 days, followed by a rest period of 21 days (28-day treatment cycle). It is recommended that patients be treated for a minimum of 6 cycles. Oral azacitidine 300 mg azacitidine orally once daily. Each repeated cycle consists of a treatment period of 14 days followed by a treatment free period of 14 days (28-day treatment cycle).
Proposed	Not applicable
Pharmaceutical Form(s) and Strength(s)	
Current	Azacitidine 25 mg/mL powder for suspension for injection Azacitidine 200 mg and 300 mg film-coated tablets for oral use
Proposed	Not applicable
Is the Product Subject to Additional Monitoring in the European Union (EU)?	No

PART II: SAFETY SPECIFICATION

PART II — MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

1. INDICATION

For the purposes of this RMP, throughout the document:

- Vidaza and Azacitidine Celgene will collectively be referred to as azacitidine for injection.
- Onureg will be referred to as oral azacitidine.

The current approved indication for azacitidine for injection is:

Azacitidine for injection is indicated for the treatment of adult patients who are not eligible for HSCT with:

- INT-2 and high-risk MDS according to the IPSS.
- CMML with 10% to 29% marrow blasts without myeloproliferative disorder.
- AML with 20% to 30% blasts and multi-lineage dysplasia according to the WHO classification.
- AML with > 30% marrow blasts according to the WHO classification.

The current approved indication for oral azacitidine is:

Onureg is indicated as maintenance therapy in adult patients with AML who achieved CR or CRi following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, HSCT.

2. EPIDEMIOLOGY OF THE DISEASE

2.1. Incidence, Prevalence, Mortality and Demographic Profile of the AML Population

The incidence, prevalence, mortality, and demographics of the population of patients with AML are summarised in Table 3.

Table 3: Epidemiology of Patients with AML

Indication/ Target Population	Azacitidine for injection: • adult patients who are not eligible for HSCT with AML with 20% to 30% blasts and multi-lineage dysplasia according to the WHO classification. • adult patients who are not eligible for HSCT with AML with > 30% marrow blasts according to the WHO classification. Oral azacitidine: • maintenance therapy for adult patients with AML who achieved CR or CRi following induction therapy and who are not candidates for, including those who choose not to proceed to, HSCT.
Incidence of Target Indication	• The HAEMACARE project (Cancer Registry Based project on Haematologic malignancies) determined the incidence of haematologic malignancies in Europe by morphologic subtype (International Classification of Diseases for Oncology [ICD-O] classification) through malignancies registered in 2000 to 2002 by 44 European-based cancer registries. • The overall crude incidence rate of AML in the HAEMACARE project was 3.62 per 100,000 (95% confidence interval [CI] 3.54 to 3.70; N = 8107 cases) (Sant, 2010). • The Surveillance of Rare Cancers in Europe (RARECARE) project estimated the incidence, prevalence, and mortality of rare cancers based upon ICD-O classification (Visser, 2012) through malignancies registered in 1995 to 2002 in 64 European-based cancer registries. The overall annual crude incidence rate of AML in the RARECARE project is 3.7 per 100,000 (Visser, 2012). • Based upon incidence rates taken from the HAEMACARE (3.62) and RARECARE (3.7) projects and a total 2013 EU28 population of 507,162,571 (Eurostat, 2014), the estimated annual number of new diagnoses of AML can be estimated at 18,359 to 18,765. • Current estimates of AML incidence from 2 European cancer registry databases, the NORDCAN database and the Haematological Malignancy Research Network (HMRN) range from 1.4 to 4.1 per 100,000 person-years (HMRN, 2019; Danckert, 2019).
Prevalence of Target Indication	• Prevalence estimates for AML were calculated from the RARECARE project based on 22 cancer registries with data from 1988 through 2002. The number of cases observed from 1988 through 2002 and alive as of 01 Jan 2003 (15-year prevalence) was estimated to be 7.7 per 100,000. The expected number of prevalent cases in Europe (EU27) was computed by applying the crude prevalence to the 2008 European population (EU27 = 497.5 million) provided by Eurostat, yielding an estimate of 11.0 per 100,000 or 54,619 persons (Visser, 2012). Using the updated estimate of 507,162,571, the estimated number of prevalent AML cases is 55,788. • Long-term survival (defined as more than 3 years) from a Swedish national registry reported a prevalence of 9.0 per 100,000 population (Juliusson, 2017). • Current estimates of 10-year AML prevalence from NORDCAN and HMRN range from 7.1 to 8.7 per 100,000 population (HMRN, 2019; Danckert, 2019).

Table 3: Epidemiology of Patients with AML (Continued)

Natural History, Including Mortality and Morbidity	• Five-year observed and relative survival rates as calculated from the RARECARE project are 15% and 19%, respectively. As expected, relative survival decreases with increasing age with values of 67% in the age group 0 to 14 years, 56% in the age group 15 to 24 years, 30% in the age group 25 to 64 years and only 5% in the 65 years or older age group (Visser, 2012). • Among long-term (defined as more than 3 years) AML survivors in Sweden 28% had allogenic stem cell transplantation (alloSCT) and 11.5% had acute promyelocytic leukaemia (Juliusson, 2017). The proportions of patients with normal (34.1%), complex karyotype (6.3%) and 7q-/-7 (5.7%) were higher in the alloSCT group compared to the non-alloSCT group. • In a study of 298 Finnish AML patients in CR, relapse-free survival without transplant was 1.7 years (95% CI: 0.81 to 2.60), and 70% of patients with favourable karyotypes had relapse-free survival at 4 years (Koistinen, 2007). • Five-year survival was 71%, 47% and 37% for patients with favourable, intermediate/normal and intermediate/abnormal karyotypes, respectively. Only 8% of patients with an adverse karyotype were alive at 5 years ($p < 0.01$) (Koistinen, 2007). • AML is a malignant disorder of haemopoietic stem cells characterised by clonal expansion of abnormally differentiated blasts of myeloid lineage. Patients may present with extramedullary disease, including involvement of the central nervous system. Rapid proliferation of malignant blasts may be accompanied by tumour lysis syndrome or disseminated intravascular coagulation, both of which can be rapidly fatal without aggressive supportive management and treatment of the underlying AML (Short, 2018). • AML patients may present with signs and symptoms related to pancytopenia, which include infections, fever, weakness, fatigue and haemorrhagic findings like petechiae, menorrhagia and epistaxis. Occasionally, there is sternal discomfort or tenderness and pain in lower extremities. There may be cutaneous or gingival infiltration by leukaemia cells. Physical examination may reveal pallor, lymph node enlargement, hepatomegaly and splenomegaly (Kulsoom, 2018). • The 5-year overall survival for patients who had early remission after induction chemotherapy and patients who had delayed remission after induction chemotherapy were 83% (95% CI: 0.79 to 0.87) and 35% (95% CI: 0.31 to 0.39), respectively ($p < 0.001$) (Ciftciler, 2019). • The 5-year disease-free survival for patients who had early remission after induction chemotherapy and patients who had delayed remission after induction chemotherapy were 81% (95% CI: 0.75 to 0.07) and 28% (95% CI: 0.21 to 0.35), respectively ($p < 0.001$) (Ciftciler, 2019). • Patients who receive no further therapy after remission rapidly relapse due to the regrowth of occult residual leukaemia cells. For patients with early remission, the relapse rate was 15.5% while in late remission patients, the relapse rate was 43.6% (Ciftciler, 2019).
Risk Factors for the Disease	• The incidence of AML is affected by age and gender. The condition is infrequently diagnosed before the age of 40 in adults; thereafter, the incidence of AML increases progressively with age. The incidence is slightly higher in males. In a meta-analysis of 7 prospective cohort studies evaluating the relationship between body mass index and the incidence of AML, the relative risk (RR) of AML was statistically significant in obese individuals ($p < 0.001$) (Castillo, 2012).

Table 3: Epidemiology of Patients with AML (Continued)

Risk Factors for the Disease (Continued)	• Various environmental and chemical exposures have been associated with an increased risk of AML (Deschler, 2006). Predominant among them is benzene. In a meta-analysis of 9 epidemiologic studies of occupational benzene exposure, a fixed-effects model yielded a summary-effect estimate of 1.38 (95% CI: 1.15 to 1.64). Dose-specific effect estimates derived from 4 studies were homogeneous and presented a clear dose-response pattern (low: 1.94; medium: 2.32; high: 3.20) (Khalade, 2010). Cigarette smoking is the only lifestyle factor strongly associated with AML risk; of note, benzene is a component of tobacco smoke. Exposure to ionising radiation among survivors of the atomic bomb explosions in Japan increased the incidence of AML, with a peak at 5 to 7 years after exposure. Therapeutic radiation has been linked to the development of secondary AML (Deschler, 2006). • Therapy-related MDS and AML are well known late complications of cytotoxic chemotherapy (Godley, 2008). Therapy-associated AML (tAML) or MDS (tMDS) has been reported in patients with haematologic malignancy, with solid tumours, and in patients with autoimmune diseases for whom cytotoxic agents are sometimes prescribed. Two major classes of drugs are associated with tMDS or tAML – alkylating agents and topoisomerase II inhibitors. Characteristic chromosomal abnormalities are identified with each of these specific classes of chemotherapies. • Risks of AML among patients treated with autologous peripheral blood stem cell transplantation for a variety of potentially curable malignancies have been recognised for many years (Kollmannsberger, 1998). Genotoxic damage and stresses imposed on haematopoietic stem cells associated with prior chemotherapy administered for treatment of their specific malignancy as well as mobilising chemotherapy are likely to play a role. Inherited polymorphisms in genes governing drug metabolism and DNA repair also may contribute to leukaemogenesis (Godley, 2008). • Among patients with normal cytogenetics, mutations in several genes have been identified. In 2010, an international expert panel, on behalf of the European LeukemiaNet (ELN), developed a standardised reporting/classification system to identify 4 risk groups (favourable, intermediate-1 [INT-1], INT-2, adverse) based upon cytogenetic and molecular genetic data in patients with AML (Döhner, 2010). Among 1550 adults with primary AML who had pretreatment cytogenetic or mutational status (Nucleophosmin-1, CCAAT/enhancer-binding protein alpha, FMS-like tyrosine kinase-3) available, these 4 risk groups separated patients by several outcome parameters (ie, complete remission, disease-free survival, overall survival). Of note, important differences in the ELN distribution were noted between younger and older patients, as were the distributions of several genetic subsets within each ELN subgroup, indicating important age-related differences in AML risk associated with particular cytogenetic and mutational findings (Mrózek, 2012).
Demographic Profile of the Target Population	• AML is a disease that primarily affects older adults. More than half of the patients newly diagnosed with AML in developed countries are aged over 65 years and the median age at diagnosis is 67 to 69 years (Pollyea, 2011; Smith, 2011). The incidence rate is 0.7 per 100,000 for the age group of 0 to 14 years, 0.8 for the group 15 to 24 years, 2.4 for the group 25 to 64 years and 13.7 for the oldest age group (65 years or older). • For patients in CR, the median age is similar between early remission and late remission (46 years and 44 years, respectively). Proportionally, there are more male patients in CR, with a higher proportion of patients in late remission (Ciftciler, 2019). • AML is more common in male patients (Sant, 2010; Smith, 2011; Visser, 2012). In the HAEMACARE project, the crude incidence rate of AML was 3.90 per 100,000 (95% CI: 3.78 to 4.02) in males and 3.35 in females (95% CI: 3.25 to 3.46) (Sant, 2010). According to the RARECARE project, the overall annual incidence rate of AML is 4.0 per 100,000 in males and 3.4 per 100,000 in females (Visser, 2012).

Table 3: Epidemiology of Patients with AML (Continued)

Demographic Profile of the Target Population (Continued)	• The incidence of AML was compared among the 6 largest "non-White" ethnic groups in England between 2001 and 2007 by linking self-assigned ethnicity information from the Hospital Episode Statistics database to the National Cancer Intelligence Network (Shirley, 2013). No significant differences in the AML incidence rates were observed between Whites and the 6 ethnic groups examined (Indian, Pakistani, Bangladeshi, Black African, Black Caribbean, Chinese), nor was there evidence of intra-ethnic group heterogeneity. • Geographic differences were noted in the HAEMACARE project. The incidence of AML was significantly lower than the European average in Eastern Europe (2.07) and higher in the United Kingdom and Ireland (3.24). Of interest, less geographic variation in the incidence of AML and chronic myelogenous leukaemia was noted than for MDS and other myeloproliferative neoplasms. These findings may be affected by under-reporting (Sant, 2010).
Main Treatment Options	• The standard treatment modality for AML is chemotherapy. Treatment decisions are usually based on age, history of myeloid disorders (MDS, CMML, myeloproliferative neoplasm [secondary AML]) prior exposure to cytotoxic therapies (therapy-related AML), cytogenetic risk and performance status (Döhner, 2017). Therapeutic approaches are usually divided into 2 phases: induction of remission and post-remission (consolidation) therapy. Complete remission is defined as the presence of < 5% blasts in the bone marrow, together with recovery of absolute neutrophil and platelet counts in the peripheral blood (Cheson, 2003). When CR/CRi is achieved, there are 3 basic treatment choices for post-remission therapy: additional chemotherapy or, less commonly, stem cell transplantation from a donor (alloSCT) or stem cell transplantation using the patient's own stem cells (autologous stem cell transplantation). • In patients aged < 60 years, those with the best prognoses (favourable cytogenetics, no antecedent haematologic disease or secondary leukaemia) are often treated with chemotherapy with the standard induction scheme ("7+3" regimen; Döhner, 2017, NCCN, 2021) comprising 7 days of continuous infusion of cytosine arabinoside (100 to 200 mg/m^2) + 3 days of an intravenous (IV) anthracycline (eg daunorubicin 60 to 90 mg/m^2; mitoxantrone 12 mg/m^2) plus post-remission therapy. Younger patients with unfavourable cytogenetics and/or antecedent haematologic disease or secondary leukaemia can be treated with 7+3 therapy, followed by inclusion in a clinical trial or HSCT. A CR is reached in 60% to 80% of these younger patients (Estey, 2006; Döhner, 2017; NCCN, 2021). • Older patients with good Eastern Cooperative Oncology Group (ECOG) performance status (0 to 2) and minimal comorbidities can be treated with induction chemotherapy; however, only 30% to 60% of elderly AML patients fall into this group (Deschler, 2006). Treatment outcomes are poor in these patients, with CR rates of 45% to 60%, shorter duration of remission compared to younger patients, and median survival of 7 to 12 months (Burnett, 2007; Dombret, 2008; Estey, 2007; Klepin, 2014). Standard consolidation treatment beyond 1 to 2 cycles is not associated with better outcomes in this age group (NCCN, 2021). Most patients will relapse, and the effectiveness of salvage treatments for many of these patients (patients who attain remission after intensive induction therapy and in whom HSCT is not feasible) remains limited. • For patients who are not candidates for intensive induction therapy, lower-intensity therapy such as azacitidine, decitabine or low-dose cytarabine are considered acceptable treatment options. Other options include gemtuzumab ozogamicin (CD33-positive), enasidenib (for IDH-2 mutated AML), or best supportive care (hydroxyurea, transfusion support) (NCCN 2021; Döhner, 2017). • In the EU, 2 drugs, Rydapt® and Ceplene®, have been approved as post-remission maintenance therapy; however, there are limitations to both therapies and neither has demonstrated a significant effect on overall survival in the AML maintenance setting.

Table 3: Epidemiology of Patients with AML (Continued)

Important Comorbidities	• Cardiac dysfunction. • Renal and hepatic dysfunction. • Diabetes. • Clinical features related to AML, including: – Anaemia (Greer, 2004). – Neutropenia, febrile neutropenia and infection (Greer, 2004; Fanci, 2008; Syrjälä, 2010). – Thrombocytopenia and bleeding (Greer, 2004; Webert, 2006). – Hyperleucocytosis (Milligan, 2006). – Leukaemic cutis (Greer, 2004). – Sweet's syndrome (Miller, 2005). – Tumour lysis syndrome (Miller, 2005; Montesinos, 2008). – Metabolic abnormalities (hypokalaemia, hypocalcaemia; Miller 2005).

2.2. Incidence, Prevalence, Mortality and Demographic Profile of the MDS Population

The incidence, prevalence, mortality, and demographics of the population of patients with MDS are summarised in Table 4. The MDS population treated with azacitidine for injection includes patients with INT-2 and high-risk MDS, CMML (10% to 29% marrow blasts without myeloproliferative disorder) and AML with 20% to 30% blasts and multi-lineage dysplasia.

Table 4: Epidemiology of Patients with MDS

Indication/Target Population	• INT-2 and high-risk MDS according to the IPSS • CMML (10% to 29% marrow blasts without myeloproliferative disorder) • AML with 20% to 30% blasts and multi-lineage dysplasia according to the WHO classification.
Incidence of Target Indication	• The incidence of MDS in Europe appears to be relatively consistent (Neukirchen, 2011; Phekoo, 2006). Based on 216 newly-diagnosed patients identified between 1996 and 2005 in the city of Düsseldorf, the overall age-standardised incidence rate (per 100,000 person-years) was 2.51 for MDS as defined by WHO subtypes (Neukirchen, 2011). Among 2112 adult myeloid malignancies in the South Thames area diagnosed between 1999 and 2000, the incidence (European standard population) of MDS was 3.47 per 100,000 (Phekoo, 2006). The observed similarities in age-standardised incidence rates from Germany and the United Kingdom suggest that the incidence of MDS is similar throughout Western Europe (Neukirchen, 2011; Phekoo, 2006). • The age-adjusted incidence rate for MDS in the United States (US) is 4.9 per 100,000. The age-adjusted incidence rate for refractory anaemia with excess blasts (RAEB) is 0.7 per 100,000 (Howlader, 2014). • There are no prevalence data for MDS from the US and EU cancer registry databases. Using data from the Düsseldorf MDS Registry, in which the point prevalence of MDS was assessed, an age-standardised prevalence of approximately 7 per 100,000 persons was reported. Given the similar incidence and no known differences in disease duration or treatment options between Western European countries, the prevalence of MDS is expected to be similar throughout the EU (Neukirchen, 2011).

Table 4: Epidemiology of Patients with MDS (Continued)

Incidence of Target Indication (Continued)	• Incidence and prevalence estimates have not been reported for specific IPSS sub-groups of MDS. In a multi-centre, retrospective study of 897 patients diagnosed by the German and Austrian MDS Study group between 1976 and 2002, 17.6% of patients were INT-2 risk and 20.7% were high risk, based on the IPSS (Nösslinger, 2010). In a retrospective cohort study of 600 consecutive patients with MDS treated at the MD Anderson Cancer Center in Houston, Texas between January 2002 and December 2004, approximately half were either INT-2 (29.1%) or high risk (21.2%) patients according to IPSS (Naqvi, 2011). • For CMML, RARECARE reported an overall annual incidence rate of 0.3 per 100,000 between 1995 and 2002. The estimated prevalence of CMML on 01 Jan 2008 was 0.7 per 100,000, or an estimated 3442 cases in the EU27 (Visser, 2012). • The incidence of CMML in the US is 0.4 per 100,000 (Howlader, 2014).
Natural History Including Mortality and Morbidity	• The RARECARE study reported a 29% 5-year relative survival rate for MDS based on data from 46 European cancer registries between 2000 and 2002 (Visser, 2012). • In the MDS Multicentre Registry study, the median time of survival from diagnosis was 75 months (range, 1.7 to 350). The 2- and 5-year survival probabilities were 86% and 61%, respectively (Germing, 2012). • Among MDS patients reported to the Surveillance, Epidemiology and End Results (SEER) 17 regions database during 2001 to 2003, the 3-year observed survival was 35%. Age and sex were significantly associated with survival, whereas race was not. Younger patients demonstrated better survival, and men with MDS were 25% more likely to die than women (Ma, 2007). • As reported by Naqvi (2011), patients with IPSS low-risk classification had a median survival of 33.6 months, whereas the median survival of the high-risk group was 8.7 months ($p < 0.001$). Survival curves stratified by Adult Comorbidity Evaluation-27 (ACE-27) comorbidity scores identified no significant effect on survival in patients in the low-risk category ($p < 0.68$), whereas patients in the INT-1 and INT-2 groups ($p < 0.001$) and high-risk category ($p < 0.04$) had significantly worse survival with increasing ACE-27 score. Patients younger than 65 years had longer median survival than those older than 65 years (27.9 versus 14.4 months; $p < 0.001$). Comorbidities had no significant effect on survival among those older than 65 years. • Progression to AML occurs at a variable rate depending on the presence of adverse prognostic risk factors. In the Multicentre Registry study, the cumulative AML progression risk was 4.7% after 2 years of diagnosis and 14.7% (competing risk method) (Germing, 2012). • The RARECARE study reported that, among patients with CMML, the 5-year relative survival rate was 18% (Visser, 2012).
Risk Factors for the Disease	• Although the aetiology of MDS remains unclear, risk factors for the disease include gender, age and exposure to ionising radiation, chemicals, drugs or other environmental agents (Silverman, 2000).
Demographic Profile of Target Population	• The overall age standardised incidence rate was 4.30 and 3.32 per 100,000 person-years for men and women, respectively, in the Düsseldorf MDS Registry. The incidence rate ratio comparing men to women was 1.78 (Neukirchen, 2011). • Using data from the Düsseldorf MDS Registry, in 2003 the median age of prevalent male and female patients was 69 and 78 years, respectively (Neukirchen, 2011). • Incidence rates increase sharply with age, rising from 9.9 per 100,000 at ages 60 to 69 years, to 30.3 per 100,000 at ages 70 to 79 years, and 58.0 per 100,000 among persons aged 80 years and older (Howlader, 2014).

Table 4: Epidemiology of Patients with MDS (Continued)

Demographic Profile of Target Population (Continued)	• The incidence of MDS is roughly twice as high for men than women in the oldest age groups (40.3 versus 22.6 per 100,000 in men and women aged 70 to 79 years, and 87.4 versus 41.5 per 100,000 in men and women aged 80 years and older (Howlader, 2014). • Among CMML patients identified in the RARECARE project, incidence rates for males and females were 0.3 and 0.2 per 100,000, respectively. The incidence rates for those aged 25 to 64 years and those aged 65 years and over were 0.1 and 1.6 per 100,000, respectively (Visser, 2012). • Incidence rates of CMML rose less markedly with age among persons identified in the SEER registry (1.0 per 100,000 in those aged 60 to 69 years, 2.8 per 100,000 in those aged 70 to 79 years and 4.6 per 100,000 in those aged 80 years and older). Incidence rates are also higher in males than females in these age groups (Howlader, 2014).
Main Treatment Options	• The only potentially curative approach that currently exists for treating MDS patients is allogeneic HSCT (Greenberg, 2010). This approach is typically only employed in younger patients with higher-risk disease because of morbidity/mortality and the lack of a suitable donor in older patients; hence, allogeneic HSCT is only a potential solution in a small subset (approximately 5%) of MDS patients (Silverman, 2002; Greenberg, 2010). • Current therapeutic agents for treating patients with higher-risk MDS remain limited and are patient specific. Current therapeutic options are dependent upon whether the patient is a candidate for intensive therapy. Clinical features relevant for this determination include the patients' age, performance status, comorbidities, and cytogenetic karyotype. • High-intensity chemotherapy (AML-induction and consolidation chemotherapy) includes high-dose cytarabine plus an anthracycline. Complete response rates vary from 47% to 68%; however, intensive chemotherapy is associated with a high mortality (up to 35%), prolonged hospitalisation, and significant decrease in quality of life during the period of induction (Alessandrino, 2002; Ossenkoppele, 2004; Sekeres, 2004). • For those patients considered ineligible for intensive chemotherapy, lower-intensity options such as decitabine or azacitidine are considered acceptable treatment options. In the latest National Comprehensive Cancer Network (NCCN) MDS guidelines, it is stated that azacitidine is the preferred treatment for intermediate and high-risk patients over decitabine or clinical trials (NCCN MDS Guidelines, 2018).
Important Comorbidities	• Anaemia (List, 2002; Steensma, 2006; Greenberg, 1999; Bowen 2003; Stone, 2004). • Neutropenia and infections (Steensma, 2006; Greenberg, 1999; Pomeroy, 1991; Nordic MDS Group, 2004). • Thrombocytopenia and bleeding (Steensma, 2006; Greenberg, 1999; Luger, 2002; Nordic MDS Group, 2004; Jädersten, 2005). • Transformation to AML (Steensma, 2006; Matsushima, 2003; Fukumoto, 2005).

PART II — MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION

1. NONCLINICAL PART OF THE SAFETY SPECIFICATION

Most of the nonclinical studies with azacitidine were conducted prior to the establishment of International Council for Harmonisation (ICH) guidelines and Good Laboratory Practice (GLP) regulations. The majority of these nonclinical studies were reported as peer-reviewed publications and have been used to support the development of azacitidine. The safety of azacitidine in humans has been evaluated in multiple clinical trials and postmarketing experience (see Part II SV for global exposure to azacitidine). Although most of nonclinical data for azacitidine were generated prior to implementation of ICH guidelines and GLP regulations, current nonclinical data appropriately assess azacitidine toxicity. Importantly, the safety profile of azacitidine in MDS and AML patients has been well-established based on over 10 years' postmarketing exposure, including more than 450,000 patients. Additional nonclinical studies with azacitidine are therefore unlikely to add value to the existing nonclinical safety assessment.

In general, azacitidine toxicity including effects on target organs (bone marrow, lymphoid tissues, liver, kidney and gastrointestinal tract), carcinogenicity, and reproductive and developmental toxicity occurred in animals at doses lower than the clinical doses.

A summary of the nonclinical findings and their relevance to human usage is outlined in Table 5.

Table 5: Nonclinical Risks and Relevance to Human Use

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Repeat-dose Toxicity Studies Repeat-dose toxicity studies were conducted in mice, dogs, and monkeys. In mice, maximum tolerated dose of 18 mg/m^2/day was determined after 7 days of IV dosing based on clinical signs and body weight changes. At 9 mg/m^2/day for 7 days in mice, azacitidine caused pancytopenia correlating with bone marrow hypocellularity, lymphoid depletion in spleen and thymus, and single cell necrosis in the intestine. In dogs following 10 days of IV dosing, reversible lymphoid depletion, decreased red cell mass, white blood cells and platelets linked to bone marrow depletion, and liver/kidney degeneration were observed at $\leq$ 11 mg/m^2/day. Mortality was noted at 22 mg/m^2/day in dogs. In monkeys given azacitidine by the IV route daily for 14 days, reversible decreases in red blood cells and white blood cells, and bone marrow and lymphoid depletion were seen at 15 mg/m^2/day. A dose of 32 mg/m^2/day resulted in deaths. A 14-day oral toxicity study in dogs at $\geq$ 0.4 mg/kg/day (8 mg/m^2/day) resulted in mortality, severe pancytopenia, intestinal gland/lumen dilation and single cell necrosis in the intestines, cellular depletion in bone marrow, and lymphoid depletion in the thymus, spleen, and lymph nodes. Adverse effects were greatest in the second week of dosing, continuing into the recovery period. These repeat-dose toxicity studies revealed bone marrow, liver, kidney, gastrointestinal tract, and lymphoid organs as the primary target organs of toxicity. Toxicity to bone marrow, liver, kidney and lymphoid tissues was apparent clinically by alterations in haematology parameters.	Repeat-dose toxicity studies revealed bone marrow, liver, kidney, gastrointestinal tract, and lymphoid organs as the primary target organs of toxicity. Toxicity was apparent clinically by alterations in haematology and serum chemistry parameters. Dose adjustments to be made in the case of haematological toxicity and/or in special populations are described in Section 4.2 of the SmPCs for azacitidine for injection and oral azacitidine. Monitoring of complete blood counts is included in Sections 4.2 of the SmPCs for azacitidine for injection and oral azacitidine, and Section 4.4 of the SmPC for azacitidine for injection; haematological events and other findings observed clinically, including gastrointestinal effects, are described in Section 4.8 of the SmPCs for azacitidine for injection and oral azacitidine.

Table 5: Nonclinical Risks and Relevance to Human Use (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Genotoxicity/Carcinogenicity Azacitidine induces both gene mutations and chromosomal aberrations in bacterial and mammalian cell systems in vitro. The potential carcinogenicity of azacitidine was evaluated in at least 4 carcinogenicity studies in mice and rats. Azacitidine induced tumours of the haematopoietic system in female mice, when administered intraperitoneally (IP) at 2.2 mg/kg (6.6 mg/m^2) administered 3 times per week for 52 weeks. An increased incidence of tumours in the lymphoreticular system, lung, mammary gland, and skin was observed in mice treated with azacitidine IP for 50 weeks. A tumourigenicity study in rats dosed twice weekly at 2.6 mg/kg (15 mg/m^2) or 5.2 mg/kg (31.2 mg/m^2) for 9 months revealed an increased incidence of testicular tumours. Although these studies were conducted by the IP route for up to only 9- or 52-weeks duration, each of the studies revealed a carcinogenic potential at doses of approximately 2 to 5 mg/kg up to 3 × /wk. None of the studies were conducted in accordance with current GLP and ICH guidelines.	Azacitidine toxicity in animals, as documented in published studies, might be related to azacitidine interaction with nucleic acids and subsequently, its impact on cell proliferation and survival (Altanerová, 1975; Benedict, 1977, Carr 1984; Cavaliere, 1987; Harrison, 1983; Stoner, 1973). At the doses proposed for patients with MDS and AML, azacitidine is expected to be well tolerated. However, because of the genotoxic and carcinogenic effects revealed in the toxicology programme, the therapeutic benefit of azacitidine in MDS and AML patients must be considered in the context of the potential risk for carcinogenicity. Malignancies (including injection site tumours) were included as an Important Potential Risk since the first approved RMP Version 3.0 for azacitidine for injection. To align with Revision 2 of the Good Pharmacovigilance Practices Module V and the definition of an Important Potential Risk, the risk for malignancies was reclassified in EU RMP Version 14.0 as a Potential Risk from an Important Potential Risk for azacitidine for injection. Malignancies was no longer deemed to be a safety concern for azacitidine for injection in consideration of the changes in the scientific level of evidence for benefit-risk profile impact based on clinical experience and routine risk minimisation measures being considered effective. Thus, malignancies is not included as a safety concern for oral azacitidine. The results of preclinical genotoxicity and carcinogenicity studies are outlined in Section 5.3 of the SmPCs for azacitidine for injection and oral azacitidine.
Reproductive and Developmental Toxicity The reproductive and developmental toxicity of azacitidine has been evaluated in numerous published studies over the period from 1966 to the present. Because of the pharmacologic capacity of azacitidine to result in cytotoxicity to rapidly dividing cells and affect gene expression, embryos are extremely sensitive to a single low dose during embryonic development. Azacitidine causes embryolethality and teratogenicity at administered dose levels in animals that are lower than the intended clinical dose. Embryo lethality was readily produced in mice given azacitidine during early gestation at doses of 6 mg/m^2. In rats, embryolethality, resorptions and/or malformations	Azacitidine demonstrated its ability to cause harm to the embryo and foetus at very low doses in rodents. There are no adequate data on the use of azacitidine in pregnant women. The potential risk for humans is unknown. Azacitidine is not recommended during pregnancy (especially during the first trimester, unless clearly necessary) and in women of childbearing potential not using contraception. The advantages of treatment should be weighed against the possible risk for the foetus in every individual case. If a patient or partner becomes pregnant while taking azacitidine, the patient should be informed of the potential risk to the foetus.

Table 5: Nonclinical Risks and Relevance to Human Use (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
were seen at repeat doses as little as 0.3 mg/kg (1.8 mg/m^2) in early pregnancy. Multiple reproductive studies have shown that dividing cells are most susceptible to azacitidine. A limited number of studies on male fertility in rodents have revealed adverse effects on the male reproductive organs, sperm counts, decreased pregnancy rates, increased loss of embryos in untreated mated females and resulting progeny. Azacitidine is teratogenic in rats given a single dose of as little as 0.5 mg/kg (3 mg/m^2). None of the studies were conducted in accordance with current GLP and ICH guidelines.	Women of childbearing potential have to use effective contraception during and for a defined period of time after treatment. Men must use effective contraception during and up to 3 months after treatment (see Sections 4.6 and 5.3 of the SmPCs for azacitidine for injection and oral azacitidine, and Section 4.4 of the SmPC for oral azacitidine). Men should be advised not to father a child while receiving treatment (see Section 4.6 of the SmPCs for azacitidine for injection and oral azacitidine, and Section 4.4 of the SmPC for oral azacitidine).
Cardiovascular Toxicity Increased heart rate, decreased blood pressure and prolonged corrected QT interval and increased serum creatine kinase and creatine kinase isozyme-2 concentration were observed in a cardiovascular (CV) safety pharmacology dog study at high plasma concentrations following IV dosing. The ability to attribute the CV changes to a direct effect of azacitidine is confounded by various adverse clinical signs noted in these dogs. Follow-up in vitro studies using isolated rat aorta, guinea pig right atria, and isolated perfused guinea pig hearts concluded that azacitidine had no direct effect on heart rate, contractility, and vasodilatory parameters. Therefore, alterations of CV parameters noted in the safety pharmacology study in dogs were considered as an indirect result of severe clinical signs noted at high IV doses of azacitidine.	A review of the available human clinical and safety data was conducted for RMP Version 5.0. The safety data revealed no suggestion that azacitidine administration is directly associated with QT interval prolongation, torsade de pointes or ventricular tachycardia. To date, no safety signal for QT prolongation has been identified from clinical and exhaustive postmarketing exposure to azacitidine. Therefore, the confounded results in the CV nonclinical study (animal species: dogs) is not considered relevant for humans.

PART II — MODULE SIII: CLINICAL TRIAL EXPOSURE

1. CLINICAL TRIAL EXPOSURE

1.1. Exposure to Azacitidine in the Pivotal and Supportive Studies

The activity of azacitidine for injection has been demonstrated in 4 completed clinical studies in MDS, comprising a pivotal study AZA PH GL 2003 CL 001 and 3 supportive studies, Cancer and Leukaemia Group B (CALGB) 9221, CALGB 8921 and CALGB 8421, and 1 pivotal study in AML (AZA-AML-001). Of the 679 patients who received azacitidine for injection (Safety Population), 48 patients received IV azacitidine and 631 patients received SC azacitidine. Overall 679 patients have received azacitidine for injection in the 5 completed clinical studies (pivotal and supportive).

The activity of oral azacitidine in AML maintenance has been demonstrated in 1 clinical study (Study CC-486-AML-001). Final analysis of this study is complete. Patients on long-term treatment in this study are being followed up, but no further outcome analyses are anticipated. Overall, 236 patients have received oral azacitidine in this study.

1.2. AML Clinical Studies

1.2.1. Oral Azacitidine

A total of 236 patients have received oral azacitidine in clinical study CC-486-AML-001, representing 355.06 person-years of exposure. Exposure to oral azacitidine in AML patients in Study CC-486-AML-001 is presented by duration of exposure in Table 6, and by age group, gender and ethnic origin in Table 7.

Table 6: Duration of Exposure to Oral Azacitidine in Study CC-486-AML-001 (Safety Population)

Duration of Exposure	Distribution of Number of Cycles (n [%]) Oral Azacitidine (N = 236)	Patient-years
1 or more cycles	236 (100)	355.06
2 or more cycles	222 (94.1)	354.20
3 or more cycles	204 (86.4)	351.47
4 or more cycles	196 (83.1)	349.40
5 or more cycles	186 (78.8)	346.23
6 or more cycles	174 (73.7)	341.32
12 or more cycles	125 (53.0)	308.61
18 or more cycles	90 (38.1)	269.27
24 or more cycles	74 (31.4)	243.88
30 or more cycles	58 (24.6)	209.35
Overall	**236 (100)**	**355.06**

Table 7: Duration of Exposure to Oral Azacitidine in Study CC-486-AML-001 by Age Group, Gender and Ethnic Origin (Safety Population)

Parameter	Oral Azacitidine (N = 236)	Patient-years
Gender (n [%])		
Male	118 (50.0)	166.96
Female	118 (50.0)	188.10
Age Group (n [%])		
< 55 years	0 (0.0)	-
55 to 64 years	65 (27.5)	102.03
65 to 74 years	143 (60.6)	214.13
75 to 84 years	27 (11.4)	38.86
≥ 85 years	1 (0.4)	0.05
Ethnic Origin		
White	215 (91.1)	321.42
Black or African American	1 (0.4)	2.40
Asian	6 (2.5)	5.05
Native Hawaiian or Other Pacific Islanders	0 (0.0)	-
American Indian or Alaskan Native	0 (0.0)	-
Other	12 (5.1)	23.82
Missing	2 (0.8)	2.38

The baseline characteristics of patients randomised to oral azacitidine in Study CC-486-AML-001 are summarised in Table 8.

Table 8: Baseline Characteristics of Patients Randomised to Oral Azacitidine in Study CC-486-AML-001 (Safety Population)

Characteristic	Oral Azacitidine (N = 236)
Gender (n [%])	
Male	118 (50.0)
Female	118 (50.0)
Age in Years	
Mean ± SD	67.9 ± 5.70
Range	55 to 86
Age Group (n [%])	
< 75 years	208 (88.1)
≥ 75 years	28 (11.9)

SD = standard deviation.

1.2.2. Azacitidine for Injection

A total of 236 patients have received azacitidine for injection in pivotal AML study AZA-AML-001, representing 174.9 person-years of exposure. Exposure to azacitidine for injection in AML patients in the pivotal clinical study (AZA-AML-001) is presented by duration of exposure in Table 9 and by dose in Table 10.

Table 9: Duration of Exposure to Azacitidine for Injection in Study AZA-AML-001 (Safety Population)

Parameter	Azacitidine for Injection (N = 236)
Total Exposure (person-years)[a]	**174.9**
Duration of Exposure (days)[b]	
n	236
Mean ± SD	270.7 ± 223.99
Median	191.5
Min, Max	30, 929
Number of Cycles	
n	236
Mean ± SD	8.8 ± 7.39
Median	6.0
Min, Max	1, 28
Distribution of Number of Cycles (n [%])	
1 or more	236 (100)
2 or more	201 (85.2)
3 or more	171 (72.5)
4 or more	158 (66.9)
5 or more	146 (61.9)
6 or more	124 (52.5)
12 or more	76 (32.2)
> 12	68 (28.8)

CSR = Clinical Study Report; Max = maximum; Min = minimum; SD = standard deviation.
[a] Total exposure in person-years was defined as (duration of exposure in days/365.25).
[b] Duration of exposure was defined as the period from date of first dose through date of (1) last dose + 28 days.
Source: AZA-AML-001 CSR.

Table 10: Summary of Dose Information for Azacitidine for Injection (Safety Population)

Parameter	Azacitidine for Injection (N = 236)
Average Prescribed Daily Dose (mg/m^2)	
n	236
Mean ± SD	73.4 ± 5.12
Median	75.0
Min, Max	42, 75
Average Total Daily Dose (mg/day)	
n	236
Mean ± SD	129.8 ± 17.69
Median	131.1
Min, Max	61, 182
Cumulative Dose (mg)	
n	236
Mean ± SD	7816.5 ± 6818.00
Median	5309.5
Min, Max	405, 29,500

CSR = Clinical Study Report; Max = maximum; Min = minimum; SD = standard deviation.
Source: AZA-AML-001 CSR.

The baseline characteristics of patients randomised to azacitidine for injection in Study AZA-AML-001 are summarised in Table 11.

Table 11: Baseline Characteristics of Patients Randomised to Azacitidine for Injection in Study AZA-AML-001 (Intent-to-Treat Population)

Characteristic	AZA-AML-001 N = 241
Gender (n [%])	
Male	139 (57.7)
Female	102 (42.3)
Race (n [%])	
White/Caucasian	185 (76.8)
Black	2 (0.8)
Asian	37 (15.4)
Hawaiian/Pacific Islander	1 (0.4)
Other	1 (0.4)
Not applicable	15 (6.2)

Table 11: Baseline Characteristics of Patients Randomised to Azacitidine for Injection in Study AZA-AML-001 (Intent-to-Treat Population) (Continued)

Characteristic	AZA-AML-001 N = 241
Age in Years	
Mean ± SD	75.4 ± 5.60
Range	64 to 91
Age Group (n [%])	
< 75 years	103 (42.7)
≥ 75 years	138 (57.3)
Weight (kg)	
Mean ± SD	72.4 ± 15.15
Range	36 to 141
BSA (m^2)	
Mean ± SD	1.8 ± 0.22
Range	1 to 2

BSA = body surface area; CSR = Clinical Study Report; SD = standard deviation.
Source: AZA-AML-001 CSR.

More than half of the patients in Study AZA-AML-001 were male (57.7%), aged ≥ 75 years (57.3%), and the majority of patients were White (76.8%).

1.3. MDS Clinical Studies

A total of 443 patients have received azacitidine for injection (395 SC, 48 IV) in the 4 completed clinical studies in MDS (pivotal and supportive), representing 388.6 person-years of exposure. Of these 443 patients, 175 were included in pivotal study AZA PH GL 2003 CL 001 and 268 patients were included in the 3 supportive studies (CALGB 9221, CALGB 8921 and CALGB 8421).

Exposure to azacitidine for injection in MDS patients in the pivotal (AZA PH GL 2003 CL 001) and supportive (CALGB 9221, CALGB 8921 and CALGB 8421) clinical studies is summarised by duration in Table 12 and by dose in Table 13.

Table 12: Cumulative Exposure to Azacitidine for Injection in MDS Studies by Month (Safety Population)

Cumulative Exposure	Number of Person-Years		
	AZA PH GL 2003 CL 001 N = 175	CALGB Studies N = 268	Overall N = 443
1 month	13.4	20.4	33.8
3 months	39.0	55.4	94.3
6 months	71.6	94.5	166.1

Table 12: Cumulative Exposure to Azacitidine for Injection in MDS Studies by Month (Safety Population) (Continued)

Cumulative Exposure	Number of Person-Years		
	AZA PH GL 2003 CL 001 N = 175	CALGB Studies N = 268	Overall N = 443
12 months	119.6	139.0	258.6
24 months	161.4	177.3	338.8
36 months	168.8	192.7	361.5
48 months	169.2	200.5	369.8
60 months	–	205.8	375.0
72 months	–	209.7	378.9
84 months	–	211.8	381.1
96 months	–	213.5	382.7
180 months	–	219.4	388.6
Median (range)	0.83 (0.13, 3.14)	0.45 (0.02, 13.31)	0.62 (0.02, 13.31)

Notes: Total exposure is calculated from the first dose to 42 days after the last dose for Study AZA PH GL 2003 CL 001 and from first dose to 30 days after the last dose for Studies CALGB 9221, CALGB 8921 and CALGB 8421. Details of the azacitidine for injection treatments are based on the safety population.
Source: Data on file (available upon request).

Table 13: Exposure to Azacitidine for Injection in MDS Studies by Dose (Safety Population)

Dose	AZA PH GL 2003 CL 001 N = 175		CALGB Studies[a] N = 267		Overall N = 443	
	n (%)	Person-Years	n (%)	Person-Years	n (%)	Person-Years
Daily Dose[b]						
37.5 mg/m^2[c]	23 (13.1)	14.7	82 (30.7)	45.4	105 (23.8)	60.0
50 mg/m^2[d]	7 (4.0)	2.5	56 (21.0)	23.6	63 (14.3)	26.2
75 mg/m^2[e]	175 (100)	152.0	266 (99.6)	115.3	441 (99.8)	267.3
100 mg/m^2[f]	0	0	53 (19.9)	35.0	53 (12.0)	35.0
Median Daily Dose (range)	-	74.79 (35.58, 78.45)	-	75.00 (31.19, 100.00)	-	74.98 (31.19, 100.00)

[a] Patient [redacted] in Study CALGB 8421 received study drug but the prescribed daily dose was unknown. Therefore, this patient is excluded.
[b] Patients could have received more than 1 dose level due to dose adjustments. Patients with dosing adjustments at given treatment cycles are included in their respective azacitidine dosing categories. Dose groups are based on the actual dose for Study AZA PH GL 2003 CL 001 and the prescribed dose for Studies CALGB 9221, CALGB 8921 and CALGB 8421.
[c] Includes doses of 18 to 41 mg/m^2 and 13 to 44 mg/m^2 in Study AZA PH GL 2003 CL 001 and the CALGB studies, respectively.
[d] Includes doses of 45 to 63 mg/m^2 and > 44 to 62.5 mg/m^2 in Study AZA PH GL 2003 CL 001 and the CALGB studies, respectively.
[e] Includes doses of 66 to 82 mg/m^2 and > 62.5 to 87.5 mg/m^2 in Study AZA PH GL 2003 CL 001 and the CALGB studies, respectively.
[f] Includes doses of > 87.5 to 150 mg/m^2 in the CALGB studies.
Notes: Total exposure is calculated from the first dose to 42 days after the last dose for Study AZA PH GL 2003 CL 001 and from first dose to 30 days after the last dose for Studies CALGB 9221, CALGB 8921 and CALGB 8421. Details of the azacitidine treatments are based on the safety population.
Source: Data on file (available upon request).

In both the pivotal and supportive studies, the median daily dose of azacitidine for injection was 75 mg/m^2, with almost all patients (> 99%) treated at this dose level (Table 13).

The baseline characteristics of patients randomised to azacitidine for injection in the 4 clinical studies in MDS are summarised in Table 14, and exposure to azacitidine for injection in these patients is summarised by gender and age in Table 15, by ethnic origin in Table 16 and by baseline French-American-British (FAB) status in Table 17.

Table 14: Baseline Characteristics of Patients Randomised to Azacitidine for Injection in MDS Studies (Intent-to-Treat Population)

Characteristic	AZA PH GL 2003 CL 001[a] N = 179[c]	CALGB 9221 N = 150[d]	CALGB 8921[b] N = 72[e]	CALGB 8421 N = 48[f]
Gender (n [%])				
Male	132 (73.7)	103 (68.7)	49 (68.1)	31 (64.6)
Female	47 (26.3)	47 (31.3)	23 (31.9)	17 (35.4)

Table 14: Baseline Characteristics of Patients Randomised to Azacitidine for Injection in MDS Studies (Intent-to-Treat Population) (Continued)

Characteristic	AZA PH GL 2003 CL 001[a] N = 179[c]	CALGB 9221 N = 150[d]	CALGB 8921[b] N = 72[e]	CALGB 8421 N = 48[f]
Race (n [%])				
White/Caucasian	177 (98.9)	140 (93.3)	68 (94.4)	48 (100)
Black	0	2 (1.3)	2 (2.8)	0
Hispanic	0	5 (3.3)	1 (1.4)	0
Asian	2 (1.1)	3 (2.0)	0	0
Other	0	0	1 (1.4)	0
Age in Years				
Mean ± SD	68.0 ± 7.57	67.2 ± 10.02	64.6 ± 12.07	63.1 ± 10.72
Range	42 to 83	31 to 92	23 to 82	35 to 81
Age Group (n [%])				
< 65 years	57 (31.9)	53 (35.3)	26 (36.1)	21 (43.8)
65 to 74 years	84 (46.9)	61 (40.7)	25 (34.7)	24 (50.0)
≥ 75 years	38 (21.2)	36 (24.0)	16 (22.2)	3 (6.3)
Height (cm)				
Mean ± SD	170.1 ± 8.19	170.7 ± 9.72	170.3 ± 10.14	169.6 ± 9.36
Range	148 to 191	145 to 197	142 to 191	155 to 191
Weight (kg)				
Mean ± SD	76.5 ± 14.08	78.4 ± 17.37	78.2 ± 19.46	71.7 ± 13.83
Range	47 to 134	45 to 135	46 to 156	49 to 108
BSA (m^2)				
Mean ± SD	1.9 ± 0.19	1.90 ± 0.236	1.87 ± 0.244	1.82 ± 0.208
Range	1.4 to 2.5	1.20 to 2.56	1.40 to 2.48	1.46 to 2.20

BSA = body surface area; CSR = Clinical Study Report; SD = standard deviation.
Source: AZA PH GL 2003 CL 001, CALGB 9221, CALGB 8921 and CALGB 8421 CSRs.
[a] The data in Study AZA PH GL 2003 CL 001 represent the 179 patients in the azacitidine treatment group; however, 4 patients did not actually receive azacitidine for injection.
[b] The data in Study CALGB 8921 represent the 72 patients in the treatment group; however, 2 patients did not actually receive azacitidine for injection.
[c] N = 171 and 165 for height and weight data, respectively.
[d] N = 143, 146 and 147 for weight, height and BSA data, respectively.
[e] N = 66 for weight data, 67 for age and age group data, and 68 for height and BSA data.
[f] N = 42, 43 and 45 for height, weight and BSA data, respectively.

Table 15: Exposure to Azacitidine for Injection in MDS Studies by Gender and Age (Safety Population)

Gender/ Age	AZA PH GL 2003 CL 001 N = 175		CALGB Studies N = 268		Overall N = 443	
	n (%)	Person-Years	n (%)	Person-Years	n (%)	Person-Years
Male						
< 65 years	41 (23.4)	37.4	69 (25.7)	69.0	110 (24.8)	106.4
≥ 65 years	89 (50.9)[a]	87.9	112 (41.8)	92.2	201 (45.4)	180.1
≥ 75 years	27 (15.4)	23.5	39 (14.6)	27.7	66 (14.9)	51.2
Female						
< 65 years	15 (8.6)	17.2	35 (13.1)	27.3	50 (11.3)	44.5
≥ 65 years	30 (17.1)[b]	26.7	52 (19.4)	30.9	82 (18.5)	57.6
≥ 75 years	11 (6.3)	9.4	16 (6.0)	8.8	27 (6.1)	18.2

[a] Includes all male patients ≥ 65 years old (including 27 males aged ≥ 75 years).
[b] Includes all female patients ≥ 65 years old (including 11 females aged ≥ 75 years).
Notes: Total exposure is calculated from the first dose to 42 days after the last dose for Study AZA PH GL 2003 CL 001 and from first dose to 30 days after the last dose for Studies CALGB 9221, CALGB 8921 and CALGB 8421.
Source: Data on file (available upon request).

Table 16: Exposure to Azacitidine for Injection in MDS Studies by Ethnic Origin (Safety Population)

Ethnic Origin	AZA PH GL 2003 CL 001 N = 175		CALGB Studies N = 268		Overall N = 443	
	n (%)	Person-Years	n (%)	Person-Years	n (%)	Person-Years
White/ Caucasian	173 (98.9)	166.6	254 (94.8)	208.6	427 (96.4)	375.3
Black	0	0	4 (1.5)	2.8	4 (0.9)	2.8
Other/Unknown	2 (1.1)	2.6	10 (3.7)	7.9	12 (2.7)	10.5

Notes: Total exposure is calculated from the first dose to 42 days after the last dose for Study AZA PH GL 2003 CL 001 and from first dose to 30 days after the last dose for Studies CALGB 9221, CALGB 8921 and CALGB 8421.
Source: Data on file (available upon request).

Table 17: Exposure to Azacitidine for Injection in MDS Studies by Baseline FAB Classification (Safety Population)

Baseline Parameter	AZA PH GL 2003 CL 001 N = 175		CALGB Studies N = 268		Overall N = 443	
	n (%)	Person-Years	n (%)	Person-Years	n (%)	Person-Years
FAB Classification[a]						
RAEB	102 (58.3)	105.5	110 (41.0)	92.3	212 (47.9)	197.8
RAEB-T	59 (33.7)	49.6	65 (24.3)	36.6	124 (28.0)	86.2
Other	14 (8.0)	14.1	93 (34.7)	90.5	107 (24.2)	104.6

FAB = French-American-British; RAEB = refractory anaemia with excess blasts; RAEB-T = refractory anaemia with excess blasts in transformation.

[a] For Study AZA PH GL 2003 CL 001, the Independent Review Committee determined baseline FAB classification was used. For Studies CALGB 9221, CALGB 8921 and CALGB 8421, the adjudicated baseline FAB was used.

Notes: Total exposure is calculated from the first dose to 42 days after the last dose for Study AZA PH GL 2003 CL 001 and from first dose to 30 days after the last dose for Studies CALGB 9221, CALGB 8921 and CALGB 8421.

Source: Data on file (available upon request).

The majority of patients were male (approximately 70%), Caucasian and ≥ 65 years of age (Table 14), and were reflective of the target population (see Module Part II SI). In both the pivotal and supportive studies, the majority of patients were classified as having RAEB or refractory anaemia with excess blasts in transformation (RAEB-T) at baseline (Table 17). While nearly 60% of patients were classified as having RAEB in Study AZA PH GL 2003 CL 001, the corresponding percentage was lower (41%) in the supportive studies (Table 17).

PART II — MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

1. EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

The important exclusion criteria in the pivotal clinical studies across the development programme (Study CC-486-AML-001 for oral azacitidine and Studies AZA-AML-001 and AZA PH GL 2003 CL 001 for azacitidine for injection) are described in Table 18.

Table 18: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion Criteria	Reason for Exclusion	Is it Considered to be Included as Missing Information? If No, Rationale.
Known or suspected hypersensitivity to azacitidine	Safety reasons. To protect patient safety by ensuring that patients with known hypersensitivity to the medicinal product were not included in the clinical studies.	No. Azacitidine is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients (Section 4.3 of the SmPCs for oral azacitidine and azacitidine for injection).
Breastfeeding	Safety reasons. To prevent exposure to infants and toddlers. It is unknown whether azacitidine/metabolites are excreted in human milk.	No. Due to the potential serious adverse reactions in the breastfed child, azacitidine is contraindicated during breastfeeding (Sections 4.3 and 4.6 of the SmPCs for oral azacitidine and azacitidine for injection).
Renal Impairment	Safety reasons. Azacitidine and/or its metabolites are primarily excreted by the kidney. Renal impairment may result from an underlying medical condition that could influence the interpretation of the study data.	No. <u>Oral azacitidine</u> A population pharmacokinetic (PK) analysis following a 300 mg dose of oral azacitidine determined that the effect of severe renal impairment on oral azacitidine was similar to the clinical renal impairment study with injectable azacitidine discussed below (~40% increase in area under the concentration-time curve [AUC]). The exposure of azacitidine is approximately 75% lower after oral administration relative to the exposure achieved following SC administration; therefore, an increase in exposure of approximately 40% following oral administration is still considered safe and tolerable. Thus, no initial dose adjustment of oral azacitidine is recommended in patients with mild, moderate, or severe renal impairment (Sections 4.2 and 5.2 of the SmPC for oral azacitidine). <u>Azacitidine for injection</u> The influence of renal impairment on the PK of azacitidine was evaluated in 6 cancer subjects with normal renal function (creatinine clearance [CLcr] > 80 mL/min) and 6 subjects with severe renal impairment (CLcr < 30 mL/min) following daily SC dosing at 75 mg/m^2/day (AZA PH US 2007 PK 006). Severe renal impairment increased azacitidine exposure by approximately 70% after single and 41% after multiple subcutaneous administrations. This increase in exposure was not correlated with an increase in adverse events and initial dose

Table 18: Important Exclusion Criteria in Pivotal Clinical Studies (Continued)

Exclusion Criteria	Reason for Exclusion	Is it Considered to be Included as Missing Information? If No, Rationale.
Renal Impairment (Continued)		modification was not recommended in subjects with renal impairment after SC or IV administration. Subsequent dose modifications should be based on renal toxicities (Section 4.2 of the SmPC for azacitidine for injection). The SmPC for azacitidine for injection contains advice that patients with renal impairment should be closely monitored for toxicity (Section 4.4 of the SmPC for azacitidine for injection).
Pregnancy	Safety reasons. Studies in mice have shown reproductive toxicity. It has also been demonstrated that azacitidine is carcinogenic and mutagenic in rats and mice.	No. There are no adequate data on the use of azacitidine in pregnant women. The potential risk for humans is unknown. Based on results from animal studies and its mechanism of action, azacitidine should not be used during pregnancy, especially during the first trimester, unless clearly necessary (Section 4.6 of the SmPCs for oral azacitidine and azacitidine for injection).
Age Below 18	Safety reasons Paediatric patients were not the target population for the approved indications.	No. The safety and efficacy of azacitidine in children and adolescents aged below 18 years have not yet been established (Section 4.2 of the SmPCs for oral azacitidine and azacitidine for injection). Use is not recommended in this age group.
Advanced malignant hepatic tumours	Safety reasons. Prior published investigation reported that azacitidine is potentially hepatotoxic in patients with pre-existing liver disease.	No. <u>Oral azacitidine</u> Any patient with malignant disease, including hepatic tumours, diagnosed within the previous 12 months were excluded from Study CC-486-AML-001. There is no evidence that oral azacitidine increases the risk of advanced malignant hepatic tumours based on the Study CC-486-AML-001 in AML maintenance therapy indication. Patients were in CR or CRi at study enrolment and tumour burden due to metastasis was unlikely at the time of study entry. Taking into consideration similar active ingredient and the long-term postmarketing experience with azacitidine for injection, these patient populations are not considered missing information for oral azacitidine. <u>Azacitidine for injection</u> Azacitidine for injection is contraindicated in patients with advanced malignant hepatic tumours (Section 4.3 of the SmPC for azacitidine for injection). Section 4.4 of the SmPC for azacitidine for injection indicates that patients with extensive tumour burden due to metastatic disease have been reported to experience progressive hepatic coma and death during azacitidine treatment.

Table 18: Important Exclusion Criteria in Pivotal Clinical Studies (Continued)

Exclusion Criteria	Reason for Exclusion	Is it Considered to be Included as Missing Information? If No, Rationale.
Hepatic Impairment	Safety reasons. Hepatic impairment may result from an underlying medical condition that could influence the interpretation of the study data.	No. Oral azacitidine No dose adjustment for oral azacitidine is recommended for patients with mild hepatic impairment; patients with moderate and severe hepatic impairment should be monitored more frequently for adverse reactions and appropriate dose adjustment should be made (Section 4.2 of the SmPC for oral azacitidine). Section 5.2 of the SmPC for oral azacitidine provides information that no formal studies have been conducted in patients with hepatic impairment. Hepatic impairment is unlikely to affect the PK to a clinically relevant extent since azacitidine undergoes spontaneous hydrolysis and deamination mediated by cytidine deaminase. Azacitidine for injection No specific modification to the starting dose is recommended for patients with hepatic impairment prior to starting treatment with azacitidine for injection; subsequent dose modifications should be based on haematology laboratory values (Section 4.2 of the SmPC for azacitidine for injection). The SmPC for azacitidine for injection contains advice that patients with severe hepatic organ impairment should be carefully monitored for adverse events (AEs; Section 4.2 of the SmPC for azacitidine for injection).
Congestive Heart Failure	Safety reasons. Heart failure not related to azacitidine therapy could influence the interpretation of the study data, in particular that regarding the safety of azacitidine.	No. Oral azacitidine Patients with unstable angina, significant cardiac arrhythmia and moderate to severe CHF were excluded from the pivotal registration study for oral azacitidine (CC-486-AML-001). There is no evidence that oral azacitidine increases the risk of cardiac events based on the study results. Taking into consideration the long-term postmarketing experience with azacitidine for injection in patients with cardiac impairment, these patient populations are not considered missing information for oral azacitidine. Azacitidine for injection Section 4.4 of the SmPC for azacitidine for injection indicates that patients with a history of severe CHF, clinically unstable cardiac disease or pulmonary disease were excluded from the pivotal registration studies (AZA-AML-001 and AZA PH GL 2003 CL 001) and, therefore, the safety and efficacy of azacitidine in these patients has not been established. Data from a non-Celgene sponsored clinical trial (EUDRACT 2008-004583-40) in patients with a known history of CV or pulmonary disease showed a significantly increased incidence of cardiac events with azacitidine for injection. It is therefore advised to exercise caution when prescribing azacitidine to these patients. Cardiopulmonary assessment before and during the treatment should be considered (Section 4.4 of the SmPC for azacitidine for injection).

2. LIMITATIONS OF ADVERSE DRUG REACTION DETECTION 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 or cumulative exposure.

3. LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 19: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme.
Lactating women	Not included in the clinical development programme.
Patients with relevant comorbidities:	
Patients with renal impairment	Oral azacitidine A population PK analysis following a 300 mg dose of oral azacitidine was conducted on subjects from Studies CC-486-CAGEN-001, CC-486-AML-001 and AZA-MDS-004. Patients with mild (CLcr: ≥ 60 to < 90 mL/min, N = 117), moderate (CLcr: ≥ 30 to < 60 mL/min, N = 56), and severe (CLcr: < 30 mL/min, N = 3) renal impairment had 19%, 25%, and 38% increases in azacitidine plasma AUC, respectively, compared to subjects with normal renal function (N = 110). In the pivotal registration study CC-486-AML-001, subjects with mild or moderate renal impairment (CrCL of > 30 mL/min) were included and were not correlated with an increase in AEs. In addition, the exposure of azacitidine (AUC) is approximately 75% lower after oral administration relative to the exposure achieved following SC administration; therefore, an increase in exposure of approximately 40% following oral administration in subjects with severe renal impairment is still considered safe and tolerable. Thus, no initial dose adjustment of oral azacitidine is recommended in patients with mild, moderate, or severe renal impairment. Azacitidine for injection Study AZA PH US 2007 PK 006, a Phase 1, open-label, multicentre, parallel group study evaluated the PK and safety of azacitidine for injection in adult cancer patients with and without impaired renal function; the PK of azacitidine for injection in 6 patients with normal renal function (CLcr > 80 mL/min/1.73 m²) and 6 patients with severe renal impairment (CLcr ≤ 30 mL/min/1.73 m²) were compared following daily SC dosing (Days 1 to 5) at 75 mg/m²/day. Severe renal impairment increased azacitidine exposure (AUC) by approximately 70% after single and 41% after multiple SC administrations. This increase in exposure was not correlated with an increase in AEs. Study AZA PH US 2007 CL 005, a Phase 1, open-label, dose-escalation study evaluated the safety, PK and pharmacodynamics of oral azacitidine in patients with MDS, CMML or AML. An additional analysis based on renal function was conducted on subjects administered SC azacitidine (Additional Report AZA PH US 2007 CL005-Renal Function). The PK of azacitidine for injection in 14 patients with normal renal function (CLcr > 80 mL/min/1.73 m²), 1 patient with severe (CLcr ≤ 30 mL/min/1.73 m²), 7 patients with moderate (30 < CLcr ≤ 50 mL/min/1.73 m²), and 23 patients with mild renal impairment (50 < CLcr ≤ 80 mL/min/1.73 m²) were compared following daily SC dosing (Days 1 to 7) at 75 mg/m²/day. Overall, azacitidine PK parameters observed in subjects with normal renal function and mild, moderate, and severe renal impairment were comparable and within the same range of values. Taken together, azacitidine for injection can be administered in patients with renal impairment without initial dose modification.

Table 19: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes (Continued)

Type of Special Population	Exposure
Patients with hepatic impairment	Not included in the clinical development programme.
Patients with CV impairment	Patients with a history of severe CHF, clinically unstable cardiac disease or pulmonary disease were excluded from the pivotal registration studies (CC-486-AML-001, AZA-AML-001 and AZA PH GL 2003 CL 001).
Patients with a disease severity different from inclusion criteria in clinical trials	Data from the 4 completed MDS clinical studies form the basis for the use of azacitidine for injection as a treatment for patients with INT-2 or high-risk MDS, with the majority of patients classified as having RAEB or RAEB-T at baseline in both the pivotal and supportive studies (92% and 65.3% of patients, respectively; Part II Module SIII). No patients with lower-risk MDS (refractory anaemia [RA] or refractory anaemia with ringed sideroblasts [RARS] by FAB classification) were included in pivotal MDS Study AZA PH GL 2003 CL 001 or supportive Studies CALGB 8421 and 8921. In Study CALGB 9221, however, 35 (23.3%) patients with RA and 9 (6.0%) patients with RARS at baseline were included (CALGB 9221 Clinical Study Report). There were no clear trends in the frequency of treatment-emergent AEs by MDS subtype (FAB classification) and no clinically relevant differences in the percentages of individual events. Based on the similar safety profiles across MDS subtypes, no specific safety concerns relating to the use of azacitidine in low-risk MDS patients have been identified. Data from the pivotal study AZA-AML-001 and a subset (N = 113) of patients with WHO-defined AML and multi-lineage dysplasia (FAB-defined RAEB-T) from the MDS study AZA PK GL 2003 CL 001 form the basis for the use of azacitidine for injection for the treatment of patients with AML. Study AZA-AML-001 recruited patients with > 30% bone marrow blasts (consistent with the indication) and the median blast count in the intent-to-treat population at baseline was 72.0%. No patients with WHO-defined AML with 20% to 30% bone marrow blasts were included in this study. Subgroup analyses were not performed to investigate safety data by disease severity in Study AZA-AML-001; therefore, there is no information relating to the safety of azacitidine in patients with different severities of AML in this study. A subset of 113 patients enrolled in Study AZA PH GL 2003 CL 001 had RAEB-T (WHO AML with 20% to 30% bone marrow blasts). These patients also had multi-lineage dysplasia, a requirement for a diagnosis of MDS, but not for AML. No clinically important differences in safety were noted between the patients enrolled in these two studies. There is no evidence to suggest there would be any specific safety concerns relating to use of azacitidine in patients with less severe AML. This special population is not applicable to oral azacitidine.

Table 19: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes (Continued)

Type of Special Population	Exposure
Population with relevant different ethnic origin	The majority of patients treated with azacitidine for injection in the MDS clinical studies were White/Caucasian (> 93%) (Part II Module SIII). Other ethnic origins included Black (1.3% and 2.8% in Studies CALGB 9221 and CALGB 8921, respectively); Hispanic (3.3% and 1.4% in Studies CALGB 9221 and CALGB 8921, respectively); and Asian (1.1% and 2.0% in Studies AZA PH GL 2003 CL 001 and CALGB 9221, respectively). Similarly, the majority of patients treated with azacitidine for injection in the AML clinical study AZA-AML-001 were White/Caucasian (76.8%) (Part II Module SIII). Other ethnic origins included Asian (15.4%), Black (0.8%); and Hawaiian/Pacific Islander (0.4%). Overall, although some differences were noted in the frequencies of individual treatment-emergent AEs between White and Asian patients treated with azacitidine for injection, the differences may be due to the small sample size in the Asian subpopulation. These small differences by race were not of clinical relevance, as the observations were noted across the 3 active treatment groups. As a result, no specific dose adjustments are recommended for azacitidine for injection based on race or ethnic origin. The majority of patients treated with oral azacitidine in the AML clinical study CC-486-AML-001 were White (91.1%) (Part II Module SIII). Other ethnic origins included Asian (2.5%), Black or African American (0.4%) and other (5.1%). Since the numbers of patients in the Asian and Black or other racial groups were small, no meaningful comparisons could be made. Two Celgene-sponsored studies specific to ethnic populations have been completed: • Study AZA-MDS-001 in Taiwanese patients (44 patients exposed to SC azacitidine; completion date, 11 Feb 2014). • Study AZA-MDS-002 in Chinese patients (72 patients exposed to SC azacitidine; completion date, 30 Jun 2015). Overall, the safety profile of azacitidine for injection in Taiwanese and Chinese patients was consistent with the known safety profile of azacitidine for injection, and can be appropriately managed with routine monitoring. Section 5.2 of the SmPC for oral azacitidine states that the effects of race/ethnicity on the PK of oral azacitidine are unknown.
Subpopulations carrying relevant genetic polymorphisms	Genetic polymorphisms have not been studied in the clinical trial populations for oral azacitidine and azacitidine for injection.
Other	<u>Paediatric population</u> MDS comprises a heterogeneous group of haematopoietic disorders predominantly affecting the elderly. All patients recruited in the AZA PH GL 2003 CL 001 study were > 18 years of age and were > 15 years of age in the CALGB studies. Similarly, AML is a disorder primarily affecting the elderly: all patients in Study AZA-AML-001 were aged ≥ 64 years and all patients in Study CC-486-AML-001 were aged ≥ 55 years. Thus, experience in paediatric populations is limited. There are two completed studies investigating azacitidine for injection in the treatment of AML (Study AZA-AML-004) and MDS (including juvenile myelomonocytic leukaemia) (Study AZA-JMML-001) in paediatric patients. As

Table 19: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes (Continued)

Type of Special Population	Exposure
Other (continued)	of 18 May 2019, there were 7 patients enrolled in Study AZA-AML-004 and 28 patients enrolled in Study AZA-JMML-001. Elderly population In the general population, the median age at diagnosis for patients with AML or MDS ranges between 65 and 70 years of age. The MDS clinical programme was representative of this elderly patient population with 82.6% (366/443) of patients 65 years of age or older. Study AZA-AML-001 included an older population (57.3% aged ≥ 75 years) because enrolment was restricted to patients aged ≥ 65 years. No clinically significant differences were observed when the safety data were analysed for age in either the AML or MDS studies with azacitidine for injection; however, there is limited safety information available with azacitidine in patients aged ≥ 85 years, with 14 (5.9%) patients aged ≥ 85 years in Study AZA-AML-001. Most patients (72.5%; 171/236) treated with oral azacitidine in Study CC-486-AML-001 were aged 65 years or older; however, only 1 patient (0.4%) was aged ≥ 85 years.

PART II — MODULE SV: POSTAUTHORISATION EXPERIENCE

1. POSTAUTHORISATION EXPOSURE

1.1. Method Used to Calculate Exposure

The cumulative value for exposure represents the estimated number of unique patients exposed to azacitidine at least once from 19 May 2004 through 18 May 2019.

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

1. Celgene's Sales/Shipment Data – these data consist of all shipments of Celgene product to all applicable countries and include commercial and free-of-charge units for both branded and generic product (as applicable). The data are used to determine the units (eg, milligrams) of a product that was sold to a geography to estimate the number of patients who would have been exposed to that product, based on expected dosing in the geography. Shipment data are used to estimate the active patients for a period of time by dividing the total units sold by the average units per patient (note that average units per patient is derived from epidemiologic or market research).
2. Claims Data – these data consist of two distinct sources of electronic health care claims data in the US: Optum Clinformatics Datamart and Symphony Claims for Hem/Onc. Claims data consisting of distinct patient identifiers and prescription fill rates for each product are used to derive discontinuation and restart rates.
3. Controlled Distribution Databases – this data source is not applicable for azacitidine, since azacitidine does not have a controlled distribution programme.

1.2. Exposure

The overall cumulative exposure to azacitidine through 18 May 2019 is estimated to be 464,771 patients from all geographic areas, including 2709 patients in Celgene-sponsored trials, 18,584 patients in non-Celgene-sponsored trials (including 8656 patients from National Cancer Institute-sponsored clinical studies in the US from 2012 and earlier), and 443,478 patients from commercial exposure.

A summary of worldwide commercial exposure by region is provided in Table 20.

Table 20: Summary of Worldwide Commercial Exposure

Region	Cumulative Exposure
Australia/New Zealand	8846
Canada	1259
China	4425
European Economic Area[a]	161,030
Japan	39,992
Rest of World[b]	74,108
United States	153,818
TOTAL	**443,478**

[a] Includes the EU28 countries, plus Liechtenstein, Norway, and Iceland.
[b] Includes countries and regions not otherwise specified in the table.

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

1. POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Azacitidine as a neoplastic agent does not cause addiction. To date, no new safety signal has been identified relating to the misuse or abuse of azacitidine.

PART II — MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

1. IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

The summary of safety concerns for the first approved RMP for azacitidine for injection (Version 3.0, December 2008) is presented in Table 21. A description of the changes to the list of safety concerns in the approved RMPs is provided in Annex 8.

Table 21: Summary of Safety Concerns for RMP Version 3.0

Important Identified Risks:	• Myelosuppression • Haemorrhagic events • Infections • Renal and urinary events • Gastrointestinal events • Hepatic events • Injection site reactions
Important Potential Risks:	• Psychiatric disorders • Malignancies (including injection site tumours) • Off-label use (in adults, including low-risk MDS patients, and children) • Neurological events and muscle weakness • Male infertility • Medication errors
Missing Information:	• Use in hepatic impairment • Use in renal impairment • Use in cardiac impairment • Interactions with other drugs (including cytotoxics) • Pregnancy and lactation • Use in elderly patients affected by renal impairment • Use in children

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

1.1.1. Oral Azacitidine

Gastrointestinal events (nausea, vomiting and diarrhoea) have manageable clinical impact in patients treated with oral azacitidine in relation to the severity of the indication treated. In the pivotal study CC-486-AML-001, gastrointestinal events as defined by the System Organ Class (SOC) of Gastrointestinal Disorders were reported in 91.1% of patients in the oral azacitidine group and 61.8% in the placebo group. The most commonly reported gastrointestinal events were nausea (oral azacitidine: 64.8%; placebo: 23.6%), vomiting (59.7%; 9.9%), and diarrhoea (50.4%; 21.5%), the majority of which were Grade 1 or 2 in severity in both treatment groups. Grade 3 or 4 events were reported in 16.9% and 6.4% of patients in the oral azacitidine and placebo groups, respectively. Serious events were reported in 7.6% and 3.4% of patients in the oral azacitidine and placebo groups, respectively. In the SOC of Gastrointestinal Disorders, dose

reduction or dose interruption were reported in 5.5% and 13.1% of patients in the oral azacitidine group, respectively, and 0% and 3.4% of patients in the placebo group, respectively. There were few gastrointestinal events leading to discontinuation: 5.1% in the oral azacitidine group and 0.4% of patients in the placebo group. There were no gastrointestinal events that led to death. Gastrointestinal events (nausea, vomiting and diarrhoea) were largely manageable with dose modifications and prophylactic medications, few events resulted in discontinuation of therapy, and none were fatal. Such events do not pose a therapeutic challenge as oncologists are well versed in monitoring and managing gastrointestinal events associated with cancer treatment. Thus, gastrointestinal events (nausea, vomiting and diarrhoea) is not considered an important risk for oral azacitidine. Routine risk minimisation measures are sufficient to manage the risk of gastrointestinal events (nausea, vomiting and diarrhea). Guidance on the administration of anti-emetic prophylaxis and treatment of diarrhoea at the onset of symptoms is included in Sections 4.2 and 4.4 of the updated SmPC for oral azacitidine. Furthermore, dose adjustments and recommended action for Grade 3 or higher nausea, vomiting or diarrhoea are provided in Section 4.2 of the SmPC.

Off-label use is not considered an important risk for inclusion in the list of safety concerns for oral azacitidine. Oral azacitidine and azacitidine for injection should not be used interchangeably. The indications for oral azacitidine differ from that of azacitidine for injection and hence the intended patient populations are different (indications are described in Part II Module SI, Section 1). Due to substantial differences in the PK parameters (compared with injectable treatment at 75 mg/m^2 QD × 7 days, oral azacitidine at 300 mg once daily for 14 and 21 days provides cumulative exposure per cycle of 38% and 57%, respectively), the recommended dose and schedule for oral azacitidine are different from those for azacitidine for injection. Given that both oral and injectable formulations share the same active ingredient, the type of safety concerns for azacitidine such as infections (common important identified risk for both formulations) would be generally similar, as clinical consequence of cytopenias such as neutropenia or febrile neutropenia. The differences in the safety profile that exist between the 2 formulations are related to the different routes of administration. Patients treated with injectable azacitidine that would get switched to oral azacitidine due to off-label use would experience an increased incidence of gastrointestinal events as a result of oral administration. In Section 4.2 of the SmPC, guidance is provided to not interchange oral azacitidine with azacitidine for injection due to differences in exposure, dose and schedule of treatment, and for healthcare professionals to verify the name of the medicinal product, dose and administration route. Routine risk minimisation measures for off-label use as provided in the SmPC are deemed sufficient.

Haemorrhagic events have manageable clinical impact in patients treated with oral azacitidine in relation to the severity of the indication treated. Results of the pivotal study CC-486-AML-001 showed that the proportion of patients who reported haemorrhagic events (defined using the same search criteria as used for azacitidine for injection) in oral azacitidine-treated patients was comparable to those in placebo-treated patients. Grade 3 or 4 events were reported in 0.8% of patients in the oral azacitidine group and none in the placebo group. Serious haemorrhagic events were reported in 3.4% of patients in the oral azacitidine group compared to 3.0% in the placebo group. There were 3 haemorrhagic events that led to death that were confounded by head injury, fall and use of anticoagulant therapy. There were no deaths due to haemorrhagic events that were

considered treatment-related by the Investigator. Thus, haemorrhagic events are not considered important risks for oral azacitidine.

All risks not considered as important for inclusion in the list of safety concerns for azacitidine injection referenced in Section 1.1.2 were also evaluated for oral azacitidine based on the same risk definitions applied for the injection formulation.

Haematological toxicities such as myelosuppression with azacitidine injection are already well known to healthcare professionals. While myelosuppression is a known risk for the active substance, it is not deemed an important identified risk for oral azacitidine based on data from Study CC-486-AML-001. Overall, Grade 3 or 4 myelosuppression events (based on the same search criteria used in Vidaza PSUR) occurred in 55.9% of patients in oral azacitidine group compared to 41.6% in the placebo group. The most common Grade 3 or 4 AE in the oral azacitidine group was neutropenia with 41.1%. Serious AEs occurred in similar proportions of patients in the oral azacitidine group (8.1%) and the placebo group (6.4%). These events were largely manageable with dose modifications and standard therapeutic intervention, and few events resulted in discontinuation of study therapy. None of these events was fatal. Health care professionals have appropriate measures in place as part of routine clinical practice for prevention and treatment of haematological toxicities. Thrombocytopenia and neutropenia are included in Section 4.8 of the SmPC for oral azacitidine. Further, infections remains an important identified risk, and represents the potential clinical consequences of the development of neutropenia.

Below are risks occurring with a low frequency in patients treated with oral azacitidine and considered to be acceptable in AML maintenance indication based on pivotal Study CC-486-AML-001 as described below:

- Renal failure of any grade occurred in 3.0% of patients in the oral azacitidine group and 2.1% of patients in the placebo group. When adjusted for time of exposure, incidence rates for these events were 1.94 per 100 person-years for the oral azacitidine group and 2.15 per 100 person-years for the placebo group. Renal failure events were mostly Grade 1 or 2 in severity, and none of these events resulted in death or study drug discontinuation.
- Hepatic failure events were infrequent in both treatment groups, with events of any grade occurring in 1.3% of patients in both the oral azacitidine and placebo groups. When adjusted for time of exposure, incidence rates for these events were 0.83 per 100 person-years for the oral azacitidine group and 1.29 per 100 person-years for the placebo group. There were no serious events of fatal hepatic failure in either treatment group.
- Cardiac events included the subcategories of cardiac arrhythmias, myocardial infarction, and cardiac failure. There were no events of electrocardiogram QT prolonged reported. Cardiac failure of any grade occurred in 19.9% of patients in the oral azacitidine group and 16.7% of patients in the placebo group. When adjusted for time of exposure, incidence rates for these events were 15.05 per 100 person-years for the oral azacitidine group and 18.29 per 100 person-years for the placebo group. These events were mostly Grade 1 or 2 in severity; few of these events were fatal, and none resulted in study therapy discontinuation.

1.1.2. Azacitidine for Injection

Adverse reactions with minimal clinical impact on patients and not associated with any relevant risk (in relation to the life-threatening haematologic malignancies being treated) include insomnia and anxiety.

Adverse reactions such as higher grades of confusional state could have an impact on the quality of life; however, the clinical impact of this reaction is considered minimal in relation to the severity of the underlying life-threatening haematologic malignancies being treated.

Adverse reactions of higher grade with acceptable clinical impact on patients treated for life-threatening haematologic malignancies include renal failure, hepatic failure, interstitial lung disease, tumour lysis syndrome, ischaemic colitis, other psychiatric disorders, malignancies (including injection site tumours), male infertility, prenatal development toxicity and cardiac events. Some of the above reactions may have serious consequences but occur with a low frequency, such as tumour lysis syndrome. These reactions are not considered to impact the benefit-risk profile of azacitidine in the target population. No additional risk minimisation measures are in place for these reactions. They are not considered to be important for inclusion in the list of safety concerns.

Haematological toxicities such as myelosuppression with azacitidine for injection are already well known to health care professionals. The health care professionals have appropriate measures in place as part of routine clinical practice for prevention and treatment of these haematological toxicities. These reactions are included in Section 4.8 of the SmPC for azacitidine for injection. Further, haemorrhagic events and infections remain important identified risks, and represent the potential clinical consequences of the development of thrombocytopenia and neutropenia, respectively.

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

1.2.1. Oral Azacitidine

Important Identified Risks

Important Identified Risk	Risk-benefit Impact
Infections	Infections are common/very common events that may be serious and can prove fatal (Silverman, 2000). These infections may necessitate treatment with antibiotics and/or granulocyte colony-stimulating factor (G-CSF; for neutropenic infections). Serious or severe infections may contribute to morbidity and mortality. Serious infections have been observed in patients receiving oral azacitidine (Section 4.8 of the SmPC for oral azacitidine). Patients should be monitored for infections. Monitoring of complete blood counts, dosage adjustments for neutropenia with fever and guidance regarding supportive care including use of G-CSF are provided in Sections 4.2 and 4.4 of the SmPC for oral azacitidine. See Section 3.1.1.1 for further details.

Important Potential Risks

None

Missing Information

None

1.2.2. Azacitidine for Injection

Important Identified Risks

Important Identified Risk	Risk-benefit Impact
Haemorrhagic events	Bleeding may occur with patients receiving azacitidine. Serious adverse reactions such as gastrointestinal haemorrhage and intracranial haemorrhage have been reported. Patients should be monitored for signs and symptoms of bleeding (see Section 4.8 of the SmPC for azacitidine for injection). Monitoring of complete blood counts (to check for thrombocytopenia) and dosage advice is provided in Sections 4.2 and 4.4 of the SmPC for azacitidine for injection. Haemorrhagic events are common/very common events that may be serious and can prove fatal (Bowen, 2003; Silverman, 2000). Serious or severe haemorrhagic events may contribute to morbidity and mortality. See Section 3.1.2.1 for further details.
Infections	Infections are common/very common events that may be serious and can prove fatal (Silverman, 2000). These infections may necessitate treatment with antibiotics and/or G-CSF (for neutropenic infections). Serious or severe infections may contribute to morbidity and mortality. Myelosuppression may lead to neutropenia and an increased risk of infection. Serious infections such as sepsis (including neutropenic sepsis) and pneumonia have been reported in patients receiving azacitidine for injection (Section 4.8 of the SmPC for azacitidine for injection). Infections may be managed with the use of anti-infectives plus growth factor support (eg, G-CSF) for neutropenia (see Section 4.8 of the SmPC for azacitidine for injection). Dose recommendations and advice for monitoring of blood counts (to check for neutropenia) are provided in Sections 4.2 and 4.4 of the SmPC for azacitidine for injection. Soft tissue infections, including cellulitis and necrotising fasciitis (in rare cases leading to death) have been reported with azacitidine in the postmarketing setting (see Sections 4.4 and 4.8 of the SmPC for azacitidine for injection). See Section 3.1.2.2 for further details.

Important Potential Risks

None

Missing Information

None

2. NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

No changes are proposed to the safety concerns for azacitidine for injection.

Infections is proposed as a new important identified risk for oral azacitidine.

3. DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

3.1. Presentation of Important Identified Risks and Important Potential Risks

3.1.1. Oral Azacitidine

3.1.1.1. Important Identified Risk: Infections

Information concerning the risk of Infections is summarised in Table 22.

Table 22: Important Identified Risk –Infections

Infections
Potential Mechanisms Bacterial infections (particularly respiratory and dermal) are among the common clinical characteristics of AML and MDS and can usually be attributed to the underlying cytopenias. Azacitidine, a nucleoside analogue, has demonstrated antiviral and antibacterial properties (Bouchard, 1990). While the hypomethylating effects of azacitidine have been shown to lead to re-expression of previously silenced gene products, including Epstein-Barr virus (EBV; Chan, 2004), no reports of reactivation of latent viruses leading to overt clinical disease in azacitidine-treated patients have been communicated to Celgene. Although early treatment with azacitidine may cause neutropenia and an increased risk of infection, treatment resulted in less infection when compared to conventional care regimens once its positive effects on cell counts had been established.
Evidence Source(s) and Strength of Evidence In the clinical study in AML maintenance (CC-486-AML-001), serious adverse reactions were reported in patients receiving oral azacitidine.
Characterisation of the Risk **Frequency with 95% CI** *AML maintenance* In Study CC-486-AML-001, events of infection were reported in 147 (62.3%; 95% CI: 55.8% to 68.5%) patients treated with oral azacitidine. The most frequently reported events of infection in patients treated with oral azacitidine were upper respiratory tract infection, influenza, nasopharyngitis and urinary tract infection, reported in 13.1%, 7.6%, 7.2% and 7.2% of patients, respectively. The incidence for patients unexposed to oral azacitidine was 52.8%, giving a RR of infection of 1.2 (95% CI: 0.9 to 1.5) in patients treated with oral azacitidine. **Seriousness/Outcomes** *AML maintenance* Serious events of infection were recorded in 39 (16.5%) patients treated with oral azacitidine in Study CC-486-AML-001. The most commonly-reported (experienced by ≥ 2 patients) infection serious adverse events (SAEs) were pneumonia (9 patients); sepsis and cellulitis (4 patients each); influenza (3 patients); and lung infection, neutropenic sepsis and gastroenteritis (2 patients each). The outcomes of these infection SAEs are presented below.

Outcome	**Number of Patients**
Resolved	31
Not Resolved	5
Fatal	3
Total	**39**

Table 22: Important Identified Risk –Infections (Continued)

Infections
Severity and Nature of Risk *AML maintenance* In Study CC-486-AML-001, Grade 3 or 4 infection AEs were experienced by 48 (20.3%) patients treated with oral azacitidine. The most commonly reported Grade 3 or 4 infection events in patients treated with oral azacitidine were pneumonia (3.0% of patients); cellulitis and lung infection (1.7% each); and sepsis, device related infection, herpes zoster and influenza (1.3% each).
Risk Groups and Risk Factors Risk factors include chemotherapy-induced immunosuppression, myelosuppression, stem cell transplant, and graft-versus-host disease. There is the potential risk of re-activation of latent viruses, including EBV, in patients who become immunocompromised secondary to disease or treatment with anticancer agents that can affect the host immune system. A study by Chan and colleagues found that expression of previously silent viral antigens observed in 1 viral antigen (Zta) was detected in only 1 of the study's 10 patients, and this re-expression did not result in clinical infection or the development of secondary EBV malignancy (Chan, 2004). In higher-risk patients with MDS (> 10% blasts), there is a high rate of transformation to AML or progressive bone marrow failure, which can lead to infection (Fukumoto, 2005). However, in an international, multicentre, controlled, open-label, randomised, parallel-group, Phase 3 comparative study, azacitidine treatment was associated with a reduction in cytopenias, and their related symptoms (Section 5.1 of the SmPC for azacitidine for injection). An examination of the azacitidine safety database did not reveal any case reports linking treatment, viral reactivation (for example EBV) and the development of clinical disease, including non-Hodgkin's lymphoma.
Preventability Serious infections were reported in patients receiving oral azacitidine. Infections may be managed with the use of anti-infectives plus growth factor support (eg, G-CSF) for neutropenia.
Impact on the Risk-benefit Balance of the Product Serious or severe infections may contribute to morbidity and mortality. Risk minimisation measures are in place in the SmPC for azacitidine for injection and oral azacitidine, including appropriate warnings and guidance regarding management of infections, the need for complete blood count monitoring, and dose adjustments.
Public Health Impact Haematologic malignancies (most commonly acute leukaemias) cause anaemia, neutropenia and thrombocytopenia (Weinzierl, 2013). AML patients often present with complications of cytopenias, including weakness, fatigue, bleeding and infection. Infections are very common adverse drug reactions (ADRs) in patients receiving oral azacitidine for AML maintenance therapy, with pneumonia and respiratory tract infections the most common events (Section 4.8 of the SmPC for oral azacitidine). Infections do not commonly lead to hospitalisation, and can be managed in the ambulatory or clinical setting. There were few reports of infections that resulted in death.
Data Source Study CC-486-AML-001. **Medical Dictionary for Regulatory Activities (MedDRA) Terms** *AML (maintenance)* Preferred Terms (PTs) listed within the MedDRA v22.0 SOC of infections and infestations are collectively referred to as infections.

3.1.2. Azacitidine for Injection

3.1.2.1. Important Identified Risk: Haemorrhagic Events

Information concerning the risk of Haemorrhagic events is summarised in Table 23. This risk is relevant to the patient population receiving azacitidine for injection only.

Table 23: Important Identified Risk –Haemorrhagic Events

Haemorrhagic Events
Potential Mechanisms Haemorrhagic events (eg, ecchymosis, epistaxis, gingival bleeding and petechiae) are among the clinical characteristics of AML and MDS and can usually be attributed to the underlying cytopenias.
Evidence Source(s) and Strength of Evidence Bleeding events have been reported in patients receiving azacitidine for injection. In the clinical studies in MDS (AZA PH GL 2003 CL 001, CALGB 9221, CALGB 8921 and CALGB 8421) and in AML (AZA-AML-001), serious adverse reactions such as gastrointestinal haemorrhage and intracranial haemorrhage, have been reported in patients receiving azacitidine for injection.
Characterisation of the Risk **Frequency with 95% CI** *AML* In Study AZA-AML-001, haemorrhagic events were reported in 94 (39.83%; 95% CI: 33.54% to 46.38%) patients treated with azacitidine for injection. The incidence for patients unexposed to azacitidine for injection was 37.5%, giving a RR of haemorrhage of 1.06 (95% CI: 0.85 to 1.34) in patients treated with azacitidine for injection. The incidence of haemorrhagic events in the overall population was 38.6%, giving an excess risk attributable to azacitidine of 5.98%. Thus, for every 100 previously untreated AML patients, an excess of approximately 2 patients would be expected to develop a haemorrhagic event as a result of the treatment with azacitidine for injection. *MDS* In Studies AZA PH GL 2003 CL 001, CALGB 8421, CALGB 8921 and CALGB 9221 haemorrhagic events were reported in 273 (61.63%; 95% CI: 56.92% to 66.18%) patients treated with azacitidine for injection. The incidence for patients unexposed to azacitidine for injection was 42.4%, giving a RR of haemorrhage of 1.45 (95% CI: 1.24 to 1.71) in patients treated with azacitidine for injection. The incidence of haemorrhagic events in the overall population was 56.5%, giving an excess risk attributable to azacitidine for injection of 31.2%. Thus, for every 100 previously untreated MDS patients, an excess of approximately 19 patients would be expected to develop a haemorrhagic event as a result of the treatment with azacitidine for injection. **Seriousness/Outcomes** *AML* Serious haemorrhagic events were recorded in 16 patients treated with azacitidine for injection in Study AZA-AML-001. Patients treated with azacitidine for injection experienced SAEs of haemorrhage intracranial, subarachnoid haemorrhage, epistaxis and haematoma (2 patients each), disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, conjunctival haemorrhage, gastrointestinal haemorrhage, haematemesis, melaena, mouth haemorrhage, rectal haemorrhage, upper gastrointestinal haemorrhage, subdural haematoma, cerebral haemorrhage and pulmonary alveolar haemorrhage (one patient each).

Table 23: Important Identified Risk –Haemorrhagic Events (Continued)

Haemorrhagic Events

The outcomes of these haemorrhagic event SAEs are presented below.

Outcome	Number of Patients
Death[a]	4
Ongoing at Death	4
Recovered/Resolved	7
Unknown/Not Provided	1
Total	16

[a] Includes patients who experienced AEs of Grade 5 severity (Death) and patients with AEs of lower severities with a recorded outcome of death. The number of deaths presented in the CSR for Study AZA-AML-001 corresponds to the number of patients who experienced AEs of Grade 5 severity (n = 3).

MDS

A total of 41 patients treated with azacitidine for injection experienced haemorrhagic event SAEs in the 4 clinical studies in MDS. Serious haemorrhagic events were recorded in 16 patients treated with azacitidine for injection patients in Study AZA PH GL 2003 CL 001. Patients treated with azacitidine for injection experienced SAEs of cerebral haemorrhage and epistaxis (4 patients each), eye haemorrhage, gingival bleeding, rectal haemorrhage and haematuria (2 patients each), retinal haemorrhage, gastrointestinal haemorrhage, haematemesis, haemorrhoidal haemorrhage, intestinal haemorrhage, mouth haemorrhage, traumatic intracranial haemorrhage, haemorrhage intracranial and haemoptysis (one patient each).

In Study CALGB 8421 patients treated with azacitidine for injection experienced SAEs of gastrointestinal haemorrhage (2 patients), disseminated intravascular coagulation, gastritis haemorrhagic, catheter site haemorrhage, cerebral haemorrhage, haematuria, haemoptysis and petechiae (one patient each). In Study CALGB 8921 patients treated with azacitidine for injection experienced SAEs of gastrointestinal haemorrhage (2 patients), haematochezia and haemorrhage intracranial (one patient each). In Study 9221 patients treated with azacitidine for injection experienced SAEs of gastrointestinal haemorrhage, haemorrhage intracranial, haematuria (2 patients each), gingival bleeding, haematochezia, melaena, rectal haemorrhage, post procedural haemorrhage, urogenital haemorrhage, epistaxis and haematoma (one patient each).

The outcomes of these haemorrhagic event SAEs are presented below.

Outcome	Number of Patients
Death	11
Recovery/Resolved with Sequelae	3
Recovery/Resolved without Sequelae	27
Total	41

Severity and Nature of Risk

AML

In Study AZA-AML-001 Grade 3 or 4 haemorrhagic events were experienced by 19 (8.1%) patients treated with azacitidine for injection. The most commonly reported Grade 3 or 4 haemorrhagic events in patients treated with azacitidine for injection were epistaxis, experienced by 3 (1.3%) patients and gastrointestinal haemorrhage, upper gastrointestinal haemorrhage, haemorrhage intracranial, subarachnoid haemorrhage and haematoma, experienced by 2 (0.8%) patients each.

Haemorrhagic events leading to treatment discontinuation or interruption were reported in 5 (2.1%) and 3 (1.3%) patients treated with azacitidine for injection, respectively.

Table 23: Important Identified Risk –Haemorrhagic Events (Continued)

Haemorrhagic Events
MDS In pivotal study AZA PH GL 2003 CL 001, Grade 3 or 4 haemorrhagic events were experienced by 27 (15.4%) patients treated with azacitidine for injection. The most common Grade 3 or 4 events were epistaxis, cerebral haemorrhage and haematuria, reported in 9 (5.1%), 4 (2.3%) and 4 (2.3%) patients treated with azacitidine for injection, respectively. In Study CALGB 8421, Grade 3 or 4 AEs of ecchymosis and petechiae were experienced by 2 (4.2%) patients treated with azacitidine for injection each and Grade 3 or 4 AEs of catheter site haemorrhage, cerebral haemorrhage, disseminated intravascular coagulation, gastritis haemorrhagic, gastrointestinal haemorrhage, haematemesis, haematochezia and upper gastrointestinal haemorrhage were experienced by 1 (2.1%) patients treated with azacitidine for injection each. In Study CALGB 8921, Grade 3 or 4 AEs of ecchymosis, gastrointestinal haemorrhage, haematochezia, haemoptysis, haemorrhage intracranial, mouth haemorrhage and purpura were each reported by single (1.4%) patients treated with azacitidine for injection. In Study CALGB 9221, epistaxis was the most common haemorrhagic Grade 3 or 4 event, reported in 5 (3.3%) patients treated with azacitidine for injection. In Study AZA PH GL 2003 CL 001, a single patient treated with azacitidine for injection discontinued due to cerebral haemorrhage. The dose of azacitidine for injection was interrupted due to haematuria in 2 (1.1%) patients and due to gingival bleeding, epistaxis and petechiae in single patients (0.6%). None of the identified haemorrhagic events led to dose reduction of azacitidine for injection. In Study CALGB 9221, none of the identified haemorrhagic events prompted discontinuation or dose interruption/reduction in patients treated with azacitidine for injection. The azacitidine dose was reduced due to haemoptysis in a single patient (2.1%) in Study CALGB 8421, and azacitidine for injection therapy was interrupted due to haematochezia in a single patient (1.4%) in Study CALGB 8921.
Risk Groups and Risk Factors In higher-risk patients with MDS (> 10% blasts), there is a high rate of transformation to AML or progressive bone marrow failure, which can lead to haemorrhage (Fukumoto, 2005). In 1 study in which 58% of newly diagnosed AML patients experienced bleeding during induction chemotherapy, risk factors for mild (WHO Grades 1 and 2) bleeding events included elevated body temperature and decreased platelet count. Risk factors for severe (WHO Grades 3 and 4) bleeding events included mild bleeding (Grade 1) on the previous day and decreased platelet count (Webert, 2006).
Preventability Bleeding may occur with patients receiving azacitidine for injection. Serious adverse reactions such as gastrointestinal haemorrhage and intracranial haemorrhage have been reported. Patients should be monitored for signs and symptoms of bleeding, particularly those with pre-existing or treatment-related thrombocytopenia (see Section 4.8 of the SmPC for azacitidine for injection). Monitoring of complete blood counts and dosage advice is provided in Sections 4.2 and 4.4 of the SmPC for azacitidine for injection.
Impact on the Risk-benefit Balance of the Product Serious or severe haemorrhagic events may contribute to morbidity and mortality.
Public Health Impact Given the underlying disorder and cytotoxic effects of therapy, prolonged thrombocytopenia and subsequent bleeding are relatively common complications following stem cell transplantation or induction chemotherapy. Previous studies have reported clinically significant bleeding in about 20% to 32% of thrombocytopenic patients with AML and in 34% to 58% of AML patients undergoing allogeneic stem cell transplantation (Webert, 2006).

Table 23: Important Identified Risk –Haemorrhagic Events (Continued)

Haemorrhagic Events
Haemorrhagic events are common/very common events that may be serious and can prove fatal (Bowen, 2003; Silverman, 2000). These events may necessitate the use of red blood cell and platelet transfusions (Bowen, 2003). The majority of patients with MDS die from bleeding or infection due to bone marrow failure (Silverman, 2000). All patients treated with azacitidine for injection should be monitored for events of haemorrhage.
Data Source Studies AZA-AML-001, AZA PH GL 2003 CL 001, CALGB 8421, CALGB 8921 and CALGB 9221. **MedDRA Terms** *AML* PTs listed within the MedDRA v16.1 sub-standardised MedDRA query (SMQ) for haemorrhage terms (narrow scope), excluding laboratory terms, are collectively referred to as haemorrhagic events. *MDS* PTs listed within the MedDRA v16.1 sub-SMQ for haemorrhage terms (narrow scope), excluding laboratory terms, are collectively referred to as haemorrhagic events.

3.1.2.2. Important Identified Risk: Infections

Information concerning the risk of Infections is summarised in Table 24.

Table 24: Important Identified Risk –Infections

Infections
Potential Mechanisms Bacterial infections (particularly respiratory and dermal) are among the common clinical characteristics of AML and MDS and can usually be attributed to the underlying cytopenias. Azacitidine, a nucleoside analogue, has demonstrated antiviral and antibacterial properties (Bouchard, 1990). While the hypomethylating effects of azacitidine have been shown to lead to re-expression of previously silenced gene products, including EBV (Chan, 2004), no reports of reactivation of latent viruses leading to overt clinical disease in azacitidine-treated patients have been communicated to Celgene. Although early treatment with azacitidine may cause neutropenia and an increased risk of infection, treatment resulted in less infection when compared to conventional care regimens once its positive effects on cell counts had been established.
Evidence Source(s) and Strength of Evidence In the clinical studies in MDS (AZA PH GL 2003 CL 001, CALGB 9221, CALGB 8921 and CALGB 8421) and in AML (AZA-AML-001), serious adverse reactions such as sepsis (including neutropenic sepsis) and pneumonia have been reported in patients receiving azacitidine for injection.
Characterisation of the Risk **Frequency with 95% CI** *AML* In Study AZA-AML-001, events of infection were reported in 184 (77.97%; 95% CI: 72.13% to 83.08%) patients treated with azacitidine for injection. The incidence for patients unexposed to azacitidine for injection was 69.4%, giving a RR of infection of 1.12 (95% CI: 1.01 to 1.25) in patients treated with azacitidine for injection. The incidence of infection in the overall population was 73.7%, giving an excess risk attributable to azacitidine for injection of 11.0%. Thus, for every 100 previously untreated AML patients, an excess of approximately 9 patients would be expected to develop an event of infection as a result of the treatment with azacitidine for injection.

Table 24: Important Identified Risk –Infections (Continued)

Infections

MDS

In Studies AZA PH GL 2003 CL 001, CALGB 8421, CALGB 8921 and CALGB 9221 events of infection were reported in 314 (70.88%; 95% CI: 66.41% to 75.07%) patients treated with azacitidine for injection. The incidence for patients unexposed to azacitidine for injection was 55.6%, giving a RR of infection of 1.27 (95% CI: 1.12 to 1.44) in patients treated with azacitidine for injection. The incidence of infection in the overall population was 68.0%, giving an excess risk attributable to azacitidine for injection of 21.5%. Thus, for every 100 previously untreated MDS patients, an excess of approximately 15 patients would be expected to develop an event of infection as a result of the treatment with azacitidine for injection.

Seriousness/Outcomes

AML

Serious infection events were recorded in 114 patients treated with azacitidine for injection in Study AZA-AML-001. The most commonly-reported infection SAEs (experienced by ≥ 2% of patients) were pneumonia (48 patients), sepsis (12 patients), neutropenic sepsis and urinary tract infection (7 patients each), and cellulitis (5 patients). The outcomes of these infection SAEs are presented below.

Outcome	Number of Patients
Death[a]	32
Ongoing at Death	5
Not Recovered/Not Resolved	3
Recovered with Sequelae	6
Recovered/Resolved	67
Unknown/Not Provided	1
Total	114

[a] Includes patients who experienced AEs of Grade 5 severity (Death) and patients with AEs of lower severities with a recorded outcome of death. The number of deaths presented in the CSR for Study AZA-AML-001 corresponds to the number of patients who experienced AEs of Grade 5 severity (n = 24).

MDS

A total of 126 patients treated with azacitidine for injection experienced infection SAEs in the 4 clinical studies in MDS. Serious infection events were recorded in 55 azacitidine-treated patients in Study AZA PH GL 2003 CL 001. The SAEs experienced by more than 1 patient treated with azacitidine for injection included pneumonia (20 patients), sepsis (6 patients), urinary tract infection (5 patients), neutropenic sepsis (4 patients), bronchopneumonia and septic shock (3 patients each), bacteraemia, bronchopulmonary aspergillosis, cellulitis, lower respiratory tract infection, lung infection, perianal abscess, and upper respiratory tract infection (2 patients each).

In Study CALGB 8421 the SAEs experienced by more than 1 patient treated with azacitidine for injection included sepsis (5 patients), bacterial infection and pneumonia (3 patients each) and infection (2 patients). In Study CALGB 8921 the SAEs experienced by more than 1 patient treated with azacitidine for injection included pneumonia (7 patients), sepsis (4 patients) and cellulitis (2 patients). In Study CALGB 9221 the SAEs experienced by more than 1 patient treated with azacitidine for injection included pneumonia (7 patients), cellulitis and lobar pneumonia (4 patients each), diverticulitis and sepsis (3 patients each) and bronchitis (2 patients).

Table 24: Important Identified Risk –Infections (Continued)

Infections
The outcomes of these infection SAEs are presented below.

Outcome	**Number of Patients**
Death	28
Unresolved/Ongoing	5
Recovery/Resolved with Sequelae	3
Recovery/Resolved without Sequelae	88
Unknown	2
Total	126

Severity and Nature of Risk

AML

In Study AZA-AML-001, Grade 3 or 4 infection AEs were experienced by 119 (50.4%) patients treated with azacitidine for injection. The most commonly reported Grade 3 or 4 infection events in patients treated with azacitidine for injection were pneumonia (19.1% of patients), sepsis (5.1%), urinary tract infection (3.4%), neutropenic sepsis (3.0%), cellulitis (2.5%), Escherichia sepsis and pneumonia fungal (2.1% each).

MDS

In pivotal Study AZA PH GL 2003 CL 001, Grade 3 or 4 infection AEs were experienced by 52 (29.7%) patients treated with azacitidine for injection. Grade 3 or 4 infection events reported in more than 1patient treated with azacitidine for injection comprised pneumonia (18 [10.3%] patients), sepsis (7 [4.0%] patients), neutropenic sepsis (4 [2.3%] patients), septic shock, upper respiratory tract infection, urinary tract infection (3 [1.7%] patients each), cellulitis, lower respiratory tract infection, lung infection, nasopharyngitis and perianal abscess (2 [1.1%] patients each).

In Study CALGB 8421, the most commonly reported Grade 3 or 4 infection events in patients treated with azacitidine for injection were sepsis (4 [8.3%] patients), bacterial infection (3 [6.3%] patients), cellulitis and pneumonia (2 [4.2%] patients each). In Study CALGB 8921, the most commonly reported Grade 3 or 4 infection events in patients treated with azacitidine for injection were pneumonia (7 [10.0%] patients) and sepsis (2 [2.9%] patients. In Study CALGB 9221, the most commonly reported Grade 3 or 4 infection events in patients treated with azacitidine for injection were pneumonia (7 [4.7%] patients), lobar pneumonia (4 [2.7%] patients), bacterial infection and sepsis (2 [1.3%] patients each).

In Study AZA PH GL 2003 CL 001, pneumonia (7 [4.0%] patients), upper respiratory tract infection (3 [1.7%] patients) and bronchopneumonia (2 [1.1%] patients) were the only identified infection AEs that led to dose interruption in ≥ 2 patients treated with azacitidine for injection. Neutropenic sepsis and pneumonia led to dose reduction in 1 (0.6%) azacitidine-treated patient each, and bronchopulmonary aspergillosis, clostridium difficile colitis, pneumonia, pyelonephritis and septic shock prompted discontinuation in 1 (0.6%) patients treated with azacitidine for injection.

In Study CALGB 8421, dose interruption was prompted by bacterial infection and hepatitis viral in 1 (2.1%) patient treated with azacitidine for injection each, but none of the identified infection AEs led to dose discontinuation or reduction. In Study CALGB 8921, dose reduction was prompted by sepsis in 1 (1.4%) patient treated with azacitidine for injection but none of the identified infection AEs led to dose discontinuation. In this study, AEs of influenza, klebsiella sepsis, pneumonia klebsiella and staphylococcal infection each led to dose interruption in 1 (1.4%) patient treated with azacitidine for injection. In Study CALGB 9221, diverticulitis, lobar pneumonia and pneumonia led to dose interruption in 2 (1.3%) patients treated with azacitidine for injection each, with cellulitis staphylococcal, injection site infection, peritonsillitis, pharyngitis streptococcal, sinusitis and upper respiratory tract infection leading to dose reduction in 1 (0.7%) patient treated with azacitidine for injection each. None of the identified infection AEs led to dose discontinuation or reduction in patients treated with azacitidine for injection in Study CALGB 9221.

Table 24: Important Identified Risk –Infections (Continued)

Infections
Risk Groups and Risk Factors Risk factors include chemotherapy-induced immunosuppression, myelosuppression, stem cell transplant, and graft-versus-host disease. There is the potential risk of re-activation of latent viruses, including EBV, in patients who become immunocompromised secondary to disease or treatment with anticancer agents that can affect the host immune system. A study by Chan and colleagues found that expression of previously silent viral antigens observed in 1 viral antigen (Zta) was detected in only 1 of the study's 10 patients, and this re-expression did not result in clinical infection or the development of secondary EBV malignancy (Chan, 2004). In higher-risk patients with MDS (> 10% blasts), there is a high rate of transformation to AML or progressive bone marrow failure, which can lead to infection (Fukumoto, 2005). However, in an international, multicentre, controlled, open-label, randomised, parallel-group, Phase 3 comparative study, azacitidine treatment was associated with a reduction in cytopenias, and their related symptoms (Section 5.1 of the SmPC for azacitidine for injection). An examination of the azacitidine safety database did not reveal any case reports linking treatment, viral reactivation (for example EBV) and the development of clinical disease, including non-Hodgkin's lymphoma.
Preventability *Azacitidine for Injection* Myelosuppression may lead to neutropenia and an increased risk of infection. Serious adverse reactions such as sepsis (including neutropenic sepsis for azacitidine for injection) and pneumonia were reported in patients receiving azacitidine for injection. Infections may be managed with the use of anti-infectives plus growth factor support (eg, G-CSF) for neutropenia (see Section 4.8 of the SmPC for azacitidine for injection). Dose recommendations and advice for monitoring of blood counts (neutropenia) are provided in Sections 4.2 and 4.4 of the SmPC for azacitidine for injection. Soft tissue infections, including cellulitis and necrotising fasciitis (in rare cases leading to death) have been reported with azacitidine for injection in the postmarketing setting (see Sections 4.4 and 4.8 of the SmPC for azacitidine for injection).
Impact on the Risk-benefit Balance of the Product Serious or severe infections may contribute to morbidity and mortality. Risk minimisation measures are in place in the SmPC for azacitidine for injection and oral azacitidine, including appropriate warnings and guidance regarding use of prophylaxis for infections, the need for complete blood count monitoring, and dose adjustments.
Public Health Impact Haematologic malignancies (most commonly acute leukaemias) cause anaemia, neutropenia and thrombocytopenia (Weinzierl, 2013). AML patients often present with complications of cytopenias, including weakness, fatigue, bleeding and infection. Infections are common/very common events that may be serious and can prove fatal (Silverman, 2000). These infections may necessitate treatment with antibiotics and/or G-CSF (for neutropenic infection). The majority of patients with MDS die from bleeding or infection due to bone marrow failure (Silverman, 2000). All azacitidine-treated patients should be monitored for events of infection. There was no overall increase in the risk of infection based on assessment by person-years.
Data Source Studies AZA-AML-001, AZA PH GL 2003 CL 001, CALGB 8421, CALGB 8921 and CALGB 9221. **MedDRA Terms** *AML* PTs listed within the MedDRA v16.1 SOC of infections and infestations are collectively referred to as infections. *MDS* PTs listed within the MedDRA v16.1 SOC of infections and infestations are collectively referred to as infections.

3.2. Presentation of the Missing Information

Not applicable.

PART II — MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

1. SUMMARY — ONGOING SAFETY CONCERNS

1.1. Oral Azacitidine

Important identified and potential risks, together with missing information, for oral azacitidine are summarised in Table 25.

Table 25: Summary of Safety Concerns for Oral Azacitidine

Important Identified Risks:	• Infections
Important Potential Risks:	• None
Missing Information:	• None

1.2. Azacitidine for Injection

Important identified and potential risks, together with missing information, for azacitidine for injection are summarised in Table 26.

Table 26: Summary of Safety Concerns for Azacitidine for Injection

Important Identified Risks:	• Haemorrhagic events • Infections
Important Potential Risks:	• None
Missing Information:	• None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORISATION SAFETY STUDIES)

1. ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine Pharmacovigilance activities in Celgene as described in the Celgene Pharmacovigilance System Master File and Drug Safety's Standard Operating Procedures are in accordance with "Good Pharmacovigilance Practices in the European Union."

In addition to expedited reporting, Celgene vigilantly undertakes follow-up on all ADRs, including serious ADRs that are provided to health authorities to ensure that all details of the case are captured for optimal clinical evaluation. This includes efforts to obtain all relevant information and to establish the final outcome of the ADRs.

1.1. Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

1.1.1. Specific Adverse Reaction Follow-up Questionnaires

As part of routine pharmacovigilance activities, targeted questions have been developed in the current follow-up questionnaires for Haemorrhagic Events and Infections (Annex 4).

2. ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no planned or ongoing Category 1, 2 or 3 additional pharmacovigilance activities.

3. SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no planned or ongoing Category 1, 2 or 3 additional pharmacovigilance activities.

PART IV: PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

1. PLANNED AND ONGOING POSTAUTHORISATION EFFICACY STUDIES THAT ARE CONDITIONS OF THE MARKETING AUTHORISATION OR THAT ARE SPECIFIC OBLIGATIONS

There are no efficacy studies that are specific obligations and/or conditions of the marketing authorisation.

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

1. RISK MINIMISATION PLAN

1.1. Routine Risk Minimisation Measures

1.1.1. Oral Azacitidine

Routine risk minimisation measures for oral azacitidine are described in Table 27.

Table 27: Description of Routine Risk Minimisation Measures for Oral Azacitidine by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important Identified Risks	
Infections	**Routine risk communication** **SmPC for oral azacitidine** **Section 4.8 Undesirable effects** ADRs of infections are listed. **Package Leaflet (PL) for oral azacitidine** This document details the risks associated with oral azacitidine use, their symptoms, and any actions to be taken by the patient. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** **SmPC for oral azacitidine** **Section 4.2 Posology and method of administration** Recommendations on dose adjustments and interruption based on haematology laboratory value monitoring, to reduce the risk. **Section 4.4 Special warnings and precautions for use** Advice regarding management of infections is provided. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine and treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic medicinal products.
Important Potential Risks	
None.	
Missing Information	
None.	

1.1.2. Azacitidine for Injection

Routine risk minimisation measures for azacitidine for injection are described in Table 28.

Table 28: Description of Routine Risk Minimisation Measures for Azacitidine for Injection by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important Identified Risks	
Haemorrhagic Events	**Routine risk communication** **SmPC for azacitidine for injection** **Section 4.8 Undesirable effects** Details on haemorrhagic ADRs. **PL for azacitidine for injection** This document details the risks associated with use of azacitidine for injection, their symptoms, and any actions to be taken by the patient. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** **SmPC for azacitidine for injection** **Section 4.2 Posology and method of administration** Recommendations on dose adjustments and delay based on haematology laboratory values including platelet count, to reduce the risk. **Section 4.4 Special warnings and precautions for use** Dose recommendations and advice for monitoring of complete blood counts are provided. Warnings regarding thrombocytopenia and how to monitor this risk. **Section 4.8 Undesirable effects** Advice that patients should be monitored for signs and symptoms of bleeding, particularly those with pre-existing or treatment-related thrombocytopenia. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine and treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic medicinal products.
Infections	**Routine risk communication** **SmPC for azacitidine for injection** **Section 4.8 Undesirable effects** ADRs of infections, including necrotising fasciitis, are listed. **PL for azacitidine for injection** This document details the risks associated with use of azacitidine for injection, their symptoms, and any actions to be taken by the patient. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** **SmPC for azacitidine for injection** **Section 4.2 Posology and method of administration** Recommendations on dose adjustments and delay based on haematology laboratory values including absolute neutrophil count, to reduce the risk. **Section 4.4 Special warnings and precautions for use** Dose recommendations and advice for monitoring of complete blood counts are provided. Warnings regarding neutropenia and how to monitor this risk. Warnings regarding necrotising fasciitis.

Table 28: Description of Routine Risk Minimisation Measures for Azacitidine for Injection by Safety Concern (Continued)

Safety Concern	Routine Risk Minimisation Activities
Infections (continued)	**Section 4.8 Undesirable effects** Advice regarding management of infections is provided. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine and treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic medicinal products.
Important Potential Risks	
None.	
Missing Information	
None.	

1.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Section 1.1 are sufficient to manage the safety concerns of azacitidine.

1.3. Summary of Risk Minimisation Measures

A summary of the EU-RMP for oral azacitidine is outlined in Table 29. A summary of the EU-RMP for azacitidine for injection is outlined in Table 30.

1.3.1. Oral Azacitidine

Table 29: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities for Oral Azacitidine by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Infections	**Routine risk minimisation measures:** Section 4.2 of the SmPC — Dose adjustments are provided. Section 4.4 of the SmPC — Advice regarding management of infections is provided. Section 4.8 of the SmPC — ADRs of infections are listed. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific ADR follow-up form for infections (Annex 4). **Additional pharmacovigilance activities:** None.
Important Potential Risks		
None.		

Table 29: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities for Oral Azacitidine by Safety Concern (Continued)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Missing Information		
None.		

1.3.2. Azacitidine for Injection

Table 30: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Haemorrhagic Events	**Routine risk minimisation measures:** Section 4.2 of the SmPC — Dose recommendations are provided. Section 4.4 of the SmPC — Warnings regarding thrombocytopenia and how to monitor this risk. Section 4.8 of the SmPC — Details on haemorrhagic ADRs and advice regarding monitoring. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific ADR follow-up form for haemorrhagic events (Annex 4). **Additional pharmacovigilance activities:** None.
Infections	**Routine risk minimisation measures:** Section 4.2 of the SmPC — Dose recommendations are provided. Section 4.4 of the SmPC — Warnings regarding neutropenia and how to monitor this risk. Warnings regarding necrotising fasciitis. Section 4.8 of the SmPC — ADRs of infections, including necrotising fasciitis, are listed, and advice regarding management. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific ADR follow-up form for infections (Annex 4). **Additional pharmacovigilance activities:** None.
Important Potential Risks		
None.		
Missing Information		
None.		

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

1. SUMMARY OF RISK MANAGEMENT PLAN FOR AZACITIDINE FOR INJECTION

This is a summary of the Risk Management Plan (RMP) for azacitidine for injection (Azacitidine Celgene; Vidaza). The RMP details important risks of azacitidine, how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information) of azacitidine for injection.

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

This summary of the RMP for azacitidine for injection should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 azacitidine for injection's RMP.

1.1. The Medicine and What it is Used for

Azacitidine for injection (Azacitidine Celgene; Vidaza) is authorised for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with:

- intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System,
- chronic myelomonocytic leukaemia (CMML) with 10% to 29% marrow blasts without myeloproliferative disorder,
- acute myeloid leukaemia (AML) with 20% to 30% blasts and multi-lineage dysplasia according to the World Health Organisation (WHO) classification.
- AML with > 30% marrow blasts according to the WHO classification.

See SmPC for the full indication. It contains azacitidine as the active substance and it is given by subcutaneous route of administration.

Further information about the evaluation of azacitidine's benefits can be found in azacitidine for injection's EPAR for Azacitidine Celgene and Vidaza, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/azacitidine-celgene (Azacitidine Celgene); https://www.ema.europa.eu/en/medicines/human/EPAR/vidaza (Vidaza).

1.2. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of azacitidine for injection (Azacitidine Celgene; Vidaza), together with measures to minimise such risks and the proposed studies for learning more about azacitidine for injection'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 (eg, 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 Periodic Safety Update Report 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 azacitidine for injection is not yet available, it is listed under 'missing information' below.

1.3. List of Important Risks and Missing Information

Important risks of azacitidine for injection (Azacitidine Celgene; Vidaza) 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 azacitidine. 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 (eg, on the long-term use of the medicine);

Important identified and potential risks, together with missing information, are summarised in Table 1.

Table 1: List of Important Risks and Missing Information

Important Identified Risks:	• Haemorrhagic events • Infections
Important Potential Risks:	• None
Missing Information:	• None

1.4. Summary of Important Risks

Table 2: Haemorrhagic Events

Important Identified Risk	
Evidence for linking the risk to the medicine	Bleeding events have been reported in patients receiving azacitidine for injection. In the clinical studies in MDS (AZA PH GL 2003 CL 001, CALGB 9221, CALGB 8921 and CALGB 8421) and in AML (AZA-AML-001), serious adverse reactions such as gastrointestinal haemorrhage and intracranial haemorrhage have been reported in patients receiving azacitidine for injection.
Risk factors and risk groups	In higher-risk patients with MDS (> 10% blasts), there is a high rate of transformation to AML or progressive bone marrow failure, which can lead to haemorrhage (Fukumoto, 2005). In 1 study in which 58% of newly diagnosed AML patients experienced bleeding during induction chemotherapy, risk factors for mild (WHO Grades 1 and 2) bleeding events included elevated body temperature and decreased platelet count. Risk factors for severe (WHO Grades 3 and 4) bleeding events included mild bleeding (Grade 1) on the previous day and decreased platelet count (Webert, 2006).
Risk minimisation measures	**Routine risk minimisation measures:** Section 4.2 of the SmPC — Dose recommendations are provided. Section 4.4 of the SmPC — Warnings regarding thrombocytopenia and how to monitor this risk. Section 4.8 of the SmPC — Details on haemorrhagic adverse drug reactions (ADRs) and advice regarding monitoring. **Additional risk minimisation measures:** None.

Table 3: Infections

Important Identified Risk	
Evidence for linking the risk to the medicine	In the clinical studies in MDS (AZA PH GL 2003 CL 001, CALGB 9221, CALGB 8921 and CALGB 8421) and in AML (AZA-AML-001), serious adverse reactions such as sepsis (including neutropenic sepsis) and pneumonia have been reported in patients receiving azacitidine for injection.
Risk factors and risk groups	Risk factors include chemotherapy-induced immunosuppression, myelosuppression, stem cell transplant, and graft-versus-host disease. There is the potential risk of re-activation of latent viruses, including Epstein-Barr virus, in patients who become immunocompromised secondary to disease or treatment with anticancer agents that can affect the host immune system. A study by Chan and colleagues found that expression of previously silent viral antigens observed in 1 viral antigen (Zta) was detected in only 1 of the study's 10 patients, and this re-expression did not result in clinical infection or the development of secondary EBV malignancy (Chan, 2004). In higher-risk patients with MDS (> 10% blasts), there is a high rate of transformation to AML or progressive bone marrow failure, which can lead to infection (Fukumoto, 2005). However, in an international, multicentre, controlled, open-label, randomised, parallel-group, Phase 3 comparative study, azacitidine treatment was associated with a reduction in cytopenias, and their related symptoms (Section 5.1 of the SmPC for azacitidine for injection). An examination of the azacitidine safety database did not reveal any case reports linking treatment, viral reactivation (for example EBV) and the development of clinical disease, including non-Hodgkin's lymphoma

Table 3: Infections (Continued)

Important Identified Risk	
Risk minimisation measures	**Routine risk minimisation measures:** Section 4.2 of the SmPC — Dose recommendations are provided. Section 4.4 of the SmPC — Warnings regarding neutropenia and how to monitor this risk. Warnings regarding necrotising fasciitis. Section 4.8 of the SmPC — ADRs of infections, including necrotising fasciitis, are listed, and advice regarding management. **Additional risk minimisation measures:** None.

1.5. Postauthorisation Development Plan

1.5.1. Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of azacitidine for injection.

1.5.2. Other Studies in Postauthorisation Development Plan

There are no studies required for azacitidine for injection.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

1. SUMMARY OF RISK MANAGEMENT PLAN FOR ONUREG (ORAL AZACITIDINE)

This is a summary of the Risk Management Plan (RMP) for oral azacitidine (Onureg). The RMP details important risks of Onureg, how these risks can be minimised, and how more information will be obtained about Onureg's risks and uncertainties (missing information).

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

This summary of the RMP for Onureg 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 Onureg's RMP.

1.1. The Medicine and What it is Used for

Onureg is indicated as maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, haematopoietic stem cell transplantation (HSCT).

See SmPC for the full indication. It contains azacitidine as the active substance and it is given by oral route of administration.

Further information about the evaluation of Onureg's benefits can be found in the EPAR for Onureg, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:

[link to EPAR to be added once available].

1.2. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Onureg, together with measures to minimise such risks and the proposed studies for learning more about Onureg'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 (eg, 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 Periodic Safety Update Report 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 Onureg is not yet available, it is listed under 'missing information' below.

1.3. List of Important Risks and Missing Information

Important risks of Onureg 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 Onureg. 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 (eg, on the long-term use of the medicine).

Important identified and potential risks, together with missing information, are summarised in Table 1.

Table 1: List of Important Risks and Missing Information

Important Identified Risks:	• Infections
Important Potential Risks:	• None
Missing Information:	• None

1.4. Summary of Important Risks

Table 2: Infections

Important Identified Risk	
Evidence for linking the risk to the medicine	In the clinical study in AML maintenance (CC-486-AML-001), serious adverse reactions were reported in patients receiving oral azacitidine.
Risk factors and risk groups	Risk factors include chemotherapy-induced immunosuppression, myelosuppression, stem cell transplant, and graft-versus-host disease. There is the potential risk of re-activation of latent viruses, including Epstein-Barr virus, in patients who become immunocompromised secondary to disease or treatment with anticancer agents that can affect the host immune system. A study by Chan and colleagues found that expression of previously silent viral antigens observed in 1viral antigen (Zta) was detected in only 1 of the study's 10 patients, and this re-expression did not result in clinical infection or the development of secondary EBV malignancy (Chan, 2004). In higher-risk patients with MDS (> 10% blasts), there is a high rate of transformation to AML or progressive bone marrow failure, which can lead to infection (Fukumoto, 2005). However, in an international, multicentre, controlled, open-label, randomised, parallel-group, Phase 3 comparative study, azacitidine treatment was associated with a reduction in cytopenias, and their related symptoms (Section 5.1 of the SmPC for azacitidine for injection). An examination of the

Table 2: Infections (Continued)

Important Identified Risk	
	azacitidine safety database did not reveal any case reports linking treatment, viral reactivation (for example EBV) and the development of clinical disease, including non-Hodgkin's lymphoma.
Risk minimisation measures	**Routine risk minimisation measures:** Section 4.2 of the SmPC — Dose recommendations are provided. Section 4.4 of the SmPC — Advice regarding management of infections is provided. Section 4.8 of the SmPC — Adverse drug reactions (ADRs) of infections are listed. **Additional risk minimisation measures:** None.

1.5. Postauthorisation Development Plan

1.5.1. Studies which are Conditions of the Marketing Authorisation

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

1.5.2. Other Studies in Postauthorisation Development Plan

There are no required additional pharmacovigilance activities for Onureg.

PART VII: ANNEXES

1. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex Number	Document Title
1	EudraVigilance Interface
2	Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme
3	Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan
4	Specific ADR Follow-up Forms
5	Protocols for Proposed and Ongoing Studies in RMP Part IV
6	Details of Proposed Additional Risk Minimisation Activities (if Applicable)
7	Other Supporting Data (Including Referenced Material)
8	Summary of Changes to the RMP Over Time

ANNEX 4: SPECIFIC ADR FOLLOW-UP FORMS

Important Identified Risk	Follow-up Form Title
Haemorrhagic Events	Thrombocytopenia/Bleeding
Infections	Infection in General (Including Opportunistic Infection, Abscess, Soft Tissue Infections including Necrotizing Fasciitis)

Haemorrhagic events

THROMBOCYTOPENIA/BLEEDING

1) Please provide location of the bleeding/hemorrhage.

2) Relevant medical history: Does the patient have:

a. History of anemia? Was patient transfusion dependent? If yes, since when and how frequent?

b. Episodes of hypotension? Hypertension? Gingivorrhagia or epistaxis? Headaches? Pallor? Dyspnea? Weakness? Please describe.

c. History of bleeding/hemorrhage? Coagulation disorder? Please describe.

3) Please provide relevant concomitant medications, including thromboprophylaxis (type/dose/dates as well as corresponding lab monitoring values if applicable), and possible platelet transfusion need to prevent hemorrhagic event.

4) Please provide date of diagnosis of underlying disease, stage at the time of diagnosis and stage of the patient's disease at the time of the event.

THROMBOCYTOPENIA/BLEEDING

5) Please provide the following lab values at baseline, onset of the event (worst), and recovery:

Test	Range w/ Units	Baseline/ Date	Worst/ Date	Recovery/ Date
Platelets				
PT				
aPTT				
INR				
ESR				
LFTs				
Factor VIII				
Factor IX				

6) Please include bone marrow studies / x-ray / CT scan results for the event of thrombocytopenia/ bleeding/hemorrhage.

7) What treatments were given for the thrombocytopenia/ bleeding/ hemorrhage? Please include dates/dose.

Infections

INFECTION IN GENERAL (INCLUDING OPPORTUNISTIC INFECTION, ABSCESS, *SOFT TISSUE INFECTIONS INCLUDING NECROTIZING FASCIITIS*)

See also specific questions targeted to opportunistic infections below.

See also specific questions targeted to Necrotizing fasciitis below

Please provide the type and source of infection (e.g., bacterial, fungal, viral, etc.).

Has the patient had a history of recurrent infection?
☐ Yes
☐ No
If yes, please explain.

What was the stage of the underlying disease at the time of the infection onset?

Any history of bone marrow involvement, bone marrow transplantation or radiotherapy? If so, please provide approximate dates.

Please indicate one or more of the following
☐ De novo infection
☐ Recurrent infection
☐ Relapse

Did the patient receive infection prophylaxis?
☐ Yes
☐ No
If yes, please specify antibiotic, including dose and dates of treatment.

Did the patient receive colony stimulating factors?
☐ Yes
☐ No
If yes, please specify (including type and dates).

Please provide the following lab values: at baseline, at onset of the event (worst lab value), and at the time of recovery:

Work aid: Target Questions for Follow-up on EOI
SCK;SH Version 6.0 – Apr 2019

INFECTION IN GENERAL (INCLUDING OPPORTUNISTIC INFECTION, ABSCESS, *SOFT TISSUE INFECTIONS INCLUDING NECROTIZING FASCIITIS*)

Test	Range w/ Units	Baseline lab value/ Date *(prior to Celgene product)*	Worst lab value/ Date	Recovery lab value/ Date
WBC				
ANC				

Please provide relevant culture/serology and chest x-ray results with dates.

Opportunistic infections (*only if appropriate*)
Please indicate whether there is any suspicion or evidence of the following types of infections (partial list):

Viral* :
☐ Epstein Barr virus (EBV)
☐ Hepatitis B (HBV)
☐ Cytomegalovirus (CMV)
☐ Herpes simplex (HSV)
☐ Varicella zoster virus (VZV)
☐ Progressive multifocal leukoencephalopathy (PML)
☐ Other (please specify):

Protozoal :
☐ Pneumocystis carinii (PCP)
☐ Toxoplasmosis
☐ Other (please specify):

Malignancies:
☐ Kaposi sarcoma (KS) - associated herpes virus
☐ Other (please specify):

Fungal:
☐ Candidiasis
☐ Aspergillosis
☐ Histoplasmosis
☐ Cryptococcosis
☐ Other (please specify):

Bacterial:
☐ Tuberculosis (TBC)
☐ Mycobacterium avium (MAI)
☐ Salmonellosis
☐ Other (please specify):

Parasitic:
☐ Visceral leishmaniasis (VL)
☐ Other (please specify):

* Please refer to targeted questionnaire for viral reactivation as needed

Work aid: Target Questions for Follow-up on EOI
SCK;SH Version 6.0 – Apr 2019

INFECTION IN GENERAL (INCLUDING OPPORTUNISTIC INFECTION, ABSCESS, *SOFT TISSUE INFECTIONS INCLUDING NECROTIZING FASCIITIS*)

If the answer to any of the above is yes, please indicate whether this diagnosis has been confirmed and if so how?

Please indicate whether the patient's travel history includes geographical areas associated with parasitic infections such as VL (i.e. Brazil, Ethiopia, India, Kenya, Somalia, South Sudan, Sudan, etc.). If so, please provide dates of travel.

Please indicate whether the patient experienced symptoms of VL including: slow progression of malaise, fever, weight loss, and splenomegaly (abdominal discomfort and fullness localized to left upper quadrant), skin hyperpigmentation over a period of months. If so, please provide dates and details below.

Soft tissue infections including necrotizing fasciitis (NF) (*only if appropriate*)

Please provide the site of the body that was initially affected by the soft tissue infection:

If the soft tissue infection was due to a local precipitating event(s), please indicate the cause of the event (e.g. traumatic including surgery, minor invasive procedures [e.g. joint aspirations], and penetrating injuries [e.g. insect and animal bites] and nontraumatic including soft tissue burns):

If the suspect drug is an injectable form, please specify the route of administration:
☐ Subcutaneous (SC)
☐ Intravenous (IV)

Please specify if the starting point of the soft tissue infection was at the injection site.

Please specify if any of the below risk factors have been identified:
☐ Diabetes
☐ Chronic disease (please specify):
☐ Immunosuppressive drugs (including corticosteroids), if yes specify:
☐ Malnutrition,
☐ Age >60 years
☐ Peripheral vascular disease
☐ Alcohol /drug abuse (please specify):
☐ Renal failure
☐ Obesity
☐ Recent childbirth
☐ Recent infection with rash (eg varicella)
☐ Recent stay in health care facility
☐ Recent dental work
☐ Others (please specify):

Work aid: Target Questions for Follow-up on EOI
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INFECTION IN GENERAL (INCLUDING OPPORTUNISTIC INFECTION, ABSCESS, *SOFT TISSUE INFECTIONS INCLUDING NECROTIZING FASCIITIS*)

Please provide the identified infectious causative pathogen and source of identification (eg skin or blood culture/serology results with dates).

Please provide any additional diagnostic test results if available (eg Scan; MRI; Skin biopsy; Muscle biopsy, etc.).

Please provide additional lab data including:

Test	Range w/ Units	Baseline lab value/ Date *(prior to Celgene product)*	Worst lab value/ Date	Recovery lab value/ Date
CPK MM				
CPK				
lactate				
BUN				
Creatinine				
glucose				
INR				
PT				
D- Dimer				
Serum C-reactive protein				

Please provide post-surgery pathology results including cultures from deep specimen samples during the intervention.

Please provide any available information concerning the patient's hobbies/occupation (fishing, weight lifting/heavy work-out/gardening, etc.).

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

Not applicable.